



## Clinical trial results:

**An open-label, multicenter, phase IIIb study assessing the long-term efficacy and safety of AOP2014 and standard first line treatment (BAT) in patients with Polycythemia Vera who previously participated in the PROUD-PV Study**

### Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2014-001357-17          |
| Trial protocol           | HU AT CZ PL SK BG ES DE |
| Global end of trial date | 29 April 2021           |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 30 March 2022 |
| First version publication date | 30 March 2022 |

### Trial information

#### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | CONTINUATION-PV |
|-----------------------|-----------------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | AOP Orphan Pharmaceuticals AG  |
| Sponsor organisation address | Leopold-Ungar-Platz 2, Wien, Austria, 1190   |
| Public contact               | Clinical Project Manager, AOP Orphan Pharmaceuticals AG, +43 1503724446, continuation-pv@aoporphan.com |
| Scientific contact           | Clinical Project Manager, AOP Orphan Pharmaceuticals AG, +43 1503724446, continuation-pv@aoporphan.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                       | 19 July 2021  |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 29 April 2021 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

- To assess the long-term efficacy of AOP2014 or BAT in terms of disease response rate in patients diagnosed with PV, who were previously treated with AOP2014 or HU in the PROUD-PV study and who completed this Study.
- To assess the long-term efficacy including changes in disease burden present during PROUD-PV study in patients diagnosed with PV, who were previously treated with AOP2014 or HU in the PROUD-PV study. Disease burden is defined as disease-related signs (clinically significant splenomegaly) and disease-related symptoms (microvascular disturbances, pruritus, headache), assessed by investigator.

Protection of trial subjects:

The Investigator obtained a freely given signed ICF, with name and date and time noted by the patient before the patient was exposed to any study-related procedure. The study was carried out in compliance with the principles of Good Clinical Practice (GCP), data protection and confidentiality were handled in compliance with local laws.

Background therapy:

Low dose aspirin (acetylsalicylic acid) (100 mg/day) is to be given to all patients for the duration of study treatment, unless contraindicated.

Evidence for comparator:

The PROUD-PV Study compared the investigational medicinal product (IMP) AOP2014 to HU, an established first-line treatment option currently approved in several European countries for PV patients requiring a cytoreductive therapy (Barbui et al, 2011). This study (CONTINUATION-PV) is a follow-on study designed to provide long-term evaluation of AOP2014 in patients with PV (who received the AOP2014 during the PROUD-PV Study) and of BAT in patients with PV (who received HU during the PROUD-PV Study). The integration of the patients who participated in the PEN-PV Study will contribute to this long-term evaluation of the IMP as well as to an alternative mode of administration (pre-filled injection pen).

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 25 November 2014 |
| 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 | Italy: 1     |
| Country: Number of subjects enrolled | Poland: 27   |
| Country: Number of subjects enrolled | Romania: 9   |
| Country: Number of subjects enrolled | Slovakia: 10 |
| Country: Number of subjects enrolled | Spain: 1     |
| Country: Number of subjects enrolled | Austria: 19  |
| Country: Number of subjects enrolled | Bulgaria: 45 |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Czechia: 26            |
| Country: Number of subjects enrolled | France: 13             |
| Country: Number of subjects enrolled | Germany: 6             |
| Country: Number of subjects enrolled | Hungary: 34            |
| Country: Number of subjects enrolled | Russian Federation: 33 |
| Country: Number of subjects enrolled | Ukraine: 30            |
| Worldwide total number of subjects   | 254                    |
| EEA total number of subjects         | 191                    |

Notes:

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### 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)                      | 174 |
| From 65 to 84 years                       | 79  |
| 85 years and over                         | 1   |

## Subject disposition

### Recruitment

Recruitment details:

Patients who completed the PROUD-PV Study and fulfilled inclusion criteria were asked to participate in this study.

### Pre-assignment

Screening details:

Patients who completed the PROUD-PV Study and fulfill inclusion and exclusion criteria were enrolled into the study after giving their informed consent. Out of 217 patients who completed the PROUD-PV, 171 patients were enrolled. Because of a serious breach, 2 patients were later excluded from the analyses, 169 patients were included.

### Period 1

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

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | AOP2014 |

Arm description:

Patients treated with AOP2014. The dose of AOP2014 was adjusted to the dose which delivered the optimal disease response.

|  |                         |
|--|-------------------------|
| Arm type                               | Experimental            |
| Investigational medicinal product name | AOP2014                 |
| Investigational medicinal product code | ropeginterferon alfa-2b |
| Other name                             | Peg-P-IFN- $\alpha$ -2b |
| Pharmaceutical forms                   | Solution for injection  |
| Routes of administration               | Subcutaneous use        |

Dosage and administration details:

AOP2014 was administered at the starting dose of 100  $\mu$ g every 2 weeks for up to 12 months of treatment. During the initial treatment phase (first 12 weeks following randomization), the dose of AOP2014 was adjusted to the dose which delivered the optimal disease response (Hematocrit [Hct] <45%, platelets <400 x 10<sup>9</sup>/L and leukocytes <10 x 10<sup>9</sup>/L). If no complete response was achieved, patients were treated at the individual highest tolerable dose, which had been achieved and kept during the maintenance treatment phase.

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

Arm description:

Patients treated with Hydroxyurea or Best Available Treatment

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Hydroxyurea       |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Capsule           |
| Routes of administration               | Oral use          |

Dosage and administration details:

Hydroxyurea was administered per os at the starting dose of 500 mg daily for up to 12 months of treatment. During the initial treatment phase (first 12 weeks following randomization), the dose of Hydroxyurea was adjusted to the dose which delivered the optimal disease response (Hematocrit [Hct] <45%, platelets <400 x 10<sup>9</sup>/L and leukocytes <10 x 10<sup>9</sup>/L). If no complete response was achieved, patients were treated at the individual highest tolerable dose, which had been achieved and kept during the maintenance treatment phase.

| <b>Number of subjects in period 1</b>        | AOP2014 | Control |
|--|---------|---------|
| Started                                      | 127     | 127     |
| EOT in PROUD-PV                              | 106     | 111     |
| Enrollment to CONTINUATION-PV                | 95      | 76      |
| Analysed in CONTINUATION-PV                  | 95      | 74      |
| Completed                                    | 67      | 52      |
| Not completed                                | 60      | 75      |
| Consent withdrawn by subject                 | 4       | 6       |
| Adverse event, continuation not possible     | 7       | 2       |
| Completed PROUD-PV but not enrolled in CONTI | 11      | 35      |
| Other  | 6       | 12      |
| Lost to follow-up                            | 2       | 2       |
| Following adverse events                     | 4       | -       |
| Serious breach at site                       | -       | 2       |
| Discontinued in PROUD-PV                     | 21      | 16      |
| Administrative reason                        | 2       | -       |
| Lack of efficacy                             | 3       | -       |

## Baseline characteristics

### Reporting groups

|   |         |
|---|---------|
| Reporting group title   | AOP2014 |
| Reporting group description:<br>Patients treated with AOP2014. The dose of AOP2014 was adjusted to the dose which delivered the optimal disease response. |         |
| Reporting group title   | Control |
| Reporting group description:<br>Patients treated with Hydroxyurea or Best Available Treatment   |         |

| Reporting group values                                | AOP2014      | Control      | Total |
|---|--------------|--------------|-------|
| Number of subjects                                    | 127          | 127          | 254   |
| 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)                                  | 90           | 84           | 174   |
| From 65-84 years                                      | 36           | 43           | 79    |
| 85 years and over                                     | 1            | 0            | 1     |
| Age continuous<br>Units: years                        |              |              |       |
| median  | 60.0         | 60.0         |       |
| inter-quartile range (Q1-Q3)                          | 52.0 to 66.0 | 48.0 to 67.0 | -     |
| Gender categorical<br>Units: Subjects                 |              |              |       |
| Female  | 68           | 67           | 135   |
| Male  | 59           | 60           | 119   |
| Race<br>Units: Subjects                               |              |              |       |
| White   | 127          | 127          | 254   |
| Durration of Polycythemia Vera<br>Units: month        |              |              |       |
| arithmetic mean                                       | 12.6         | 15.7         |       |
| standard deviation                                    | ± 24.70      | ± 25.65      | -     |

### Subject analysis sets

|   |                     |
|---|---------------------|
| Subject analysis set title  | PROUD+CONTI AOP2014 |
| Subject analysis set type   | Safety analysis     |
| Subject analysis set description:<br>All the AOP2014 patients treated in PROUD-PV study, regardless whether they continued to CONTINUATION-PV |                     |
| Subject analysis set title  | PROUD+CONTI Control |

|   |                   |
|---|-------------------|
| Subject analysis set type   | Safety analysis   |
| Subject analysis set description:<br>All the control patients treated in PROUD-PV study, regardless whether they continued to CONTINUATION-PV                               |                   |
| Subject analysis set title  | CONTI FAS AOP2014 |
| Subject analysis set type   | Full analysis     |
| Subject analysis set description:<br>All AOP2014 patients enrolled to CONTINUATION-PV (without the subjects from the site with serious breach)                              |                   |
| Subject analysis set title  | CONTI FAS Control |
| Subject analysis set type   | Full analysis     |
| Subject analysis set description:<br>All AOP2014 patients enrolled to CONTINUATION-PV (without the subjects from the site with serious breach)                              |                   |
| Subject analysis set title  | CONTI PPS AOP2014 |
| Subject analysis set type   | Per protocol      |
| Subject analysis set description:<br>Subject from the CONTI FAS AOP2014 set who have no protocol deviation which would lead to exclusion from PPS at all assessment visits. |                   |
| Subject analysis set title  | CONTI PPS Control |
| Subject analysis set type   | Per protocol      |
| Subject analysis set description:<br>Subject from the CONTI FAS AOP2014 set who have no protocol deviation which would lead to exclusion from PPS at all assessment visits. |                   |

| Reporting group values                             | PROUD+CONTI AOP2014 | PROUD+CONTI Control | CONTI FAS AOP2014 |
|--|---------------------|---------------------|-------------------|
| Number of subjects                                 | 127                 | 127                 | 95                |
| Age categorical<br>Units: Subjects                 |                     |                     |                   |
| In utero   | 0                   | 0                   | 0                 |
| Preterm newborn infants (gestational age < 37 wks) | 0                   | 0                   | 0                 |
| Newborns (0-27 days)                               | 0                   | 0                   | 0                 |
| Infants and toddlers (28 days-23 months)           | 0                   | 0                   | 0                 |
| Children (2-11 years)                              | 0                   | 0                   | 0                 |
| Adolescents (12-17 years)                          | 0                   | 0                   | 0                 |
| Adults (18-64 years)                               | 90                  | 84                  | 75                |
| From 65-84 years                                   | 36                  | 43                  | 19                |
| 85 years and over                                  | 1                   | 0                   | 1                 |
| Age continuous<br>Units: years                     |                     |                     |                   |
| median   | 60                  | 60                  | 58                |
| inter-quartile range (Q1-Q3)                       | 52 to 66            | 48 to 67            | 50 to 64          |
| Gender categorical<br>Units: Subjects              |                     |                     |                   |
| Female   | 68                  | 67                  | 48                |
| Male   | 59                  | 60                  | 47                |
| Race<br>Units: Subjects                            |                     |                     |                   |
| White  | 127                 | 127                 | 95                |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Durruration of Polycythemia Vera<br>Units: month<br>arithmetic mean<br>standard deviation | 12.6<br>± 24.70 | 15.7<br>± 25.65 | 12.1<br>± 25.82 |
|---|-----------------|-----------------|-----------------|

| <b>Reporting group values</b>   | CONTI FAS Control | CONTI PPS AOP2014  | CONTI PPS Control |
|---|-------------------|--------------------|-------------------|
| Number of subjects  | 74                | 92                 | 72                |
| 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 months)  | 0                 | 0                  | 0                 |
| Children (2-11 years)   | 0                 | 0                  | 0                 |
| Adolescents (12-17 years)   | 0                 | 0                  | 0                 |
| Adults (18-64 years)  | 49                | 72                 | 48                |
| From 65-84 years  | 25                | 19                 | 24                |
| 85 years and over   | 0                 | 1                  | 0                 |
| Age continuous<br>Units: years<br>median<br>inter-quartile range (Q1-Q3)                  | 60<br>50 to 66    | 58.5<br>50.5 to 64 | 60<br>50 to 65.5  |
| Gender categorical<br>Units: Subjects   |                   |                    |                   |
| Female  | 39                | 47                 | 38                |
| Male  | 35                | 45                 | 34                |
| Race<br>Units: Subjects   |                   |                    |                   |
| White   | 74                | 92                 | 72                |
| Durruration of Polycythemia Vera<br>Units: month<br>arithmetic mean<br>standard deviation | 10.1<br>± 17.54   | 12.2<br>± 26.18    | 10.4<br>± 17.71   |



## End points

### End points reporting groups

|   |                     |
|---|---------------------|
| Reporting group title   | AOP2014             |
| Reporting group description:<br>Patients treated with AOP2014. The dose of AOP2014 was adjusted to the dose which delivered the optimal disease response.                   |                     |
| Reporting group title   | Control             |
| Reporting group description:<br>Patients treated with Hydroxyurea or Best Available Treatment   |                     |
| Subject analysis set title  | PROUD+CONTI AOP2014 |
| Subject analysis set type   | Safety analysis     |
| Subject analysis set description:<br>All the AOP2014 patients treated in PROUD-PV study, regardless whether they continued to CONTINUATION-PV                               |                     |
| Subject analysis set title  | PROUD+CONTI Control |
| Subject analysis set type   | Safety analysis     |
| Subject analysis set description:<br>All the control patients treated in PROUD-PV study, regardless whether they continued to CONTINUATION-PV                               |                     |
| Subject analysis set title  | CONTI FAS AOP2014   |
| Subject analysis set type   | Full analysis       |
| Subject analysis set description:<br>All AOP2014 patients enrolled to CONTINUATION-PV (without the subjects from the site with serious breach)                              |                     |
| Subject analysis set title  | CONTI FAS Control   |
| Subject analysis set type   | Full analysis       |
| Subject analysis set description:<br>All AOP2014 patients enrolled to CONTINUATION-PV (without the subjects from the site with serious breach)                              |                     |
| Subject analysis set title  | CONTI PPS AOP2014   |
| Subject analysis set type   | Per protocol        |
| Subject analysis set description:<br>Subject from the CONTI FAS AOP2014 set who have no protocol deviation which would lead to exclusion from PPS at all assessment visits. |                     |
| Subject analysis set title  | CONTI PPS Control   |
| Subject analysis set type   | Per protocol        |
| Subject analysis set description:<br>Subject from the CONTI FAS AOP2014 set who have no protocol deviation which would lead to exclusion from PPS at all assessment visits. |                     |

### Primary: Complete haematologic response with spleen size criterion

|  |   |
|--|---|
| End point title  | Complete haematologic response with spleen size criterion |
| End point description:<br>Disease response defined as haematologic response: Hct<45% without phlebotomy (at least 3 months since the last phlebotomy), PLTs<400 x 10 <sup>9</sup> /L, WBCs<10 x 10 <sup>9</sup> /L, and normal spleen size<br>The discontinued patients are assumed to be Non-responders |   |
| End point type   | Primary   |
| End point timeframe:<br>Each assesment visit (each 3 months)   |   |

| End point values                                  | AOP2014         | Control         | CONTI FAS<br>AOP2014 | CONTI FAS<br>Control |
|---|-----------------|-----------------|----------------------|----------------------|
| Subject group type                                | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed                       | 95              | 74              | 95                   | 74                   |
| Units: count and percentage of subject            |                 |                 |                      |                      |
| Responder at Month 72                             | 32              | 15              | 32                   | 15                   |
| Non-responder at Month 72, including discontinued | 54              | 45              | 54                   | 45                   |
| Discontinued at Month 72                          | 25              | 20              | 25                   | 20                   |

| End point values                                  | CONTI PPS<br>AOP2014 | CONTI PPS<br>Control |  |  |
|---|----------------------|----------------------|--|--|
| Subject group type                                | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed                       | 92                   | 72                   |  |  |
| Units: count and percentage of subject            |                      |                      |  |  |
| Responder at Month 72                             | 30                   | 15                   |  |  |
| Non-responder at Month 72, including discontinued | 48                   | 45                   |  |  |
| Discontinued at Month 72                          | 22                   | 20                   |  |  |

|                                   |   |
|-----------------------------------|---|
| <b>Attachments (see zip file)</b> | Analyses in per-protocol set/Primary 1 PPS.xlsx<br>Analysis in Full-analyses set/Primary 1 FAS.xlsx |
|-----------------------------------|---|

## Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Longitudinal analysis over 0 - 72 months FAS |
| Statistical analysis description:  |  |
| Longitudinal analysis to evaluate trends over treatment period of 72 months. |  |
| Comparison groups  | CONTI FAS AOP2014 v CONTI FAS Control        |
| Number of subjects included in analysis                                      | 169  |
| Analysis specification   | Pre-specified                                |
| Analysis type  | other <sup>[1]</sup>                         |
| P-value  | = 0.1289 <sup>[2]</sup>                      |
| Method   | Mixed models analysis                        |
| Parameter estimate   | Risk ratio (RR)                              |
| Point estimate   | 1.48   |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided                                      |
| lower limit  | 0.89   |
| upper limit  | 2.46   |
| Variability estimate   | Standard error of the mean                   |

Notes:

[1] - Study the trend in responses in the treatment period

[2] - The goal was to study the trend through the years. The p-value in late months is higher because of high number of discontinued patients (= Non-responders). Check the attachment for more information.

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Longitudinal analysis over 0 - 72 months PPS |
| Statistical analysis description:<br>Longitudinal analysis to evaluate trends over treatment period of 72 months. |  |
| Comparison groups   | CONTI PPS AOP2014 v CONTI PPS Control        |
| Number of subjects included in analysis   | 164  |
| Analysis specification  | Pre-specified                                |
| Analysis type   | other <sup>[3]</sup>                         |
| P-value   | = 0.0987 <sup>[4]</sup>                      |
| Method  | Mixed models analysis                        |
| Parameter estimate  | Risk ratio (RR)                              |
| Point estimate  | 1.53   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided                                      |
| lower limit   | 0.92   |
| upper limit   | 2.55   |
| Variability estimate  | Standard error of the mean                   |

Notes:

[3] - Study the trend in responses in the treatment period

[4] - The goal was to study the trend through the years. The p-value in late months is higher because of high number of discontinued patients (= Non-responders). Check the attachment for more information.

### **Primary: Complete haematologic response and improvement of disease burden**

|   |  |
|---|--|
| End point title   | Complete haematologic response and improvement of disease burden |
| End point description:<br>Disease response defined as haematologic response (Hct<45% without phlebotomy (at least 3 months since the last phlebotomy), PLTs<400 x 10 <sup>9</sup> /L, WBCs<10 x 10 <sup>9</sup> /L), resolution and/or clinically improvement of disease-related signs (clinically significant splenomegaly) and disease-related symptoms (microvascular disturbances, pruritus, headache). |  |
| End point type  | Primary  |
| End point timeframe:<br>Each assesment visit (each 3 months)  |  |

| <b>End point values</b>                           | AOP2014         | Control         | CONTI FAS AOP2014    | CONTI FAS Control    |
|---|-----------------|-----------------|----------------------|----------------------|
| Subject group type                                | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed                       | 95              | 74              | 95                   | 74                   |
| Units: count and percentage of subject            |                 |                 |                      |                      |
| Responder at Month 72                             | 35              | 17              | 35                   | 17                   |
| Non-responder at Month 72, including discontinued | 53              | 49              | 53                   | 49                   |
| Discontinued at Month 72                          | 25              | 20              | 25                   | 20                   |

| End point values                                  | CONTI PPS<br>AOP2014 | CONTI PPS<br>Control |  |  |
|---|----------------------|----------------------|--|--|
| Subject group type                                | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed                       | 92                   | 72                   |  |  |
| Units: count and percentage of subject            |                      |                      |  |  |
| Responder at Month 72                             | 35                   | 15                   |  |  |
| Non-responder at Month 72, including discontinued | 43                   | 45                   |  |  |
| Discontinued at Month 72                          | 22                   | 20                   |  |  |

|                                   |   |
|-----------------------------------|---|
| <b>Attachments (see zip file)</b> | Analysis in Full-analyses set/Primary 2 FAS.xlsx<br>Analysis in Per-protocol set/Primary 2 PPS.xlsx |
|-----------------------------------|---|

## Statistical analyses

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Longitudinal analysis over 0 - 72 months FAS |
|-----------------------------------|--|

Statistical analysis description:

Longitudinal analysis to evaluate trends over treatment period of 72 months.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | CONTI FAS Control v CONTI FAS AOP2014 |
| Number of subjects included in analysis | 169                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[5]</sup>                  |
| P-value                                 | = 0.0584 <sup>[6]</sup>               |
| Method                                  | Mixed models analysis                 |
| Parameter estimate                      | Risk ratio (RR)                       |
| Point estimate                          | 1.58                                  |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 0.98                                  |
| upper limit                             | 2.52                                  |
| Variability estimate                    | Standard error of the mean            |

Notes:

[5] - Study the trend in responses in the treatment period

[6] - The goal was to study the trend through the years. The p-value in late months is higher because of high number of discontinued patients (= Non-responders). Check the attachment for more information.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Longitudinal analysis over 0 - 72 months PPS |
|-----------------------------------|--|

Statistical analysis description:

Longitudinal analysis to evaluate trends over treatment period of 72 months.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | CONTI PPS AOP2014 v CONTI PPS Control |
| Number of subjects included in analysis | 164                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[7]</sup>                  |
| P-value                                 | = 0.0167 <sup>[8]</sup>               |
| Method                                  | Mixed models analysis                 |
| Parameter estimate                      | Risk ratio (RR)                       |
| Point estimate                          | 1.82                                  |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | 1.11                       |
| upper limit          | 2.97                       |
| Variability estimate | Standard error of the mean |

Notes:

[7] - Study the trend in responses in the treatment period

[8] - The goal was to study the trend through the years. The p-value in late months is higher because of high number of discontinued patients (= Non-responders). Check the attachment for more information.

### Secondary: Complete haematologic response (without spleen size criterion)

|                 |  |
|-----------------|--|
| End point title | Complete haematologic response (without spleen size criterion) |
|-----------------|--|

End point description:

Disease response defined as haematologic response: Hct<45% without phlebotomy (at least 3 months since the last phlebotomy), PLTs<400 x 10<sup>9</sup>/L, WBCs<10 x 10<sup>9</sup>/L. The discontinued patients are assumed to be Non-responders

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

End point timeframe:

Each assesment visit (each 3 months)

| End point values                                  | AOP2014         | Control         | CONTI FAS<br>AOP2014 | CONTI FAS<br>Control |
|---|-----------------|-----------------|----------------------|----------------------|
| Subject group type                                | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed                       | 95              | 74              | 95                   | 74                   |
| Units: count and percentage of subject            |                 |                 |                      |                      |
| Responder at Month 72                             | 48              | 22              | 48                   | 22                   |
| Non-responder at Month 72, including discontinued | 40              | 41              | 40                   | 41                   |
| Discontinued at Month 72                          | 25              | 20              | 25                   | 20                   |

| End point values                                  | CONTI PPS<br>AOP2014 | CONTI PPS<br>Control |  |  |
|---|----------------------|----------------------|--|--|
| Subject group type                                | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed                       | 92                   | 72                   |  |  |
| Units: count and percentage of subject            |                      |                      |  |  |
| Responder at Month 72                             | 45                   | 19                   |  |  |
| Non-responder at Month 72, including discontinued | 33                   | 41                   |  |  |
| Discontinued at Month 72                          | 22                   | 20                   |  |  |

|                                   |  |
|-----------------------------------|--|
| <b>Attachments (see zip file)</b> | Analysis in Full-analyses set/Secondary 1 FAS.xlsx |
|                                   | Analysis in Per-protocol set/Secondary 1 PPS.xlsx  |

## Statistical analyses

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Longitudinal analysis over 0 - 72 months FAS |
|-----------------------------------|--|

Statistical analysis description:

Longitudinal analysis to evaluate trends over treatment period of 72 months.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | CONTI FAS AOP2014 v CONTI FAS Control |
| Number of subjects included in analysis | 169                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[9]</sup>                  |
| P-value                                 | = 0.0216 <sup>[10]</sup>              |
| Method                                  | Mixed models analysis                 |
| Parameter estimate                      | Risk ratio (RR)                       |
| Point estimate                          | 1.55                                  |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 1.07                                  |
| upper limit                             | 2.26                                  |
| Variability estimate                    | Standard error of the mean            |

Notes:

[9] - Study the trend in responses in the treatment period

[10] - The goal was to study the trend through the years. The p-value in late months is higher because of high number of discontinued patients (= Non-responders). Check the attachment for more information.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Longitudinal analysis over 0 - 72 months PPS |
|-----------------------------------|--|

Statistical analysis description:

Longitudinal analysis to evaluate trends over treatment period of 72 months. in per-protocol set.

|   |                                       |
|---|---------------------------------------|
| Comparison groups                       | CONTI PPS AOP2014 v CONTI PPS Control |
| Number of subjects included in analysis | 164                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | other <sup>[11]</sup>                 |
| P-value                                 | = 0.0034 <sup>[12]</sup>              |
| Method                                  | Mixed models analysis                 |
| Parameter estimate                      | Risk ratio (RR)                       |
| Point estimate                          | 1.83                                  |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 1.22                                  |
| upper limit                             | 2.74                                  |
| Variability estimate                    | Standard error of the mean            |

Notes:

[11] - Study the trend in responses in the treatment period

[12] - The goal was to study the trend through the years. The p-value in late months is higher because of high number of discontinued patients (= Non-responders). Check the attachment for more information.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | AOP2014 |
|-----------------------|---------|

Reporting group description: -

|                       |         |
|-----------------------|---------|
| Reporting group title | Control |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events  | AOP2014                                      | Control           |  |
|---|--|-------------------|--|
| Total subjects affected by serious adverse events                   |  |                   |  |
| subjects affected / exposed   | 32 / 127 (25.20%)                            | 35 / 127 (27.56%) |  |
| number of deaths (all causes)                                       | 3  | 5                 |  |
| number of deaths resulting from adverse events                      | 3  | 5                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |                   |  |
| Acute leukaemia   | Additional description: Acute leukaemia      |                   |  |
| subjects affected / exposed   | 0 / 127 (0.00%)                              | 2 / 127 (1.57%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0  | 1 / 2             |  |
| deaths causally related to treatment / all                          | 0 / 0  | 1 / 1             |  |
| Adrenal adenoma   | Additional description: Adrenal adenoma      |                   |  |
| subjects affected / exposed   | 1 / 127 (0.79%)                              | 0 / 127 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1  | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0             |  |
| Basal cell carcinoma  | Additional description: Basal cell carcinoma |                   |  |
| subjects affected / exposed   | 0 / 127 (0.00%)                              | 2 / 127 (1.57%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0  | 2 / 2             |  |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0             |  |
| Bile duct cancer  | Additional description: Bile duct cancer     |                   |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Brain neoplasm malignant                        | Additional description: Brain neoplasm malignant |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                  | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Colon cancer                                    | Additional description: Colon cancer             |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                  | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Glioblastoma                                    | Additional description: Glioblastoma             |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1  | 0 / 0           |  |
| Malignant melanoma                              | Additional description: Malignant melanoma       |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                  | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Myelofibrosis                                   | Additional description: Myelofibrosis            |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                  | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Neoplasm of appendix                            | Additional description: Neoplasm of appendix     |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                  | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Rectal adenocarcinoma                           | Additional description: Rectal adenocarcinoma    |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Renal oncocyoma                                 | Additional description: Renal oncocyoma          |                 |  |



|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 0 / 127 (0.00%)   | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Spermatocytic seminoma                          | Additional description: Spermatocytic seminoma                |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Thyroid adenoma                                 | Additional description: Thyroid adenoma                       |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Vascular disorders                              |   |                 |  |
| Embolism  | Additional description: Embolism                              |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)   | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Hypertension                                    | Additional description: Hypertension                          |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Peripheral arterial occlusive disease           | Additional description: Peripheral arterial occlusive disease |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Thrombophlebitis superficial                    | Additional description: Thrombophlebitis superficial          |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)   | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Surgical and medical procedures                 |   |                 |  |
| Aortic valve replacement                        | Additional description: Aortic valve replacement              |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)   | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Carotid endarterectomy                          | Additional description: Carotid endarterectomy                |                 |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 0 / 127 (0.00%)                                | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Cholecystectomy                                 | Additional description: Cholecystectomy        |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Colectomy                                       | Additional description: Colectomy              |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Heart valve operation                           | Additional description: Heart valve operation  |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Hip arthroplasty                                | Additional description: Hip arthroplasty       |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                | 2 / 127 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Knee arthroplasty                               | Additional description: Knee arthroplasty      |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Knee operation                                  | Additional description: Knee operation         |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Rehabilitation therapy                          | Additional description: Rehabilitation therapy |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Renal cyst excision                             | Additional description: Renal cyst excision    |                 |  |

|  |   |                 |  |
|--|---|-----------------|--|
| subjects affected / exposed                          | 1 / 127 (0.79%)                               | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0           |  |
| Shoulder arthroplasty                                | Additional description: Shoulder arthroplasty |                 |  |
| subjects affected / exposed                          | 1 / 127 (0.79%)                               | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0           |  |
| General disorders and administration site conditions |   |                 |  |
| Multi-organ failure                                  | Additional description: Multi-organ failure   |                 |  |
| subjects affected / exposed                          | 1 / 127 (0.79%)                               | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0           |  |
| Death  | Additional description: Death                 |                 |  |
| subjects affected / exposed                          | 1 / 127 (0.79%)                               | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 1   | 0 / 0           |  |
| Oedema peripheral                                    | Additional description: Oedema peripheral     |                 |  |
| subjects affected / exposed                          | 1 / 127 (0.79%)                               | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0           |  |
| Pyrexia  | Additional description: Pyrexia               |                 |  |
| subjects affected / exposed                          | 1 / 127 (0.79%)                               | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0           |  |
| Sudden death   | Additional description: Sudden death          |                 |  |
| subjects affected / exposed                          | 0 / 127 (0.00%)                               | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all      | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 1           |  |
| Reproductive system and breast disorders             |   |                 |  |
| Uterine polyp  | Additional description: Uterine polyp         |                 |  |
| subjects affected / exposed                          | 1 / 127 (0.79%)                               | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0           |  |

|   |   |                 |  |
|---|---|-----------------|--|
| Psychiatric disorders                           |   |                 |  |
| Depression                                      | Additional description: Depression                  |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                     | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Investigations                                  |   |                 |  |
| Angiocardiogram                                 | Additional description: Angiocardiogram             |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                     | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Coagulation time prolonged                      | Additional description: Coagulation time prolonged  |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                     | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Injury, poisoning and procedural complications  |   |                 |  |
| Fall  | Additional description: Fall                        |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                     | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Gastroenteritis radiation                       | Additional description: Gastroenteritis radiation   |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                     | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Post procedural haemorrhage                     | Additional description: Post procedural haemorrhage |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                     | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Road traffic accident                           | Additional description: Road traffic accident       |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                     | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 1           |  |
| Skin laceration                                 | Additional description: Skin laceration             |                 |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 0 / 127 (0.00%)                                | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Skull fractured base                            | Additional description: Skull fractured base   |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Subcutaneous haematoma                          | Additional description: Subcutaneous haematoma |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Upper limb fracture                             | Additional description: Upper limb fracture    |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Uterine dehiscence                              | Additional description: Uterine dehiscence     |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Congenital, familial and genetic disorders      |  |                 |  |
| Porphyria non-acute                             | Additional description: Porphyria non-acute    |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Cardiac disorders                               |  |                 |  |
| Angina unstable                                 | Additional description: Angina unstable        |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Atrial fibrillation                             | Additional description: Atrial fibrillation    |                 |  |
| subjects affected / exposed                     | 3 / 127 (2.36%)                                | 2 / 127 (1.57%) |  |
| occurrences causally related to treatment / all | 1 / 3  | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |

|                              |  |                 |                 |
|------------------------------|--|-----------------|-----------------|
| Atrial flutter               | Additional description: Atrial flutter               |                 |                 |
|                              | subjects affected / exposed                          | 1 / 127 (0.79%) | 0 / 127 (0.00%) |
|                              | occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |
|                              | deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |
| Cardiac failure              | Additional description: Cardiac failure              |                 |                 |
|                              | subjects affected / exposed                          | 0 / 127 (0.00%) | 3 / 127 (2.36%) |
|                              | occurrences causally related to treatment / all      | 0 / 0           | 0 / 3           |
|                              | deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |
| Cardiac failure acute        | Additional description: Cardiac failure acute        |                 |                 |
|                              | subjects affected / exposed                          | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
|                              | occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           |
|                              | deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |
| Cardiac failure chronic      | Additional description: Cardiac failure chronic      |                 |                 |
|                              | subjects affected / exposed                          | 1 / 127 (0.79%) | 0 / 127 (0.00%) |
|                              | occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |
|                              | deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |
| Pericardial effusion         | Additional description: Pericardial effusion         |                 |                 |
|                              | subjects affected / exposed                          | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
|                              | occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |
|                              | deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |
| Left ventricular failure     | Additional description: Left ventricular failure     |                 |                 |
|                              | subjects affected / exposed                          | 0 / 127 (0.00%) | 1 / 127 (0.79%) |
|                              | occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |
|                              | deaths causally related to treatment / all           | 0 / 0           | 0 / 1           |
| Supraventricular tachycardia | Additional description: Supraventricular tachycardia |                 |                 |
|                              | subjects affected / exposed                          | 1 / 127 (0.79%) | 0 / 127 (0.00%) |
|                              | occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |
|                              | deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |
| Sinus tachycardia            | Additional description: Sinus tachycardia            |                 |                 |
|                              | subjects affected / exposed                          | 1 / 127 (0.79%) | 0 / 127 (0.00%) |
|                              | occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |
|                              | deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |
| Nervous system disorders     |  |                 |                 |

|   |  |                 |  |
|---|--|-----------------|--|
| Cerebrovascular accident<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                        | Additional description: Cerebrovascular accident           |                 |  |
|   | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
|   | 0 / 0  | 0 / 1           |  |
|   | 0 / 0  | 0 / 0           |  |
| Encephalopathy<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                  | Additional description: Encephalopathy                     |                 |  |
|   | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
|   | 0 / 1  | 0 / 0           |  |
|   | 0 / 0  | 0 / 0           |  |
| Haemorrhagic transformation stroke<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all              | Additional description: Haemorrhagic transformation stroke |                 |  |
|   | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
|   | 0 / 1  | 0 / 0           |  |
|   | 0 / 0  | 0 / 0           |  |
| Ischaemic stroke<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                | Additional description: Ischaemic stroke                   |                 |  |
|   | 2 / 127 (1.57%)  | 0 / 127 (0.00%) |  |
|   | 0 / 2  | 0 / 0           |  |
|   | 0 / 0  | 0 / 0           |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | Additional description: Anaemia                            |                 |  |
|   | 1 / 127 (0.79%)  | 2 / 127 (1.57%) |  |
|   | 1 / 1  | 1 / 2           |  |
|   | 0 / 0  | 0 / 0           |  |
| Granulocytopenia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                | Additional description: Granulocytopenia                   |                 |  |
|   | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
|   | 0 / 0  | 1 / 1           |  |
|   | 0 / 0  | 0 / 0           |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                      | Additional description: Leukopenia                         |                 |  |
|   | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
|   | 0 / 0  | 1 / 1           |  |
|   | 0 / 0  | 0 / 0           |  |
| Microcytic anaemia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                              | Additional description: Microcytic anaemia                 |                 |  |
|   | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
|   | 0 / 1  | 0 / 0           |  |
|   | 0 / 0  | 0 / 0           |  |
| Gastrointestinal disorders  |  |                 |  |

|  |   |                 |  |
|--|---|-----------------|--|
| Diverticulum intestinal<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                              | Additional description: Diverticulum intestinal         |                 |  |
|  | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
|  | 0 / 1   | 0 / 0           |  |
|  | 0 / 0   | 0 / 0           |  |
| Gastritis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | Additional description: Gastritis                       |                 |  |
|  | 0 / 127 (0.00%)   | 1 / 127 (0.79%) |  |
|  | 0 / 0   | 0 / 1           |  |
|  | 0 / 0   | 0 / 0           |  |
| Gastroesophageal reflux disease<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                      | Additional description: Gastroesophageal reflux disease |                 |  |
|  | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
|  | 0 / 1   | 0 / 0           |  |
|  | 0 / 0   | 0 / 0           |  |
| Inguinal hernia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                      | Additional description: Inguinal hernia                 |                 |  |
|  | 0 / 127 (0.00%)   | 1 / 127 (0.79%) |  |
|  | 0 / 0   | 0 / 1           |  |
|  | 0 / 0   | 0 / 0           |  |
| Hepatobiliary disorders<br>Cholelithiasis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all            | Additional description: Cholelithiasis                  |                 |  |
|  | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
|  | 0 / 2   | 0 / 0           |  |
|  | 0 / 0   | 0 / 0           |  |
| Cholecystitis acute<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                  | Additional description: Cholecystitis acute             |                 |  |
|  | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
|  | 0 / 1   | 0 / 0           |  |
|  | 0 / 0   | 0 / 0           |  |
| Skin and subcutaneous tissue disorders<br>Skin ulcer<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | Additional description: Skin ulcer                      |                 |  |
|  | 0 / 127 (0.00%)   | 1 / 127 (0.79%) |  |
|  | 0 / 0   | 0 / 2           |  |
|  | 0 / 0   | 0 / 0           |  |
| Umbilical haematoma<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                  | Additional description: Umbilical haematoma             |                 |  |
|  | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
|  | 0 / 1   | 0 / 0           |  |
|  | 0 / 0   | 0 / 0           |  |



|   |   |                 |  |
|---|---|-----------------|--|
| Renal and urinary disorders                     |   |                 |  |
| Acute kidney injury                             | Additional description: Acute kidney injury                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Bladder transitional cell carcinoma             | Additional description: Bladder transitional cell carcinoma |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Calculus urinary                                | Additional description: Calculus urinary                    |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)   | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |   |                 |  |
| Bursitis  | Additional description: Bursitis                            |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Intervertebral disc protrusion                  | Additional description: Intervertebral disc protrusion      |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Osteoarthritis                                  | Additional description: Osteoarthritis                      |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)   | 2 / 127 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Rheumatoid arthritis                            | Additional description: Rheumatoid arthritis                |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Infections and infestations                     |   |                 |  |
| Appendicitis                                    | Additional description: Appendicitis                        |                 |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| COVID-19  | Additional description: COVID-19                 |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                  | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Cholangitis infective                           | Additional description: Cholangitis infective    |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Diverticulitis                                  | Additional description: Diverticulitis           |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Pneumonia                                       | Additional description: Pneumonia                |                 |  |
| subjects affected / exposed                     | 3 / 127 (2.36%)                                  | 3 / 127 (2.36%) |  |
| occurrences causally related to treatment / all | 0 / 4  | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 1  | 0 / 2           |  |
| Pneumonia viral                                 | Additional description: Pneumonia viral          |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Pseudomembranous colitis                        | Additional description: Pseudomembranous colitis |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                  | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Pyelonephritis acute                            | Additional description: Pyelonephritis acute     |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                  | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           |  |
| Sepsis  | Additional description: Sepsis                   |                 |  |

|   |                                       |                 |  |
|---|---------------------------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 127 (0.79%)                       | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 1                                 | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                 | 0 / 1           |  |
| Septic shock                                    | Additional description: Septic shock  |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                       | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1                                 | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0                                 | 0 / 0           |  |
| Sinusitis                                       | Additional description: Sinusitis     |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                       | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1                                 | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0                                 | 0 / 0           |  |
| Tuberculosis                                    | Additional description: Tuberculosis  |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                       | 0 / 127 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1                                 | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0                                 | 0 / 0           |  |
| Metabolism and nutrition disorders              |                                       |                 |  |
| Hyponatraemia                                   | Additional description: Hyponatraemia |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                       | 1 / 127 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0                                 | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0                                 | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                                   | AOP2014                                  | Control            |  |
|---|--|--------------------|--|
| Total subjects affected by non-serious adverse events               |  |                    |  |
| subjects affected / exposed   | 115 / 127 (90.55%)                       | 117 / 127 (92.13%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |                    |  |
| Adrenal adenoma   | Additional description: Adrenal adenoma  |                    |  |
| subjects affected / exposed   | 0 / 127 (0.00%)                          | 1 / 127 (0.79%)    |  |
| occurrences (all)   | 0  | 1                  |  |
| Angiolipoma   | Additional description: Angiolipoma      |                    |  |
| subjects affected / exposed   | 0 / 127 (0.00%)                          | 1 / 127 (0.79%)    |  |
| occurrences (all)   | 0  | 1                  |  |
| Adrenal neoplasm  | Additional description: Adrenal neoplasm |                    |  |

|                                  |  |                 |  |
|----------------------------------|--|-----------------|--|
| subjects affected / exposed      | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                | 1  | 0               |  |
| Angiomyolipoma                   | Additional description: Angiomyolipoma                   |                 |  |
| subjects affected / exposed      | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                | 0  | 1               |  |
| Benign neoplasm of thyroid gland | Additional description: Benign neoplasm of thyroid gland |                 |  |
| subjects affected / exposed      | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                | 1  | 0               |  |
| Bile duct cancer                 | Additional description: Bile duct cancer                 |                 |  |
| subjects affected / exposed      | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                | 1  | 0               |  |
| Blepharal papilloma              | Additional description: Blepharal papilloma              |                 |  |
| subjects affected / exposed      | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                | 1  | 0               |  |
| Colon adenoma                    | Additional description: Colon adenoma                    |                 |  |
| subjects affected / exposed      | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                | 1  | 0               |  |
| Fibrous histiocytoma             | Additional description: Fibrous histiocytoma             |                 |  |
| subjects affected / exposed      | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                | 0  | 2               |  |
| Haemangioma of liver             | Additional description: Haemangioma of liver             |                 |  |
| subjects affected / exposed      | 0 / 127 (0.00%)  | 2 / 127 (1.57%) |  |
| occurrences (all)                | 0  | 2               |  |
| Intestinal adenocarcinoma        | Additional description: Intestinal adenocarcinoma        |                 |  |
| subjects affected / exposed      | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                | 1  | 0               |  |
| Keratoacanthoma                  | Additional description: Keratoacanthoma                  |                 |  |
| subjects affected / exposed      | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                | 0  | 1               |  |
| Lipoma                           | Additional description: Lipoma                           |                 |  |
| subjects affected / exposed      | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                | 0  | 1               |  |
| Myelofibrosis                    | Additional description: Myelofibrosis                    |                 |  |
| subjects affected / exposed      | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                | 0  | 1               |  |
| Primary myelofibrosis            | Additional description: Primary myelofibrosis            |                 |  |

|                             |  |                  |  |
|-----------------------------|--|------------------|--|
| subjects affected / exposed | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%)  |  |
| occurrences (all)           | 1  | 0                |  |
| Prostate cancer             | Additional description: Prostate cancer            |                  |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                    | 1 / 127 (0.79%)  |  |
| occurrences (all)           | 0  | 1                |  |
| Prostatic adenoma           | Additional description: Prostatic adenoma          |                  |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%)  |  |
| occurrences (all)           | 1  | 0                |  |
| Uterine leiomyoma           | Additional description: Uterine leiomyoma          |                  |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                    | 1 / 127 (0.79%)  |  |
| occurrences (all)           | 0  | 1                |  |
| Vascular disorders          |  |                  |  |
| Aneurysm                    | Additional description: Aneurysm                   |                  |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%)  |  |
| occurrences (all)           | 1  | 0                |  |
| Aortic stenosis             | Additional description: Aortic stenosis            |                  |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                    | 2 / 127 (1.57%)  |  |
| occurrences (all)           | 0  | 2                |  |
| Blood pressure fluctuation  | Additional description: Blood pressure fluctuation |                  |  |
| subjects affected / exposed | 2 / 127 (1.57%)                                    | 0 / 127 (0.00%)  |  |
| occurrences (all)           | 2  | 0                |  |
| Circulatory collapse        | Additional description: Circulatory collapse       |                  |  |
| subjects affected / exposed | 2 / 127 (1.57%)                                    | 0 / 127 (0.00%)  |  |
| occurrences (all)           | 3  | 0                |  |
| Erythromelalgia             | Additional description: Erythromelalgia            |                  |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                    | 1 / 127 (0.79%)  |  |
| occurrences (all)           | 2  | 1                |  |
| Femoral artery occlusion    | Additional description: Femoral artery occlusion   |                  |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                    | 1 / 127 (0.79%)  |  |
| occurrences (all)           | 0  | 1                |  |
| Haematoma                   | Additional description: Haematoma                  |                  |  |
| subjects affected / exposed | 2 / 127 (1.57%)                                    | 4 / 127 (3.15%)  |  |
| occurrences (all)           | 2  | 5                |  |
| Hypertension                | Additional description: Hypertension               |                  |  |
| subjects affected / exposed | 7 / 127 (5.51%)                                    | 12 / 127 (9.45%) |  |
| occurrences (all)           | 12   | 14               |  |

|   |   |                      |
|---|---|----------------------|
| Hypertensive crisis<br>subjects affected / exposed<br>occurrences (all)                   | Additional description: Hypertensive crisis                   |                      |
|   | 3 / 127 (2.36%)<br>3  | 1 / 127 (0.79%)<br>1 |
| Hypotension<br>subjects affected / exposed<br>occurrences (all)                           | Additional description: Hypotension                           |                      |
|   | 3 / 127 (2.36%)<br>3  | 1 / 127 (0.79%)<br>1 |
| Peripheral arterial occlusive disease<br>subjects affected / exposed<br>occurrences (all) | Additional description: Peripheral arterial occlusive disease |                      |
|   | 1 / 127 (0.79%)<br>1  | 1 / 127 (0.79%)<br>1 |
| Peripheral artery stenosis<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Peripheral artery stenosis            |                      |
|   | 1 / 127 (0.79%)<br>1  | 0 / 127 (0.00%)<br>0 |
| Peripheral circulatory failure<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Peripheral circulatory failure        |                      |
|   | 0 / 127 (0.00%)<br>0  | 1 / 127 (0.79%)<br>1 |
| Peripheral coldness<br>subjects affected / exposed<br>occurrences (all)                   | Additional description: Peripheral coldness                   |                      |
|   | 1 / 127 (0.79%)<br>1  | 1 / 127 (0.79%)<br>1 |
| Phlebitis<br>subjects affected / exposed<br>occurrences (all)                             | Additional description: Phlebitis                             |                      |
|   | 1 / 127 (0.79%)<br>1  | 0 / 127 (0.00%)<br>0 |
| Raynaud's phenomenon<br>subjects affected / exposed<br>occurrences (all)                  | Additional description: Raynaud's phenomenon                  |                      |
|   | 1 / 127 (0.79%)<br>1  | 1 / 127 (0.79%)<br>1 |
| Subclavian steal syndrome<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Subclavian steal syndrome             |                      |
|   | 0 / 127 (0.00%)<br>0  | 1 / 127 (0.79%)<br>1 |
| Thrombophlebitis<br>subjects affected / exposed<br>occurrences (all)                      | Additional description: Thrombophlebitis                      |                      |
|   | 0 / 127 (0.00%)<br>0  | 1 / 127 (0.79%)<br>1 |
| Varicose vein<br>subjects affected / exposed<br>occurrences (all)                         | Additional description: Varicose vein                         |                      |
|   | 1 / 127 (0.79%)<br>1  | 0 / 127 (0.00%)<br>0 |
| Vascular pain<br>subjects affected / exposed<br>occurrences (all)                         | Additional description: Vascular pain                         |                      |
|   | 1 / 127 (0.79%)<br>1  | 2 / 127 (1.57%)<br>2 |

|   |   |                      |  |
|---|---|----------------------|--|
| Venous thrombosis limb<br>subjects affected / exposed<br>occurrences (all)                            | Additional description: Venous thrombosis limb      |                      |  |
|   | 0 / 127 (0.00%)<br>0                                | 1 / 127 (0.79%)<br>1 |  |
| Surgical and medical procedures<br>Blepharoplasty<br>subjects affected / exposed<br>occurrences (all) | Additional description: Blepharoplasty              |                      |  |
|   | 1 / 127 (0.79%)<br>1                                | 0 / 127 (0.00%)<br>0 |  |
| Carpal tunnel decompression<br>subjects affected / exposed<br>occurrences (all)                       | Additional description: Carpal tunnel decompression |                      |  |
|   | 1 / 127 (0.79%)<br>1                                | 0 / 127 (0.00%)<br>0 |  |
| Cataract operation<br>subjects affected / exposed<br>occurrences (all)                                | Additional description: Cataract operation          |                      |  |
|   | 2 / 127 (1.57%)<br>3                                | 5 / 127 (3.94%)<br>6 |  |
| Endocervical curettage<br>subjects affected / exposed<br>occurrences (all)                            | Additional description: Endocervical curettage      |                      |  |
|   | 1 / 127 (0.79%)<br>1                                | 0 / 127 (0.00%)<br>0 |  |
| Eye operation<br>subjects affected / exposed<br>occurrences (all)                                     | Additional description: Eye operation               |                      |  |
|   | 0 / 127 (0.00%)<br>0                                | 1 / 127 (0.79%)<br>1 |  |
| Intraocular lens implant<br>subjects affected / exposed<br>occurrences (all)                          | Additional description: Intraocular lens implant    |                      |  |
|   | 0 / 127 (0.00%)<br>0                                | 1 / 127 (0.79%)<br>1 |  |
| Maxillofacial operation<br>subjects affected / exposed<br>occurrences (all)                           | Additional description: Maxillofacial operation     |                      |  |
|   | 0 / 127 (0.00%)<br>0                                | 1 / 127 (0.79%)<br>1 |  |
| Ovarian cystectomy<br>subjects affected / exposed<br>occurrences (all)                                | Additional description: Ovarian cystectomy          |                      |  |
|   | 1 / 127 (0.79%)<br>1                                | 0 / 127 (0.00%)<br>0 |  |
| Peripheral endarterectomy<br>subjects affected / exposed<br>occurrences (all)                         | Additional description: Peripheral endarterectomy   |                      |  |
|   | 1 / 127 (0.79%)<br>1                                | 0 / 127 (0.00%)<br>0 |  |
| Polypectomy<br>subjects affected / exposed<br>occurrences (all)                                       | Additional description: Polypectomy                 |                      |  |
|   | 1 / 127 (0.79%)<br>1                                | 0 / 127 (0.00%)<br>0 |  |
| Proctectomy   | Additional description: Proctectomy                 |                      |  |

|  |  |                 |  |
|--|--|-----------------|--|
| subjects affected / exposed                          | 1 / 127 (0.79%)                                | 0 / 127 (0.00%) |  |
| occurrences (all)                                    | 1  | 0               |  |
| Prostatic operation                                  | Additional description: Prostatic operation    |                 |  |
| subjects affected / exposed                          | 1 / 127 (0.79%)                                | 0 / 127 (0.00%) |  |
| occurrences (all)                                    | 1  | 0               |  |
| Skin neoplasm excision                               | Additional description: Skin neoplasm excision |                 |  |
| subjects affected / exposed                          | 0 / 127 (0.00%)                                | 1 / 127 (0.79%) |  |
| occurrences (all)                                    | 0  | 1               |  |
| Tooth extraction                                     | Additional description: Tooth extraction       |                 |  |
| subjects affected / exposed                          | 6 / 127 (4.72%)                                | 2 / 127 (1.57%) |  |
| occurrences (all)                                    | 7  | 2               |  |
| General disorders and administration site conditions |  |                 |  |
| Asthenia   | Additional description: Asthenia               |                 |  |
| subjects affected / exposed                          | 11 / 127 (8.66%)                               | 7 / 127 (5.51%) |  |
| occurrences (all)                                    | 20   | 24              |  |
| Axillary pain  | Additional description: Axillary pain          |                 |  |
| subjects affected / exposed                          | 1 / 127 (0.79%)                                | 0 / 127 (0.00%) |  |
| occurrences (all)                                    | 1  | 0               |  |
| Chest discomfort                                     | Additional description: Chest discomfort       |                 |  |
| subjects affected / exposed                          | 1 / 127 (0.79%)                                | 0 / 127 (0.00%) |  |
| occurrences (all)                                    | 1  | 0               |  |
| Chest pain   | Additional description: Chest pain             |                 |  |
| subjects affected / exposed                          | 5 / 127 (3.94%)                                | 1 / 127 (0.79%) |  |
| occurrences (all)                                    | 5  | 1               |  |
| Chills   | Additional description: Chills                 |                 |  |
| subjects affected / exposed                          | 3 / 127 (2.36%)                                | 2 / 127 (1.57%) |  |
| occurrences (all)                                    | 3  | 2               |  |
| Condition aggravated                                 | Additional description: Condition aggravated   |                 |  |
| subjects affected / exposed                          | 0 / 127 (0.00%)                                | 1 / 127 (0.79%) |  |
| occurrences (all)                                    | 0  | 1               |  |
| Cyst   | Additional description: Cyst                   |                 |  |
| subjects affected / exposed                          | 1 / 127 (0.79%)                                | 0 / 127 (0.00%) |  |
| occurrences (all)                                    | 1  | 0               |  |
| Drug intolerance                                     | Additional description: Drug intolerance       |                 |  |



|                             |  |                   |  |
|-----------------------------|--|-------------------|--|
| subjects affected / exposed | 0 / 127 (0.00%)                                  | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0  | 1                 |  |
| Facial pain                 | Additional description: Facial pain              |                   |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%)   |  |
| occurrences (all)           | 4  | 0                 |  |
| Fatigue                     | Additional description: Fatigue                  |                   |  |
| subjects affected / exposed | 17 / 127 (13.39%)                                | 21 / 127 (16.54%) |  |
| occurrences (all)           | 47   | 27                |  |
| Feeling cold                | Additional description: Feeling cold             |                   |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                  | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0  | 3                 |  |
| Impaired healing            | Additional description: Impaired healing         |                   |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%)   |  |
| occurrences (all)           | 2  | 0                 |  |
| Inflammation                | Additional description: Inflammation             |                   |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                  | 2 / 127 (1.57%)   |  |
| occurrences (all)           | 1  | 2                 |  |
| Influenza like illness      | Additional description: Influenza like illness   |                   |  |
| subjects affected / exposed | 10 / 127 (7.87%)                                 | 3 / 127 (2.36%)   |  |
| occurrences (all)           | 16   | 3                 |  |
| Injection site erythema     | Additional description: Injection site erythema  |                   |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                  | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0  | 1                 |  |
| Injection site haematoma    | Additional description: Injection site haematoma |                   |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%)   |  |
| occurrences (all)           | 2  | 0                 |  |
| Injection site pain         | Additional description: Injection site pain      |                   |  |
| subjects affected / exposed | 3 / 127 (2.36%)                                  | 0 / 127 (0.00%)   |  |
| occurrences (all)           | 4  | 0                 |  |
| Injection site pruritus     | Additional description: Injection site pruritus  |                   |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%)   |  |
| occurrences (all)           | 2  | 0                 |  |
| Injection site reaction     | Additional description: Injection site reaction  |                   |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                  | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0  | 1                 |  |
| Injection site warmth       | Additional description: Injection site warmth    |                   |  |

|                             |  |                 |  |
|-----------------------------|--|-----------------|--|
| subjects affected / exposed | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Mucosal inflammation        | Additional description: Mucosal inflammation       |                 |  |
| subjects affected / exposed | 3 / 127 (2.36%)                                    | 1 / 127 (0.79%) |  |
| occurrences (all)           | 3  | 2               |  |
| Non-cardiac chest pain      | Additional description: Non-cardiac chest pain     |                 |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Oedema peripheral           | Additional description: Oedema peripheral          |                 |  |
| subjects affected / exposed | 5 / 127 (3.94%)                                    | 4 / 127 (3.15%) |  |
| occurrences (all)           | 5  | 4               |  |
| Pain                        | Additional description: Pain                       |                 |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                    | 4 / 127 (3.15%) |  |
| occurrences (all)           | 1  | 5               |  |
| Peripheral swelling         | Additional description: Peripheral swelling        |                 |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                    | 1 / 127 (0.79%) |  |
| occurrences (all)           | 0  | 1               |  |
| Puncture site pain          | Additional description: Puncture site pain         |                 |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                    | 1 / 127 (0.79%) |  |
| occurrences (all)           | 0  | 1               |  |
| Pyrexia                     | Additional description: Pyrexia                    |                 |  |
| subjects affected / exposed | 13 / 127 (10.24%)                                  | 6 / 127 (4.72%) |  |
| occurrences (all)           | 21   | 7               |  |
| Sensation of foreign body   | Additional description: Sensation of foreign body  |                 |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Soft tissue inflammation    | Additional description: Soft tissue inflammation   |                 |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Thirst                      | Additional description: Thirst                     |                 |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                    | 1 / 127 (0.79%) |  |
| occurrences (all)           | 0  | 1               |  |
| Immune system disorders     |  |                 |  |
| Allergy to arthropod sting  | Additional description: Allergy to arthropod sting |                 |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |

|  |  |                 |  |
|--|--|-----------------|--|
| Drug hypersensitivity<br>subjects affected / exposed<br>occurrences (all)                  | Additional description: Drug hypersensitivity        |                 |  |
|  | 0 / 127 (0.00%)                                      | 1 / 127 (0.79%) |  |
|  | 0  | 1               |  |
|  |  |                 |  |
| Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)                       | Additional description: Hypersensitivity             |                 |  |
|  | 0 / 127 (0.00%)                                      | 2 / 127 (1.57%) |  |
|  | 0  | 2               |  |
|  |  |                 |  |
| Sarcoidosis<br>subjects affected / exposed<br>occurrences (all)                            | Additional description: Sarcoidosis                  |                 |  |
|  | 1 / 127 (0.79%)                                      | 0 / 127 (0.00%) |  |
|  | 1  | 0               |  |
|  |  |                 |  |
| Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)                       | Additional description: Seasonal allergy             |                 |  |
|  | 1 / 127 (0.79%)                                      | 1 / 127 (0.79%) |  |
|  | 1  | 1               |  |
|  |  |                 |  |
| Social circumstances<br>Stress at work<br>subjects affected / exposed<br>occurrences (all) | Additional description: Stress at work               |                 |  |
|  | 1 / 127 (0.79%)                                      | 0 / 127 (0.00%) |  |
|  | 1  | 0               |  |
|  |  |                 |  |
| Reproductive system and breast disorders   |  |                 |  |
|  | Additional description: Acquired phimosis            |                 |  |
|  | 0 / 127 (0.00%)                                      | 1 / 127 (0.79%) |  |
|  | 0  | 1               |  |
|  |  |                 |  |
|  | Additional description: Amenorrhoea                  |                 |  |
|  | 0 / 127 (0.00%)                                      | 1 / 127 (0.79%) |  |
|  | 0  | 1               |  |
|  |  |                 |  |
|  | Additional description: Benign prostatic hyperplasia |                 |  |
|  | 5 / 127 (3.94%)                                      | 0 / 127 (0.00%) |  |
|  | 5  | 0               |  |
|  |  |                 |  |
|  | Additional description: Breast disorder              |                 |  |
|  | 0 / 127 (0.00%)                                      | 1 / 127 (0.79%) |  |
|  | 0  | 1               |  |
|  |  |                 |  |
|  | Additional description: Breast pain                  |                 |  |
|  | 1 / 127 (0.79%)                                      | 0 / 127 (0.00%) |  |
|  | 1  | 0               |  |
|  |  |                 |  |
|  | Additional description: Endometrial dysplasia        |                 |  |
|  | 0 / 127 (0.00%)                                      | 1 / 127 (0.79%) |  |
|  | 0  | 1               |  |
|  |  |                 |  |
|  | Additional description: Erectile dysfunction         |                 |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 2 / 127 (1.57%)                                    | 0 / 127 (0.00%) |  |
| occurrences (all)                               | 2  | 0               |  |
| Fibrocystic breast disease                      | Additional description: Fibrocystic breast disease |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                    | 1 / 127 (0.79%) |  |
| occurrences (all)                               | 0  | 1               |  |
| Haematospermia                                  | Additional description: Haematospermia             |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%) |  |
| occurrences (all)                               | 1  | 0               |  |
| Metrorrhagia                                    | Additional description: Metrorrhagia               |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                    | 1 / 127 (0.79%) |  |
| occurrences (all)                               | 0  | 1               |  |
| Menstruation irregular                          | Additional description: Menstruation irregular     |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                    | 1 / 127 (0.79%) |  |
| occurrences (all)                               | 1  | 1               |  |
| Ovarian cyst                                    | Additional description: Ovarian cyst               |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%) |  |
| occurrences (all)                               | 1  | 0               |  |
| Prostatitis                                     | Additional description: Prostatitis                |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%) |  |
| occurrences (all)                               | 1  | 0               |  |
| Uterine cervical erosion                        | Additional description: Uterine cervical erosion   |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                    | 1 / 127 (0.79%) |  |
| occurrences (all)                               | 0  | 1               |  |
| Uterine haemorrhage                             | Additional description: Uterine haemorrhage        |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%) |  |
| occurrences (all)                               | 1  | 0               |  |
| Vaginal haemorrhage                             | Additional description: Vaginal haemorrhage        |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%) |  |
| occurrences (all)                               | 1  | 0               |  |
| Respiratory, thoracic and mediastinal disorders |  |                 |  |
| Asthma  | Additional description: Asthma                     |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%) |  |
| occurrences (all)                               | 1  | 0               |  |
| Cough   | Additional description: Cough                      |                 |  |

|                               |   |                  |  |
|-------------------------------|---|------------------|--|
| subjects affected / exposed   | 11 / 127 (8.66%)                                      | 11 / 127 (8.66%) |  |
| occurrences (all)             | 19  | 12               |  |
| Dysphonia                     | Additional description: Dysphonia                     |                  |  |
| subjects affected / exposed   | 1 / 127 (0.79%)                                       | 0 / 127 (0.00%)  |  |
| occurrences (all)             | 1   | 0                |  |
| Dyspnoea                      | Additional description: Dyspnoea                      |                  |  |
| subjects affected / exposed   | 2 / 127 (1.57%)                                       | 2 / 127 (1.57%)  |  |
| occurrences (all)             | 2   | 2                |  |
| Dyspnoea exertional           | Additional description: Dyspnoea exertional           |                  |  |
| subjects affected / exposed   | 2 / 127 (1.57%)                                       | 0 / 127 (0.00%)  |  |
| occurrences (all)             | 3   | 0                |  |
| Epistaxis                     | Additional description: Epistaxis                     |                  |  |
| subjects affected / exposed   | 2 / 127 (1.57%)                                       | 2 / 127 (1.57%)  |  |
| occurrences (all)             | 3   | 2                |  |
| Increased bronchial secretion | Additional description: Increased bronchial secretion |                  |  |
| subjects affected / exposed   | 0 / 127 (0.00%)                                       | 1 / 127 (0.79%)  |  |
| occurrences (all)             | 0   | 1                |  |
| Lung infiltration             | Additional description: Lung infiltration             |                  |  |
| subjects affected / exposed   | 1 / 127 (0.79%)                                       | 0 / 127 (0.00%)  |  |
| occurrences (all)             | 1   | 0                |  |
| Oropharyngeal pain            | Additional description: Oropharyngeal pain            |                  |  |
| subjects affected / exposed   | 7 / 127 (5.51%)                                       | 3 / 127 (2.36%)  |  |
| occurrences (all)             | 10  | 3                |  |
| Pneumonitis                   | Additional description: Pneumonitis                   |                  |  |
| subjects affected / exposed   | 1 / 127 (0.79%)                                       | 0 / 127 (0.00%)  |  |
| occurrences (all)             | 1   | 0                |  |
| Pulmonary hypertension        | Additional description: Pulmonary hypertension        |                  |  |
| subjects affected / exposed   | 1 / 127 (0.79%)                                       | 2 / 127 (1.57%)  |  |
| occurrences (all)             | 1   | 2                |  |
| Pulmonary microemboli         | Additional description: Pulmonary microemboli         |                  |  |
| subjects affected / exposed   | 0 / 127 (0.00%)                                       | 1 / 127 (0.79%)  |  |
| occurrences (all)             | 0   | 1                |  |
| Rales                         | Additional description: Rales                         |                  |  |
| subjects affected / exposed   | 1 / 127 (0.79%)                                       | 0 / 127 (0.00%)  |  |
| occurrences (all)             | 1   | 0                |  |
| Rhinitis allergic             | Additional description: Rhinitis allergic             |                  |  |

|                             |  |                 |  |
|-----------------------------|--|-----------------|--|
| subjects affected / exposed | 0 / 127 (0.00%)                            | 2 / 127 (1.57%) |  |
| occurrences (all)           | 0  | 2               |  |
| Rhinitis atrophic           | Additional description: Rhinitis atrophic  |                 |  |
| subjects affected / exposed | 1 / 127 (0.79%)                            | 0 / 127 (0.00%) |  |
| occurrences (all)           | 2  | 0               |  |
| Sneezing                    | Additional description: Sneezing           |                 |  |
| subjects affected / exposed | 0 / 127 (0.00%)                            | 1 / 127 (0.79%) |  |
| occurrences (all)           | 0  | 1               |  |
| Throat irritation           | Additional description: Throat irritation  |                 |  |
| subjects affected / exposed | 1 / 127 (0.79%)                            | 0 / 127 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Psychiatric disorders       |  |                 |  |
| Affective disorder          | Additional description: Affective disorder |                 |  |
| subjects affected / exposed | 2 / 127 (1.57%)                            | 1 / 127 (0.79%) |  |
| occurrences (all)           | 3  | 1               |  |
| Agitation                   | Additional description: Agitation          |                 |  |
| subjects affected / exposed | 0 / 127 (0.00%)                            | 1 / 127 (0.79%) |  |
| occurrences (all)           | 0  | 1               |  |
| Anxiety                     | Additional description: Anxiety            |                 |  |
| subjects affected / exposed | 5 / 127 (3.94%)                            | 4 / 127 (3.15%) |  |
| occurrences (all)           | 8  | 4               |  |
| Anxiety disorder            | Additional description: Anxiety disorder   |                 |  |
| subjects affected / exposed | 0 / 127 (0.00%)                            | 1 / 127 (0.79%) |  |
| occurrences (all)           | 0  | 1               |  |
| Apathy                      | Additional description: Apathy             |                 |  |
| subjects affected / exposed | 1 / 127 (0.79%)                            | 0 / 127 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Depressed mood              | Additional description: Depressed mood     |                 |  |
| subjects affected / exposed | 1 / 127 (0.79%)                            | 0 / 127 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Depression                  | Additional description: Depression         |                 |  |
| subjects affected / exposed | 3 / 127 (2.36%)                            | 4 / 127 (3.15%) |  |
| occurrences (all)           | 3  | 4               |  |
| Emotional distress          | Additional description: Emotional distress |                 |  |
| subjects affected / exposed | 1 / 127 (0.79%)                            | 0 / 127 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |

|  |  |                      |
|--|--|----------------------|
| Hallucination<br>subjects affected / exposed<br>occurrences (all)                            | Additional description: Hallucination    |                      |
|  | 0 / 127 (0.00%)<br>0                     | 1 / 127 (0.79%)<br>1 |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                 | Additional description: Insomnia         |                      |
|  | 4 / 127 (3.15%)<br>4                     | 7 / 127 (5.51%)<br>9 |
| Irritability<br>subjects affected / exposed<br>occurrences (all)                             | Additional description: Irritability     |                      |
|  | 1 / 127 (0.79%)<br>1                     | 0 / 127 (0.00%)<br>0 |
| Libido increased<br>subjects affected / exposed<br>occurrences (all)                         | Additional description: Libido increased |                      |
|  | 0 / 127 (0.00%)<br>0                     | 1 / 127 (0.79%)<br>3 |
| Mood altered<br>subjects affected / exposed<br>occurrences (all)                             | Additional description: Mood altered     |                      |
|  | 1 / 127 (0.79%)<br>1                     | 1 / 127 (0.79%)<br>1 |
| Mood swings<br>subjects affected / exposed<br>occurrences (all)                              | Additional description: Mood swings      |                      |
|  | 2 / 127 (1.57%)<br>3                     | 0 / 127 (0.00%)<br>0 |
| Nervousness<br>subjects affected / exposed<br>occurrences (all)                              | Additional description: Nervousness      |                      |
|  | 2 / 127 (1.57%)<br>3                     | 0 / 127 (0.00%)<br>0 |
| Panic attack<br>subjects affected / exposed<br>occurrences (all)                             | Additional description: Panic attack     |                      |
|  | 1 / 127 (0.79%)<br>1                     | 0 / 127 (0.00%)<br>0 |
| Restlessness<br>subjects affected / exposed<br>occurrences (all)                             | Additional description: Restlessness     |                      |
|  | 2 / 127 (1.57%)<br>2                     | 0 / 127 (0.00%)<br>0 |
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)                           | Additional description: Sleep disorder   |                      |
|  | 3 / 127 (2.36%)<br>3                     | 2 / 127 (1.57%)<br>2 |
| Hepatobiliary disorders<br>Biliary colic<br>subjects affected / exposed<br>occurrences (all) | Additional description: Biliary colic    |                      |
|  | 1 / 127 (0.79%)<br>1                     | 0 / 127 (0.00%)<br>0 |
| Cholecystitis  | Additional description: Cholecystitis    |                      |

|                             |   |                 |  |
|-----------------------------|---|-----------------|--|
| subjects affected / exposed | 1 / 127 (0.79%)                                   | 0 / 127 (0.00%) |  |
| occurrences (all)           | 1   | 0               |  |
| Cholecystitis chronic       | Additional description: Cholecystitis chronic     |                 |  |
| subjects affected / exposed | 2 / 127 (1.57%)                                   | 0 / 127 (0.00%) |  |
| occurrences (all)           | 2   | 0               |  |
| Cholelithiasis              | Additional description: Cholelithiasis            |                 |  |
| subjects affected / exposed | 4 / 127 (3.15%)                                   | 3 / 127 (2.36%) |  |
| occurrences (all)           | 4   | 3               |  |
| Gallbladder cholesterosis   | Additional description: Gallbladder cholesterosis |                 |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                   | 0 / 127 (0.00%) |  |
| occurrences (all)           | 1   | 0               |  |
| Gallbladder disorder        | Additional description: Gallbladder disorder      |                 |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                   | 2 / 127 (1.57%) |  |
| occurrences (all)           | 0   | 2               |  |
| Gallbladder polyp           | Additional description: Gallbladder polyp         |                 |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                   | 1 / 127 (0.79%) |  |
| occurrences (all)           | 0   | 1               |  |
| Hepatic cyst                | Additional description: Hepatic cyst              |                 |  |
| subjects affected / exposed | 3 / 127 (2.36%)                                   | 0 / 127 (0.00%) |  |
| occurrences (all)           | 3   | 0               |  |
| Hepatic steatosis           | Additional description: Hepatic steatosis         |                 |  |
| subjects affected / exposed | 4 / 127 (3.15%)                                   | 1 / 127 (0.79%) |  |
| occurrences (all)           | 4   | 1               |  |
| Hepatitis toxic             | Additional description: Hepatitis toxic           |                 |  |
| subjects affected / exposed | 3 / 127 (2.36%)                                   | 0 / 127 (0.00%) |  |
| occurrences (all)           | 4   | 0               |  |
| Hepatomegaly                | Additional description: Hepatomegaly              |                 |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                   | 2 / 127 (1.57%) |  |
| occurrences (all)           | 0   | 2               |  |
| Hepatosplenomegaly          | Additional description: Hepatosplenomegaly        |                 |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                   | 1 / 127 (0.79%) |  |
| occurrences (all)           | 0   | 1               |  |
| Hyperbilirubinaemia         | Additional description: Hyperbilirubinaemia       |                 |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                   | 1 / 127 (0.79%) |  |
| occurrences (all)           | 0   | 2               |  |
| Liver disorder              | Additional description: Liver disorder            |                 |  |



|  |  |                 |  |
|--|--|-----------------|--|
| subjects affected / exposed            | 2 / 127 (1.57%)  | 2 / 127 (1.57%) |  |
| occurrences (all)                      | 3  | 2               |  |
| Pneumobilia                            | Additional description: Pneumobilia                            |                 |  |
| subjects affected / exposed            | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                      | 1  | 0               |  |
| Portal hypertension                    | Additional description: Portal hypertension                    |                 |  |
| subjects affected / exposed            | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                      | 1  | 0               |  |
| Steatohepatitis                        | Additional description: Steatohepatitis                        |                 |  |
| subjects affected / exposed            | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                      | 1  | 0               |  |
| Investigations                         |  |                 |  |
| Alanine aminotransferase increased     | Additional description: Alanine aminotransferase increased     |                 |  |
| subjects affected / exposed            | 19 / 127 (14.96%)  | 2 / 127 (1.57%) |  |
| occurrences (all)                      | 40   | 2               |  |
| Anti-thyroid antibody positive         | Additional description: Anti-thyroid antibody positive         |                 |  |
| subjects affected / exposed            | 3 / 127 (2.36%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                      | 6  | 0               |  |
| Antinuclear antibody increased         | Additional description: Antinuclear antibody increased         |                 |  |
| subjects affected / exposed            | 4 / 127 (3.15%)  | 3 / 127 (2.36%) |  |
| occurrences (all)                      | 4  | 3               |  |
| Aspartate aminotransferase increased   | Additional description: Aspartate aminotransferase increased   |                 |  |
| subjects affected / exposed            | 17 / 127 (13.39%)  | 2 / 127 (1.57%) |  |
| occurrences (all)                      | 27   | 2               |  |
| Blood alkaline phosphatase increased   | Additional description: Blood alkaline phosphatase increased   |                 |  |
| subjects affected / exposed            | 3 / 127 (2.36%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                      | 6  | 1               |  |
| Blood bilirubin increased              | Additional description: Blood bilirubin increased              |                 |  |
| subjects affected / exposed            | 0 / 127 (0.00%)  | 2 / 127 (1.57%) |  |
| occurrences (all)                      | 0  | 2               |  |
| Blood creatine phosphokinase increased | Additional description: Blood creatine phosphokinase increased |                 |  |
| subjects affected / exposed            | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                      | 0  | 1               |  |
| Blood creatinine increased             | Additional description: Blood creatinine increased             |                 |  |

|                                       |   |                 |  |
|---------------------------------------|---|-----------------|--|
| subjects affected / exposed           | 3 / 127 (2.36%)   | 1 / 127 (0.79%) |  |
| occurrences (all)                     | 6   | 1               |  |
| Blood fibrinogen decreased            | Additional description: Blood fibrinogen decreased            |                 |  |
| subjects affected / exposed           | 0 / 127 (0.00%)   | 1 / 127 (0.79%) |  |
| occurrences (all)                     | 0   | 2               |  |
| Blood glucose increased               | Additional description: Blood glucose increased               |                 |  |
| subjects affected / exposed           | 0 / 127 (0.00%)   | 3 / 127 (2.36%) |  |
| occurrences (all)                     | 0   | 3               |  |
| Blood iron decreased                  | Additional description: Blood iron decreased                  |                 |  |
| subjects affected / exposed           | 1 / 127 (0.79%)   | 4 / 127 (3.15%) |  |
| occurrences (all)                     | 1   | 4               |  |
| Blood lactate dehydrogenase increased | Additional description: Blood lactate dehydrogenase increased |                 |  |
| subjects affected / exposed           | 3 / 127 (2.36%)   | 2 / 127 (1.57%) |  |
| occurrences (all)                     | 4   | 2               |  |
| Blood phosphorus decreased            | Additional description: Blood phosphorus decreased            |                 |  |
| subjects affected / exposed           | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences (all)                     | 1   | 0               |  |
| Blood potassium increased             | Additional description: Blood potassium increased             |                 |  |
| subjects affected / exposed           | 1 / 127 (0.79%)   | 2 / 127 (1.57%) |  |
| occurrences (all)                     | 1   | 2               |  |
| Blood potassium decreased             | Additional description: Blood potassium decreased             |                 |  |
| subjects affected / exposed           | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences (all)                     | 1   | 0               |  |
| Blood pressure abnormal               | Additional description: Blood pressure abnormal               |                 |  |
| subjects affected / exposed           | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences (all)                     | 1   | 0               |  |
| Blood pressure diastolic increased    | Additional description: Blood pressure diastolic increased    |                 |  |
| subjects affected / exposed           | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences (all)                     | 2   | 0               |  |
| Blood pressure systolic increased     | Additional description: Blood pressure systolic increased     |                 |  |
| subjects affected / exposed           | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences (all)                     | 1   | 0               |  |
| Blood pressure increased              | Additional description: Blood pressure increased              |                 |  |
| subjects affected / exposed           | 1 / 127 (0.79%)   | 1 / 127 (0.79%) |  |
| occurrences (all)                     | 1   | 2               |  |

|  |  |                 |
|--|--|-----------------|
| Blood thyroid stimulating hormone increased                    | Additional description: Blood thyroid stimulating hormone increased                    |                 |
| subjects affected / exposed                                    | 5 / 127 (3.94%)  | 1 / 127 (0.79%) |
| occurrences (all)  | 6  | 4               |
| Blood triglycerides increased                                  | Additional description: Blood triglycerides increased                                  |                 |
| subjects affected / exposed                                    | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |
| occurrences (all)  | 0  | 1               |
| Blood urea increased   | Additional description: Blood urea increased   |                 |
| subjects affected / exposed                                    | 2 / 127 (1.57%)  | 1 / 127 (0.79%) |
| occurrences (all)  | 7  | 1               |
| Blood uric acid increased                                      | Additional description: Blood uric acid increased                                      |                 |
| subjects affected / exposed                                    | 4 / 127 (3.15%)  | 2 / 127 (1.57%) |
| occurrences (all)  | 4  | 2               |
| Body temperature decreased                                     | Additional description: Body temperature decreased                                     |                 |
| subjects affected / exposed                                    | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |
| occurrences (all)  | 1  | 0               |
| Body temperature increased                                     | Additional description: Body temperature increased                                     |                 |
| subjects affected / exposed                                    | 3 / 127 (2.36%)  | 1 / 127 (0.79%) |
| occurrences (all)  | 3  | 1               |
| Colonoscopy  | Additional description: Colonoscopy  |                 |
| subjects affected / exposed                                    | 2 / 127 (1.57%)  | 0 / 127 (0.00%) |
| occurrences (all)  | 2  | 0               |
| Computerised tomogram  | Additional description: Computerised tomogram  |                 |
| subjects affected / exposed                                    | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |
| occurrences (all)  | 0  | 1               |
| Eastern Cooperative Oncology Group performance status worsened | Additional description: Eastern Cooperative Oncology Group performance status worsened |                 |
| subjects affected / exposed                                    | 1 / 127 (0.79%)  | 1 / 127 (0.79%) |
| occurrences (all)  | 1  | 1               |
| Electrocardiogram PR prolongation                              | Additional description: Electrocardiogram PR prolongation                              |                 |
| subjects affected / exposed                                    | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |
| occurrences (all)  | 1  | 0               |
| Ejection fraction decreased                                    | Additional description: Ejection fraction decreased                                    |                 |
| subjects affected / exposed                                    | 4 / 127 (3.15%)  | 1 / 127 (0.79%) |
| occurrences (all)  | 4  | 1               |
| Electrocardiogram QT interval abnormal                         | Additional description: Electrocardiogram QT interval abnormal                         |                 |

|  |  |                 |  |
|--|--|-----------------|--|
| subjects affected / exposed            | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                      | 1  | 0               |  |
| Electrocardiogram QT prolonged         | Additional description: Electrocardiogram QT prolonged         |                 |  |
| subjects affected / exposed            | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                      | 0  | 1               |  |
| Endoscopy upper gastrointestinal tract | Additional description: Endoscopy upper gastrointestinal tract |                 |  |
| subjects affected / exposed            | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                      | 1  | 0               |  |
| Gamma-glutamyltransferase increased    | Additional description: Gamma-glutamyltransferase increased    |                 |  |
| subjects affected / exposed            | 28 / 127 (22.05%)  | 5 / 127 (3.94%) |  |
| occurrences (all)                      | 91   | 5               |  |
| Haematocrit decreased                  | Additional description: Haematocrit decreased                  |                 |  |
| subjects affected / exposed            | 1 / 127 (0.79%)  | 4 / 127 (3.15%) |  |
| occurrences (all)                      | 1  | 5               |  |
| Haematocrit increased                  | Additional description: Haematocrit increased                  |                 |  |
| subjects affected / exposed            | 6 / 127 (4.72%)  | 5 / 127 (3.94%) |  |
| occurrences (all)                      | 11   | 7               |  |
| Haemoglobin decreased                  | Additional description: Haemoglobin decreased                  |                 |  |
| subjects affected / exposed            | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                      | 0  | 1               |  |
| Hepatic enzyme increased               | Additional description: Hepatic enzyme increased               |                 |  |
| subjects affected / exposed            | 8 / 127 (6.30%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                      | 16   | 2               |  |
| Lipase increased                       | Additional description: Lipase increased                       |                 |  |
| subjects affected / exposed            | 2 / 127 (1.57%)  | 2 / 127 (1.57%) |  |
| occurrences (all)                      | 7  | 2               |  |
| Lymphocyte count decreased             | Additional description: Lymphocyte count decreased             |                 |  |
| subjects affected / exposed            | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                      | 0  | 1               |  |
| Magnetic resonance imaging             | Additional description: Magnetic resonance imaging             |                 |  |
| subjects affected / exposed            | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                      | 1  | 0               |  |
| Mean cell volume increased             | Additional description: Mean cell volume increased             |                 |  |

|                                  |  |                  |  |
|----------------------------------|--|------------------|--|
| subjects affected / exposed      | 0 / 127 (0.00%)  | 2 / 127 (1.57%)  |  |
| occurrences (all)                | 0  | 2                |  |
| Neutrophil count increased       | Additional description: Neutrophil count increased       |                  |  |
| subjects affected / exposed      | 0 / 127 (0.00%)  | 1 / 127 (0.79%)  |  |
| occurrences (all)                | 0  | 1                |  |
| Nitrite urine present            | Additional description: Nitrite urine present            |                  |  |
| subjects affected / exposed      | 0 / 127 (0.00%)  | 1 / 127 (0.79%)  |  |
| occurrences (all)                | 0  | 1                |  |
| Platelet count decreased         | Additional description: Platelet count decreased         |                  |  |
| subjects affected / exposed      | 3 / 127 (2.36%)  | 12 / 127 (9.45%) |  |
| occurrences (all)                | 5  | 21               |  |
| Platelet count increased         | Additional description: Platelet count increased         |                  |  |
| subjects affected / exposed      | 3 / 127 (2.36%)  | 2 / 127 (1.57%)  |  |
| occurrences (all)                | 3  | 2                |  |
| Scan with contrast               | Additional description: Scan with contrast               |                  |  |
| subjects affected / exposed      | 0 / 127 (0.00%)  | 1 / 127 (0.79%)  |  |
| occurrences (all)                | 0  | 1                |  |
| Serum ferritin decreased         | Additional description: Serum ferritin decreased         |                  |  |
| subjects affected / exposed      | 1 / 127 (0.79%)  | 1 / 127 (0.79%)  |  |
| occurrences (all)                | 1  | 1                |  |
| Transaminases increased          | Additional description: Transaminases increased          |                  |  |
| subjects affected / exposed      | 1 / 127 (0.79%)  | 0 / 127 (0.00%)  |  |
| occurrences (all)                | 1  | 0                |  |
| Transferrin decreased            | Additional description: Transferrin decreased            |                  |  |
| subjects affected / exposed      | 2 / 127 (1.57%)  | 2 / 127 (1.57%)  |  |
| occurrences (all)                | 3  | 3                |  |
| Visual acuity tests abnormal     | Additional description: Visual acuity tests abnormal     |                  |  |
| subjects affected / exposed      | 0 / 127 (0.00%)  | 1 / 127 (0.79%)  |  |
| occurrences (all)                | 0  | 1                |  |
| Urine analysis abnormal          | Additional description: Urine analysis abnormal          |                  |  |
| subjects affected / exposed      | 1 / 127 (0.79%)  | 0 / 127 (0.00%)  |  |
| occurrences (all)                | 1  | 0                |  |
| Weight decreased                 | Additional description: Weight decreased                 |                  |  |
| subjects affected / exposed      | 3 / 127 (2.36%)  | 1 / 127 (0.79%)  |  |
| occurrences (all)                | 4  | 1                |  |
| White blood cell count decreased | Additional description: White blood cell count decreased |                  |  |

|  |  |                 |  |
|--|--|-----------------|--|
| subjects affected / exposed                    | 5 / 127 (3.94%)  | 5 / 127 (3.94%) |  |
| occurrences (all)                              | 12   | 9               |  |
| White blood cell count increased               | Additional description: White blood cell count increased |                 |  |
| subjects affected / exposed                    | 0 / 127 (0.00%)  | 2 / 127 (1.57%) |  |
| occurrences (all)                              | 0  | 2               |  |
| White blood cells urine positive               | Additional description: White blood cells urine positive |                 |  |
| subjects affected / exposed                    | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                              | 0  | 1               |  |
| Injury, poisoning and procedural complications |  |                 |  |
| Accidental overdose                            | Additional description: Accidental overdose              |                 |  |
| subjects affected / exposed                    | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                              | 1  | 0               |  |
| Animal bite                                    | Additional description: Animal bite                      |                 |  |
| subjects affected / exposed                    | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                              | 1  | 0               |  |
| Anaemia postoperative                          | Additional description: Anaemia postoperative            |                 |  |
| subjects affected / exposed                    | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                              | 1  | 0               |  |
| Ankle fracture                                 | Additional description: Ankle fracture                   |                 |  |
| subjects affected / exposed                    | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                              | 1  | 0               |  |
| Arthropod bite                                 | Additional description: Arthropod bite                   |                 |  |
| subjects affected / exposed                    | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                              | 1  | 0               |  |
| Contrast media reaction                        | Additional description: Contrast media reaction          |                 |  |
| subjects affected / exposed                    | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                              | 0  | 1               |  |
| Contusion                                      | Additional description: Contusion                        |                 |  |
| subjects affected / exposed                    | 1 / 127 (0.79%)  | 3 / 127 (2.36%) |  |
| occurrences (all)                              | 1  | 5               |  |
| Fall   | Additional description: Fall                             |                 |  |
| subjects affected / exposed                    | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                              | 1  | 0               |  |
| Foot fracture                                  | Additional description: Foot fracture                    |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                                     | 2 / 127 (1.57%) | 0 / 127 (0.00%) |  |
| occurrences (all)   | 2               | 0               |  |
| Additional description: Gastrointestinal disorder postoperative |                 |                 |  |
| Gastrointestinal disorder postoperative                         |                 |                 |  |
| subjects affected / exposed                                     | 0 / 127 (0.00%) | 1 / 127 (0.79%) |  |
| occurrences (all)   | 0               | 1               |  |
| Additional description: Forearm fracture                        |                 |                 |  |
| Forearm fracture  |                 |                 |  |
| subjects affected / exposed                                     | 1 / 127 (0.79%) | 0 / 127 (0.00%) |  |
| occurrences (all)   | 1               | 0               |  |
| Additional description: Incisional hernia                       |                 |                 |  |
| Incisional hernia   |                 |                 |  |
| subjects affected / exposed                                     | 1 / 127 (0.79%) | 0 / 127 (0.00%) |  |
| occurrences (all)   | 1               | 0               |  |
| Additional description: Joint dislocation                       |                 |                 |  |
| Joint dislocation   |                 |                 |  |
| subjects affected / exposed                                     | 1 / 127 (0.79%) | 0 / 127 (0.00%) |  |
| occurrences (all)   | 1               | 0               |  |
| Additional description: Joint injury                            |                 |                 |  |
| Joint injury  |                 |                 |  |
| subjects affected / exposed                                     | 1 / 127 (0.79%) | 0 / 127 (0.00%) |  |
| occurrences (all)   | 1               | 0               |  |
| Additional description: Ligament sprain                         |                 |                 |  |
| Ligament sprain   |                 |                 |  |
| subjects affected / exposed                                     | 2 / 127 (1.57%) | 0 / 127 (0.00%) |  |
| occurrences (all)   | 2               | 0               |  |
| Additional description: Muscle strain                           |                 |                 |  |
| Muscle strain   |                 |                 |  |
| subjects affected / exposed                                     | 1 / 127 (0.79%) | 0 / 127 (0.00%) |  |
| occurrences (all)   | 1               | 0               |  |
| Additional description: Limb injury                             |                 |                 |  |
| Limb injury   |                 |                 |  |
| subjects affected / exposed                                     | 2 / 127 (1.57%) | 2 / 127 (1.57%) |  |
| occurrences (all)   | 2               | 2               |  |
| Additional description: Overdose                                |                 |                 |  |
| Overdose  |                 |                 |  |
| subjects affected / exposed                                     | 1 / 127 (0.79%) | 0 / 127 (0.00%) |  |
| occurrences (all)   | 1               | 0               |  |
| Additional description: Postoperative wound complication        |                 |                 |  |
| Postoperative wound complication                                |                 |                 |  |
| subjects affected / exposed                                     | 1 / 127 (0.79%) | 0 / 127 (0.00%) |  |
| occurrences (all)   | 1               | 0               |  |
| Additional description: Retinal injury                          |                 |                 |  |
| Retinal injury  |                 |                 |  |
| subjects affected / exposed                                     | 1 / 127 (0.79%) | 0 / 127 (0.00%) |  |
| occurrences (all)   | 1               | 0               |  |

|  |  |                 |  |
|--|--|-----------------|--|
| Road traffic accident<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Road traffic accident      |                 |  |
|  | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%) |  |
|  | 1  | 0               |  |
|  | Additional description: Thermal burn               |                 |  |
|  | 1 / 127 (0.79%)                                    | 1 / 127 (0.79%) |  |
|  | 1  | 1               |  |
| Subcutaneous haematoma<br>subjects affected / exposed<br>occurrences (all) | Additional description: Subcutaneous haematoma     |                 |  |
|  | 0 / 127 (0.00%)                                    | 1 / 127 (0.79%) |  |
|  | 0  | 1               |  |
| Tibia fracture<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Tibia fracture             |                 |  |
|  | 0 / 127 (0.00%)                                    | 1 / 127 (0.79%) |  |
|  | 0  | 1               |  |
| Traumatic haematoma<br>subjects affected / exposed<br>occurrences (all)    | Additional description: Traumatic haematoma        |                 |  |
|  | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%) |  |
|  | 1  | 0               |  |
| Wound<br>subjects affected / exposed<br>occurrences (all)                  | Additional description: Wound                      |                 |  |
|  | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%) |  |
|  | 1  | 0               |  |
| Congenital, familial and genetic disorders                                 |  |                 |  |
|  | Additional description: Cataract congenital        |                 |  |
|  | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%) |  |
|  | 1  | 0               |  |
|  | Additional description: Marfan's syndrome          |                 |  |
|  | 1 / 127 (0.79%)                                    | 0 / 127 (0.00%) |  |
| Cardiac disorders  |  |                 |  |
|  | Additional description: Angina pectoris            |                 |  |
|  | 2 / 127 (1.57%)                                    | 0 / 127 (0.00%) |  |
|  | 4  | 0               |  |
|  | Additional description: Aortic valve calcification |                 |  |
|  | 0 / 127 (0.00%)                                    | 3 / 127 (2.36%) |  |
|  | 0  | 3               |  |
| Arrhythmia<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Arrhythmia                 |                 |  |
|  | 0 / 127 (0.00%)                                    | 1 / 127 (0.79%) |  |
|  | 0  | 1               |  |
| Atrial fibrillation  | Additional description: Atrial fibrillation        |                 |  |



|                                      |  |                 |  |
|--------------------------------------|--|-----------------|--|
| subjects affected / exposed          | 4 / 127 (3.15%)  | 4 / 127 (3.15%) |  |
| occurrences (all)                    | 4  | 14              |  |
| Atrial flutter                       | Additional description: Atrial flutter                       |                 |  |
| subjects affected / exposed          | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                    | 1  | 0               |  |
| Atrioventricular block second degree | Additional description: Atrioventricular block second degree |                 |  |
| subjects affected / exposed          | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                    | 1  | 0               |  |
| Bradycardia                          | Additional description: Bradycardia                          |                 |  |
| subjects affected / exposed          | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                    | 0  | 1               |  |
| Bundle branch block left             | Additional description: Bundle branch block left             |                 |  |
| subjects affected / exposed          | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                    | 1  | 0               |  |
| Cardiac failure                      | Additional description: Cardiac failure                      |                 |  |
| subjects affected / exposed          | 2 / 127 (1.57%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                    | 3  | 1               |  |
| Cardiac failure chronic              | Additional description: Cardiac failure chronic              |                 |  |
| subjects affected / exposed          | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                    | 3  | 0               |  |
| Cyanosis                             | Additional description: Cyanosis                             |                 |  |
| subjects affected / exposed          | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                    | 1  | 0               |  |
| Dilatation ventricular               | Additional description: Dilatation ventricular               |                 |  |
| subjects affected / exposed          | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                    | 0  | 1               |  |
| Extrasystoles                        | Additional description: Extrasystoles                        |                 |  |
| subjects affected / exposed          | 1 / 127 (0.79%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                    | 1  | 1               |  |
| Heart valve incompetence             | Additional description: Heart valve incompetence             |                 |  |
| subjects affected / exposed          | 1 / 127 (0.79%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                    | 1  | 1               |  |
| Hepatojugular reflux                 | Additional description: Hepatojugular reflux                 |                 |  |
| subjects affected / exposed          | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                    | 1  | 0               |  |
| Intracardiac thrombus                | Additional description: Intracardiac thrombus                |                 |  |

|                                |  |                 |  |
|--------------------------------|--|-----------------|--|
| subjects affected / exposed    | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)              | 1  | 0               |  |
| Mitral valve calcification     | Additional description: Mitral valve calcification     |                 |  |
| subjects affected / exposed    | 0 / 127 (0.00%)  | 2 / 127 (1.57%) |  |
| occurrences (all)              | 0  | 2               |  |
| Mitral valve incompetence      | Additional description: Mitral valve incompetence      |                 |  |
| subjects affected / exposed    | 1 / 127 (0.79%)  | 2 / 127 (1.57%) |  |
| occurrences (all)              | 1  | 2               |  |
| Pericardial cyst               | Additional description: Pericardial cyst               |                 |  |
| subjects affected / exposed    | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)              | 0  | 1               |  |
| Palpitations                   | Additional description: Palpitations                   |                 |  |
| subjects affected / exposed    | 3 / 127 (2.36%)  | 1 / 127 (0.79%) |  |
| occurrences (all)              | 4  | 1               |  |
| Right atrial enlargement       | Additional description: Right atrial enlargement       |                 |  |
| subjects affected / exposed    | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)              | 0  | 1               |  |
| Sinoatrial block               | Additional description: Sinoatrial block               |                 |  |
| subjects affected / exposed    | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)              | 0  | 1               |  |
| Sinus tachycardia              | Additional description: Sinus tachycardia              |                 |  |
| subjects affected / exposed    | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)              | 1  | 0               |  |
| Supraventricular extrasystoles | Additional description: Supraventricular extrasystoles |                 |  |
| subjects affected / exposed    | 1 / 127 (0.79%)  | 1 / 127 (0.79%) |  |
| occurrences (all)              | 1  | 3               |  |
| Tachycardia                    | Additional description: Tachycardia                    |                 |  |
| subjects affected / exposed    | 4 / 127 (3.15%)  | 2 / 127 (1.57%) |  |
| occurrences (all)              | 4  | 3               |  |
| Tricuspid valve incompetence   | Additional description: Tricuspid valve incompetence   |                 |  |
| subjects affected / exposed    | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)              | 0  | 1               |  |
| Ventricular extrasystoles      | Additional description: Ventricular extrasystoles      |                 |  |
| subjects affected / exposed    | 1 / 127 (0.79%)  | 2 / 127 (1.57%) |  |
| occurrences (all)              | 1  | 5               |  |
| Ventricular tachycardia        | Additional description: Ventricular tachycardia        |                 |  |

|  |   |                         |  |
|--|---|-------------------------|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 127 (0.79%)<br>1                            | 1 / 127 (0.79%)<br>1    |  |
| Nervous system disorders                         |   |                         |  |
| Burning sensation                                | Additional description: Burning sensation       |                         |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                            | 1 / 127 (0.79%)<br>2    |  |
| Carotid artery stenosis                          | Additional description: Carotid artery stenosis |                         |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 127 (0.79%)<br>1                            | 0 / 127 (0.00%)<br>0    |  |
| Diabetic neuropathy                              | Additional description: Diabetic neuropathy     |                         |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                            | 1 / 127 (0.79%)<br>1    |  |
| Carpal tunnel syndrome                           | Additional description: Carpal tunnel syndrome  |                         |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 127 (0.79%)<br>1                            | 0 / 127 (0.00%)<br>0    |  |
| Dizziness  | Additional description: Dizziness               |                         |  |
| subjects affected / exposed<br>occurrences (all) | 14 / 127 (11.02%)<br>25                         | 11 / 127 (8.66%)<br>16  |  |
| Dysgeusia  | Additional description: Dysgeusia               |                         |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                            | 2 / 127 (1.57%)<br>2    |  |
| Encephalopathy                                   | Additional description: Encephalopathy          |                         |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                            | 1 / 127 (0.79%)<br>1    |  |
| Head discomfort                                  | Additional description: Head discomfort         |                         |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 127 (0.79%)<br>1                            | 0 / 127 (0.00%)<br>0    |  |
| Headache   | Additional description: Headache                |                         |  |
| subjects affected / exposed<br>occurrences (all) | 16 / 127 (12.60%)<br>34                         | 18 / 127 (14.17%)<br>28 |  |
| Hypoaesthesia                                    | Additional description: Hypoaesthesia           |                         |  |
| subjects affected / exposed<br>occurrences (all) | 4 / 127 (3.15%)<br>6                            | 0 / 127 (0.00%)<br>0    |  |
| Intercostal neuralgia                            | Additional description: Intercostal neuralgia   |                         |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 127 (0.79%)<br>1                            | 0 / 127 (0.00%)<br>0    |  |

|   |   |                      |
|---|---|----------------------|
| Loss of consciousness<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Loss of consciousness   |                      |
|   | 2 / 127 (1.57%)<br>2                            | 0 / 127 (0.00%)<br>0 |
| Lumbar radiculopathy<br>subjects affected / exposed<br>occurrences (all)    | Additional description: Lumbar radiculopathy    |                      |
|   | 0 / 127 (0.00%)<br>0                            | 1 / 127 (0.79%)<br>2 |
| Memory impairment<br>subjects affected / exposed<br>occurrences (all)       | Additional description: Memory impairment       |                      |
|   | 0 / 127 (0.00%)<br>0                            | 1 / 127 (0.79%)<br>1 |
| Migraine<br>subjects affected / exposed<br>occurrences (all)                | Additional description: Migraine                |                      |
|   | 4 / 127 (3.15%)<br>4                            | 0 / 127 (0.00%)<br>0 |
| Migraine with aura<br>subjects affected / exposed<br>occurrences (all)      | Additional description: Migraine with aura      |                      |
|   | 0 / 127 (0.00%)<br>0                            | 1 / 127 (0.79%)<br>1 |
| Neuralgia<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Neuralgia               |                      |
|   | 0 / 127 (0.00%)<br>0                            | 1 / 127 (0.79%)<br>1 |
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Neuropathy peripheral   |                      |
|   | 2 / 127 (1.57%)<br>2                            | 0 / 127 (0.00%)<br>0 |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Paraesthesia            |                      |
|   | 0 / 127 (0.00%)<br>0                            | 5 / 127 (3.94%)<br>6 |
| Parosmia<br>subjects affected / exposed<br>occurrences (all)                | Additional description: Parosmia                |                      |
|   | 1 / 127 (0.79%)<br>1                            | 0 / 127 (0.00%)<br>0 |
| Post herpetic neuralgia<br>subjects affected / exposed<br>occurrences (all) | Additional description: Post herpetic neuralgia |                      |
|   | 1 / 127 (0.79%)<br>1                            | 0 / 127 (0.00%)<br>0 |
| Peripheral nerve lesion<br>subjects affected / exposed<br>occurrences (all) | Additional description: Peripheral nerve lesion |                      |
|   | 1 / 127 (0.79%)<br>1                            | 0 / 127 (0.00%)<br>0 |
| Radiculopathy<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Radiculopathy           |                      |
|   | 1 / 127 (0.79%)<br>1                            | 0 / 127 (0.00%)<br>0 |

|                                      |   |                   |
|--------------------------------------|---|-------------------|
| Sciatica                             | Additional description: Sciatica                |                   |
|                                      | 2 / 127 (1.57%)                                 | 0 / 127 (0.00%)   |
| subjects affected / exposed          | 2   | 0                 |
| occurrences (all)                    |   |                   |
| Sinus headache                       | Additional description: Sinus headache          |                   |
|                                      | 0 / 127 (0.00%)                                 | 1 / 127 (0.79%)   |
| subjects affected / exposed          | 0   | 1                 |
| occurrences (all)                    |   |                   |
| Somnolence                           | Additional description: Somnolence              |                   |
|                                      | 2 / 127 (1.57%)                                 | 1 / 127 (0.79%)   |
| subjects affected / exposed          | 2   | 1                 |
| occurrences (all)                    |   |                   |
| Tension headache                     | Additional description: Tension headache        |                   |
|                                      | 0 / 127 (0.00%)                                 | 1 / 127 (0.79%)   |
| subjects affected / exposed          | 0   | 1                 |
| occurrences (all)                    |   |                   |
| Tremor                               | Additional description: Tremor                  |                   |
|                                      | 0 / 127 (0.00%)                                 | 1 / 127 (0.79%)   |
| subjects affected / exposed          | 0   | 1                 |
| occurrences (all)                    |   |                   |
| Trigeminal neuritis                  | Additional description: Trigeminal neuritis     |                   |
|                                      | 0 / 127 (0.00%)                                 | 1 / 127 (0.79%)   |
| subjects affected / exposed          | 0   | 1                 |
| occurrences (all)                    |   |                   |
| Blood and lymphatic system disorders |   |                   |
| Anaemia                              | Additional description: Anaemia                 |                   |
|                                      | 21 / 127 (16.54%)                               | 37 / 127 (29.13%) |
| subjects affected / exposed          | 41  | 67                |
| occurrences (all)                    |   |                   |
| Blood loss anaemia                   | Additional description: Blood loss anaemia      |                   |
|                                      | 1 / 127 (0.79%)                                 | 0 / 127 (0.00%)   |
| subjects affected / exposed          | 1   | 0                 |
| occurrences (all)                    |   |                   |
| Cytopenia                            | Additional description: Cytopenia               |                   |
|                                      | 1 / 127 (0.79%)                                 | 0 / 127 (0.00%)   |
| subjects affected / exposed          | 1   | 0                 |
| occurrences (all)                    |   |                   |
| Granulocytopenia                     | Additional description: Granulocytopenia        |                   |
|                                      | 1 / 127 (0.79%)                                 | 1 / 127 (0.79%)   |
| subjects affected / exposed          | 1   | 1                 |
| occurrences (all)                    |   |                   |
| Iron deficiency anaemia              | Additional description: Iron deficiency anaemia |                   |
|                                      | 4 / 127 (3.15%)                                 | 0 / 127 (0.00%)   |
| subjects affected / exposed          | 9   | 0                 |
| occurrences (all)                    |   |                   |
| Leukocytosis                         | Additional description: Leukocytosis            |                   |
|                                      |   |                   |

|                             |  |                   |  |
|-----------------------------|--|-------------------|--|
| subjects affected / exposed | 0 / 127 (0.00%)                            | 4 / 127 (3.15%)   |  |
| occurrences (all)           | 0  | 5                 |  |
| Leukopenia                  | Additional description: Leukopenia         |                   |  |
| subjects affected / exposed | 27 / 127 (21.26%)                          | 31 / 127 (24.41%) |  |
| occurrences (all)           | 148  | 82                |  |
| Lymphadenitis               | Additional description: Lymphadenitis      |                   |  |
| subjects affected / exposed | 0 / 127 (0.00%)                            | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0  | 1                 |  |
| Lymphadenopathy             | Additional description: Lymphadenopathy    |                   |  |
| subjects affected / exposed | 0 / 127 (0.00%)                            | 3 / 127 (2.36%)   |  |
| occurrences (all)           | 0  | 3                 |  |
| Microcytic anaemia          | Additional description: Microcytic anaemia |                   |  |
| subjects affected / exposed | 1 / 127 (0.79%)                            | 0 / 127 (0.00%)   |  |
| occurrences (all)           | 2  | 0                 |  |
| Neutropenia                 | Additional description: Neutropenia        |                   |  |
| subjects affected / exposed | 6 / 127 (4.72%)                            | 7 / 127 (5.51%)   |  |
| occurrences (all)           | 7  | 14                |  |
| Pancytopenia                | Additional description: Pancytopenia       |                   |  |
| subjects affected / exposed | 2 / 127 (1.57%)                            | 0 / 127 (0.00%)   |  |
| occurrences (all)           | 4  | 0                 |  |
| Polycythaemia               | Additional description: Polycythaemia      |                   |  |
| subjects affected / exposed | 1 / 127 (0.79%)                            | 0 / 127 (0.00%)   |  |
| occurrences (all)           | 1  | 0                 |  |
| Splenic cyst                | Additional description: Splenic cyst       |                   |  |
| subjects affected / exposed | 1 / 127 (0.79%)                            | 0 / 127 (0.00%)   |  |
| occurrences (all)           | 1  | 0                 |  |
| Splenic infarction          | Additional description: Splenic infarction |                   |  |
| subjects affected / exposed | 1 / 127 (0.79%)                            | 0 / 127 (0.00%)   |  |
| occurrences (all)           | 1  | 0                 |  |
| Splenomegaly                | Additional description: Splenomegaly       |                   |  |
| subjects affected / exposed | 13 / 127 (10.24%)                          | 8 / 127 (6.30%)   |  |
| occurrences (all)           | 13   | 8                 |  |
| Thrombocytopenia            | Additional description: Thrombocytopenia   |                   |  |
| subjects affected / exposed | 28 / 127 (22.05%)                          | 37 / 127 (29.13%) |  |
| occurrences (all)           | 81   | 101               |  |
| Thrombocytosis              | Additional description: Thrombocytosis     |                   |  |

|  |  |                      |  |
|--|--|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 127 (0.79%)<br>2                                     | 3 / 127 (2.36%)<br>4 |  |
| Ear and labyrinth disorders                      |  |                      |  |
| Cerumen impaction                                | Additional description: Cerumen impaction                |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                                     | 1 / 127 (0.79%)<br>1 |  |
| Deafness neurosensory                            | Additional description: Deafness neurosensory            |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                                     | 1 / 127 (0.79%)<br>2 |  |
| Ear discomfort                                   | Additional description: Ear discomfort                   |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 127 (0.79%)<br>1                                     | 0 / 127 (0.00%)<br>0 |  |
| Tinnitus   | Additional description: Tinnitus                         |                      |  |
| subjects affected / exposed<br>occurrences (all) | 3 / 127 (2.36%)<br>8                                     | 1 / 127 (0.79%)<br>1 |  |
| Vertigo  | Additional description: Vertigo                          |                      |  |
| subjects affected / exposed<br>occurrences (all) | 5 / 127 (3.94%)<br>5                                     | 8 / 127 (6.30%)<br>9 |  |
| Vestibular disorder                              | Additional description: Vestibular disorder              |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                                     | 1 / 127 (0.79%)<br>1 |  |
| Eye disorders                                    |  |                      |  |
| Age-related macular degeneration                 | Additional description: Age-related macular degeneration |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                                     | 1 / 127 (0.79%)<br>1 |  |
| Asthenopia                                       | Additional description: Asthenopia                       |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 127 (0.79%)<br>1                                     | 1 / 127 (0.79%)<br>1 |  |
| Blepharitis                                      | Additional description: Blepharitis                      |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 127 (0.79%)<br>1                                     | 1 / 127 (0.79%)<br>1 |  |
| Blepharochalasis                                 | Additional description: Blepharochalasis                 |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                                     | 1 / 127 (0.79%)<br>1 |  |
| Cataract   | Additional description: Cataract                         |                      |  |

|                             |  |                 |  |
|-----------------------------|--|-----------------|--|
| subjects affected / exposed | 7 / 127 (5.51%)                                  | 3 / 127 (2.36%) |  |
| occurrences (all)           | 8  | 4               |  |
| Chalazion                   | Additional description: Chalazion                |                 |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                  | 2 / 127 (1.57%) |  |
| occurrences (all)           | 0  | 2               |  |
| Conjunctival haemorrhage    | Additional description: Conjunctival haemorrhage |                 |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                  | 1 / 127 (0.79%) |  |
| occurrences (all)           | 0  | 1               |  |
| Corneal opacity             | Additional description: Corneal opacity          |                 |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                  | 1 / 127 (0.79%) |  |
| occurrences (all)           | 0  | 1               |  |
| Diabetic retinopathy        | Additional description: Diabetic retinopathy     |                 |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Dry eye                     | Additional description: Dry eye                  |                 |  |
| subjects affected / exposed | 7 / 127 (5.51%)                                  | 3 / 127 (2.36%) |  |
| occurrences (all)           | 7  | 3               |  |
| Ectropion                   | Additional description: Ectropion                |                 |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Eye haemorrhage             | Additional description: Eye haemorrhage          |                 |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Eye inflammation            | Additional description: Eye inflammation         |                 |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Eye irritation              | Additional description: Eye irritation           |                 |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                  | 1 / 127 (0.79%) |  |
| occurrences (all)           | 0  | 1               |  |
| Eye pain                    | Additional description: Eye pain                 |                 |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Eye pruritus                | Additional description: Eye pruritus             |                 |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%) |  |
| occurrences (all)           | 1  | 0               |  |
| Eyelid ptosis               | Additional description: Eyelid ptosis            |                 |  |



|                                 |   |                 |  |
|---------------------------------|---|-----------------|--|
| subjects affected / exposed     | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences (all)               | 1   | 0               |  |
| Eyelid skin dryness             | Additional description: Eyelid skin dryness             |                 |  |
| subjects affected / exposed     | 0 / 127 (0.00%)   | 1 / 127 (0.79%) |  |
| occurrences (all)               | 0   | 1               |  |
| Iridocyclitis                   | Additional description: Iridocyclitis                   |                 |  |
| subjects affected / exposed     | 0 / 127 (0.00%)   | 1 / 127 (0.79%) |  |
| occurrences (all)               | 0   | 1               |  |
| Keratopathy                     | Additional description: Keratopathy                     |                 |  |
| subjects affected / exposed     | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences (all)               | 1   | 0               |  |
| Maculopathy                     | Additional description: Maculopathy                     |                 |  |
| subjects affected / exposed     | 1 / 127 (0.79%)   | 1 / 127 (0.79%) |  |
| occurrences (all)               | 1   | 1               |  |
| Myopia                          | Additional description: Myopia                          |                 |  |
| subjects affected / exposed     | 1 / 127 (0.79%)   | 1 / 127 (0.79%) |  |
| occurrences (all)               | 1   | 1               |  |
| Posterior capsule opacification | Additional description: Posterior capsule opacification |                 |  |
| subjects affected / exposed     | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences (all)               | 1   | 0               |  |
| Presbyopia                      | Additional description: Presbyopia                      |                 |  |
| subjects affected / exposed     | 2 / 127 (1.57%)   | 0 / 127 (0.00%) |  |
| occurrences (all)               | 2   | 0               |  |
| Retinopathy                     | Additional description: Retinopathy                     |                 |  |
| subjects affected / exposed     | 2 / 127 (1.57%)   | 1 / 127 (0.79%) |  |
| occurrences (all)               | 2   | 1               |  |
| Retinopathy hypertensive        | Additional description: Retinopathy hypertensive        |                 |  |
| subjects affected / exposed     | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences (all)               | 1   | 0               |  |
| Vision blurred                  | Additional description: Vision blurred                  |                 |  |
| subjects affected / exposed     | 2 / 127 (1.57%)   | 0 / 127 (0.00%) |  |
| occurrences (all)               | 2   | 0               |  |
| Visual acuity reduced           | Additional description: Visual acuity reduced           |                 |  |
| subjects affected / exposed     | 3 / 127 (2.36%)   | 0 / 127 (0.00%) |  |
| occurrences (all)               | 3   | 0               |  |
| Vitreous haemorrhage            | Additional description: Vitreous haemorrhage            |                 |  |

|  |   |                       |  |
|--|---|-----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                                | 1 / 127 (0.79%)<br>1  |  |
| Gastrointestinal disorders                       |   |                       |  |
| Abdominal discomfort                             | Additional description: Abdominal discomfort        |                       |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                                | 2 / 127 (1.57%)<br>2  |  |
| Abdominal distension                             | Additional description: Abdominal distension        |                       |  |
| subjects affected / exposed<br>occurrences (all) | 2 / 127 (1.57%)<br>2                                | 1 / 127 (0.79%)<br>2  |  |
| Abdominal pain                                   | Additional description: Abdominal pain              |                       |  |
| subjects affected / exposed<br>occurrences (all) | 8 / 127 (6.30%)<br>10                               | 7 / 127 (5.51%)<br>14 |  |
| Abdominal pain upper                             | Additional description: Abdominal pain upper        |                       |  |
| subjects affected / exposed<br>occurrences (all) | 5 / 127 (3.94%)<br>6                                | 7 / 127 (5.51%)<br>12 |  |
| Abdominal wall disorder                          | Additional description: Abdominal wall disorder     |                       |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 127 (0.79%)<br>1                                | 0 / 127 (0.00%)<br>0  |  |
| Aphthous ulcer                                   | Additional description: Aphthous ulcer              |                       |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                                | 1 / 127 (0.79%)<br>1  |  |
| Bowel movement irregularity                      | Additional description: Bowel movement irregularity |                       |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                                | 1 / 127 (0.79%)<br>1  |  |
| Burning mouth syndrome                           | Additional description: Burning mouth syndrome      |                       |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                                | 1 / 127 (0.79%)<br>1  |  |
| Chronic gastritis                                | Additional description: Chronic gastritis           |                       |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                                | 2 / 127 (1.57%)<br>3  |  |
| Colitis  | Additional description: Colitis                     |                       |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                                | 1 / 127 (0.79%)<br>2  |  |
| Constipation                                     | Additional description: Constipation                |                       |  |
| subjects affected / exposed<br>occurrences (all) | 4 / 127 (3.15%)<br>6                                | 6 / 127 (4.72%)<br>6  |  |

|   |   |                         |
|---|---|-------------------------|
| Dental caries<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Dental caries           |                         |
|   | 1 / 127 (0.79%)<br>1                            | 0 / 127 (0.00%)<br>0    |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Diarrhoea               |                         |
|   | 11 / 127 (8.66%)<br>28                          | 15 / 127 (11.81%)<br>29 |
| Diverticulum intestinal<br>subjects affected / exposed<br>occurrences (all) | Additional description: Diverticulum intestinal |                         |
|   | 1 / 127 (0.79%)<br>1                            | 0 / 127 (0.00%)<br>0    |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Dry mouth               |                         |
|   | 2 / 127 (1.57%)<br>2                            | 1 / 127 (0.79%)<br>1    |
| Duodenogastric reflux<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Duodenogastric reflux   |                         |
|   | 0 / 127 (0.00%)<br>0                            | 1 / 127 (0.79%)<br>1    |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Dyspepsia               |                         |
|   | 6 / 127 (4.72%)<br>6                            | 2 / 127 (1.57%)<br>6    |
| Dysphagia<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Dysphagia               |                         |
|   | 0 / 127 (0.00%)<br>0                            | 1 / 127 (0.79%)<br>1    |
| Epigastric discomfort<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Epigastric discomfort   |                         |
|   | 1 / 127 (0.79%)<br>1                            | 0 / 127 (0.00%)<br>0    |
| Flatulence<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Flatulence              |                         |
|   | 0 / 127 (0.00%)<br>0                            | 1 / 127 (0.79%)<br>1    |
| Gastric disorder<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Gastric disorder        |                         |
|   | 2 / 127 (1.57%)<br>2                            | 1 / 127 (0.79%)<br>2    |
| Gastritis<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Gastritis               |                         |
|   | 4 / 127 (3.15%)<br>4                            | 1 / 127 (0.79%)<br>3    |
| Gastritis erosive<br>subjects affected / exposed<br>occurrences (all)       | Additional description: Gastritis erosive       |                         |
|   | 1 / 127 (0.79%)<br>1                            | 0 / 127 (0.00%)<br>0    |

|  |   |                      |
|--|---|----------------------|
| Gastrointestinal angiodysplasia<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Gastrointestinal angiodysplasia           |                      |
|  | 1 / 127 (0.79%)<br>1  | 0 / 127 (0.00%)<br>0 |
| Gastrointestinal disorder<br>subjects affected / exposed<br>occurrences (all)                    | Additional description: Gastrointestinal disorder                 |                      |
|  | 1 / 127 (0.79%)<br>1  | 0 / 127 (0.00%)<br>0 |
| Gastrointestinal motility disorder<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Gastrointestinal motility disorder        |                      |
|  | 2 / 127 (1.57%)<br>3  | 0 / 127 (0.00%)<br>0 |
| Gastrointestinal pain<br>subjects affected / exposed<br>occurrences (all)                        | Additional description: Gastrointestinal pain                     |                      |
|  | 0 / 127 (0.00%)<br>0  | 1 / 127 (0.79%)<br>1 |
| Gastrointestinal scarring<br>subjects affected / exposed<br>occurrences (all)                    | Additional description: Gastrointestinal scarring                 |                      |
|  | 1 / 127 (0.79%)<br>1  | 0 / 127 (0.00%)<br>0 |
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all)             | Additional description: Gastrooesophageal reflux disease          |                      |
|  | 5 / 127 (3.94%)<br>5  | 1 / 127 (0.79%)<br>1 |
| Gastrooesophageal sphincter<br>insufficiency<br>subjects affected / exposed<br>occurrences (all) | Additional description: Gastrooesophageal sphincter insufficiency |                      |
|  | 0 / 127 (0.00%)<br>0  | 1 / 127 (0.79%)<br>1 |
| Gingival bleeding<br>subjects affected / exposed<br>occurrences (all)                            | Additional description: Gingival bleeding                         |                      |
|  | 1 / 127 (0.79%)<br>1  | 2 / 127 (1.57%)<br>2 |
| Gingival hypertrophy<br>subjects affected / exposed<br>occurrences (all)                         | Additional description: Gingival hypertrophy                      |                      |
|  | 1 / 127 (0.79%)<br>1  | 0 / 127 (0.00%)<br>0 |
| Gingival pain<br>subjects affected / exposed<br>occurrences (all)                                | Additional description: Gingival pain                             |                      |
|  | 0 / 127 (0.00%)<br>0  | 1 / 127 (0.79%)<br>1 |
| Gingival recession<br>subjects affected / exposed<br>occurrences (all)                           | Additional description: Gingival recession                        |                      |
|  | 1 / 127 (0.79%)<br>1  | 0 / 127 (0.00%)<br>0 |
| Gingivitis ulcerative  | Additional description: Gingivitis ulcerative                     |                      |

|                             |   |                   |  |
|-----------------------------|---|-------------------|--|
| subjects affected / exposed | 0 / 127 (0.00%)                                   | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0   | 1                 |  |
| Haematemesis                | Additional description: Haematemesis              |                   |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                   | 0 / 127 (0.00%)   |  |
| occurrences (all)           | 1   | 0                 |  |
| Haematochezia               | Additional description: Haematochezia             |                   |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                   | 0 / 127 (0.00%)   |  |
| occurrences (all)           | 2   | 0                 |  |
| Haemorrhoidal haemorrhage   | Additional description: Haemorrhoidal haemorrhage |                   |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                   | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 1   | 1                 |  |
| Haemorrhoids                | Additional description: Haemorrhoids              |                   |  |
| subjects affected / exposed | 3 / 127 (2.36%)                                   | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 4   | 1                 |  |
| Inguinal hernia             | Additional description: Inguinal hernia           |                   |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                   | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0   | 1                 |  |
| Intra-abdominal haematoma   | Additional description: Intra-abdominal haematoma |                   |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                   | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0   | 1                 |  |
| Irritable bowel syndrome    | Additional description: Irritable bowel syndrome  |                   |  |
| subjects affected / exposed | 1 / 127 (0.79%)                                   | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 1   | 1                 |  |
| Mouth swelling              | Additional description: Mouth swelling            |                   |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                   | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0   | 1                 |  |
| Nausea                      | Additional description: Nausea                    |                   |  |
| subjects affected / exposed | 4 / 127 (3.15%)                                   | 17 / 127 (13.39%) |  |
| occurrences (all)           | 6   | 21                |  |
| Oesophagitis                | Additional description: Oesophagitis              |                   |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                   | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0   | 1                 |  |
| Pancreatitis                | Additional description: Pancreatitis              |                   |  |
| subjects affected / exposed | 0 / 127 (0.00%)                                   | 1 / 127 (0.79%)   |  |
| occurrences (all)           | 0   | 1                 |  |
| Pancreatitis chronic        | Additional description: Pancreatitis chronic      |                   |  |

|  |  |                 |  |
|--|--|-----------------|--|
| subjects affected / exposed            | 3 / 127 (2.36%)                                      | 1 / 127 (0.79%) |  |
| occurrences (all)                      | 3  | 1               |  |
| Paraesthesia oral                      | Additional description: Paraesthesia oral            |                 |  |
| subjects affected / exposed            | 1 / 127 (0.79%)                                      | 1 / 127 (0.79%) |  |
| occurrences (all)                      | 1  | 1               |  |
| Rectal fissure                         | Additional description: Rectal fissure               |                 |  |
| subjects affected / exposed            | 1 / 127 (0.79%)                                      | 0 / 127 (0.00%) |  |
| occurrences (all)                      | 1  | 0               |  |
| Rectal haemorrhage                     | Additional description: Rectal haemorrhage           |                 |  |
| subjects affected / exposed            | 1 / 127 (0.79%)                                      | 2 / 127 (1.57%) |  |
| occurrences (all)                      | 1  | 2               |  |
| Rectal polyp                           | Additional description: Rectal polyp                 |                 |  |
| subjects affected / exposed            | 0 / 127 (0.00%)                                      | 1 / 127 (0.79%) |  |
| occurrences (all)                      | 0  | 1               |  |
| Reflux gastritis                       | Additional description: Reflux gastritis             |                 |  |
| subjects affected / exposed            | 1 / 127 (0.79%)                                      | 0 / 127 (0.00%) |  |
| occurrences (all)                      | 1  | 0               |  |
| Stomatitis                             | Additional description: Stomatitis                   |                 |  |
| subjects affected / exposed            | 2 / 127 (1.57%)                                      | 2 / 127 (1.57%) |  |
| occurrences (all)                      | 2  | 5               |  |
| Toothache                              | Additional description: Toothache                    |                 |  |
| subjects affected / exposed            | 1 / 127 (0.79%)                                      | 0 / 127 (0.00%) |  |
| occurrences (all)                      | 1  | 0               |  |
| Truncus coeliacus thrombosis           | Additional description: Truncus coeliacus thrombosis |                 |  |
| subjects affected / exposed            | 1 / 127 (0.79%)                                      | 0 / 127 (0.00%) |  |
| occurrences (all)                      | 1  | 0               |  |
| Vomiting                               | Additional description: Vomiting                     |                 |  |
| subjects affected / exposed            | 3 / 127 (2.36%)                                      | 6 / 127 (4.72%) |  |
| occurrences (all)                      | 3  | 7               |  |
| Skin and subcutaneous tissue disorders |  |                 |  |
| Acanthosis nigricans                   | Additional description: Acanthosis nigricans         |                 |  |
| subjects affected / exposed            | 0 / 127 (0.00%)                                      | 1 / 127 (0.79%) |  |
| occurrences (all)                      | 0  | 1               |  |
| Actinic keratosis                      | Additional description: Actinic keratosis            |                 |  |
| subjects affected / exposed            | 0 / 127 (0.00%)                                      | 2 / 127 (1.57%) |  |
| occurrences (all)                      | 0  | 2               |  |

|  |  |                 |
|--|--|-----------------|
| Alopecia<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Alopecia                 |                 |
|  | 6 / 127 (4.72%)                                  | 0 / 127 (0.00%) |
|  | 9  | 0               |
| Blood blister<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Blood blister            |                 |
|  | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%) |
|  | 1  | 0               |
| Dermal cyst<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Dermal cyst              |                 |
|  | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%) |
|  | 1  | 0               |
| Dermatitis<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Dermatitis               |                 |
|  | 0 / 127 (0.00%)                                  | 2 / 127 (1.57%) |
|  | 0  | 2               |
| Dermatitis acneiform<br>subjects affected / exposed<br>occurrences (all)     | Additional description: Dermatitis acneiform     |                 |
|  | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%) |
|  | 1  | 0               |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Dry skin                 |                 |
|  | 2 / 127 (1.57%)                                  | 5 / 127 (3.94%) |
|  | 2  | 5               |
| Eczema<br>subjects affected / exposed<br>occurrences (all)                   | Additional description: Eczema                   |                 |
|  | 1 / 127 (0.79%)                                  | 1 / 127 (0.79%) |
|  | 6  | 1               |
| Erythema<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Erythema                 |                 |
|  | 6 / 127 (4.72%)                                  | 1 / 127 (0.79%) |
|  | 7  | 1               |
| Erythrosis<br>subjects affected / exposed<br>occurrences (all)               | Additional description: Erythrosis               |                 |
|  | 1 / 127 (0.79%)                                  | 1 / 127 (0.79%) |
|  | 1  | 1               |
| Haemorrhage subcutaneous<br>subjects affected / exposed<br>occurrences (all) | Additional description: Haemorrhage subcutaneous |                 |
|  | 1 / 127 (0.79%)                                  | 0 / 127 (0.00%) |
|  | 1  | 0               |
| Henoch-Schonlein purpura<br>subjects affected / exposed<br>occurrences (all) | Additional description: Henoch-Schonlein purpura |                 |
|  | 0 / 127 (0.00%)                                  | 1 / 127 (0.79%) |
|  | 0  | 1               |
| Hyperhidrosis<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Hyperhidrosis            |                 |
|  | 4 / 127 (3.15%)                                  | 1 / 127 (0.79%) |
|  | 4  | 1               |

|                             |   |                 |
|-----------------------------|---|-----------------|
| Hyperkeratosis              | Additional description: Hyperkeratosis            |                 |
| subjects affected / exposed | 1 / 127 (0.79%)                                   | 0 / 127 (0.00%) |
| occurrences (all)           | 1   | 0               |
| Night sweats                | Additional description: Night sweats              |                 |
| subjects affected / exposed | 2 / 127 (1.57%)                                   | 4 / 127 (3.15%) |
| occurrences (all)           | 2   | 4               |
| Photosensitivity reaction   | Additional description: Photosensitivity reaction |                 |
| subjects affected / exposed | 1 / 127 (0.79%)                                   | 0 / 127 (0.00%) |
| occurrences (all)           | 1   | 0               |
| Pruritus                    | Additional description: Pruritus                  |                 |
| subjects affected / exposed | 10 / 127 (7.87%)                                  | 9 / 127 (7.09%) |
| occurrences (all)           | 75  | 11              |
| Pruritus generalised        | Additional description: Pruritus generalised      |                 |
| subjects affected / exposed | 1 / 127 (0.79%)                                   | 0 / 127 (0.00%) |
| occurrences (all)           | 2   | 0               |
| Psoriasis                   | Additional description: Psoriasis                 |                 |
| subjects affected / exposed | 2 / 127 (1.57%)                                   | 1 / 127 (0.79%) |
| occurrences (all)           | 2   | 1               |
| Rash                        | Additional description: Rash                      |                 |
| subjects affected / exposed | 3 / 127 (2.36%)                                   | 5 / 127 (3.94%) |
| occurrences (all)           | 3   | 7               |
| Rash erythematous           | Additional description: Rash erythematous         |                 |
| subjects affected / exposed | 1 / 127 (0.79%)                                   | 1 / 127 (0.79%) |
| occurrences (all)           | 1   | 1               |
| Rash papular                | Additional description: Rash papular              |                 |
| subjects affected / exposed | 1 / 127 (0.79%)                                   | 0 / 127 (0.00%) |
| occurrences (all)           | 1   | 0               |
| Rosacea                     | Additional description: Rosacea                   |                 |
| subjects affected / exposed | 0 / 127 (0.00%)                                   | 2 / 127 (1.57%) |
| occurrences (all)           | 0   | 2               |
| Skin disorder               | Additional description: Skin disorder             |                 |
| subjects affected / exposed | 1 / 127 (0.79%)                                   | 0 / 127 (0.00%) |
| occurrences (all)           | 1   | 0               |
| Skin exfoliation            | Additional description: Skin exfoliation          |                 |
| subjects affected / exposed | 1 / 127 (0.79%)                                   | 0 / 127 (0.00%) |
| occurrences (all)           | 1   | 0               |



|  |  |                 |  |
|--|--|-----------------|--|
| Skin fissures<br>subjects affected / exposed<br>occurrences (all)<br><br>Skin hyperpigmentation<br>subjects affected / exposed<br>occurrences (all)<br><br>Skin swelling<br>subjects affected / exposed<br>occurrences (all)<br><br>Skin ulcer<br>subjects affected / exposed<br>occurrences (all)<br><br>Urticaria<br>subjects affected / exposed<br>occurrences (all)<br><br>Xeroderma<br>subjects affected / exposed<br>occurrences (all) | Additional description: Skin fissures          |                 |  |
|  | 1 / 127 (0.79%)                                | 0 / 127 (0.00%) |  |
|  | 1  | 0               |  |
|  | Additional description: Skin hyperpigmentation |                 |  |
|  | 0 / 127 (0.00%)                                | 1 / 127 (0.79%) |  |
|  | 0  | 1               |  |
|  | Additional description: Skin swelling          |                 |  |
|  | 1 / 127 (0.79%)                                | 0 / 127 (0.00%) |  |
|  | 1  | 0               |  |
|  | Additional description: Skin ulcer             |                 |  |
|  | 0 / 127 (0.00%)                                | 7 / 127 (5.51%) |  |
|  | 0  | 9               |  |
|  | Additional description: Urticaria              |                 |  |
|  | 1 / 127 (0.79%)                                | 0 / 127 (0.00%) |  |
|  | 1  | 0               |  |
|  | Additional description: Xeroderma              |                 |  |
|  | 2 / 127 (1.57%)                                | 0 / 127 (0.00%) |  |
|  | 4  | 0               |  |
| Renal and urinary disorders<br>Calculus urinary<br>subjects affected / exposed<br>occurrences (all)<br><br>Chronic kidney disease<br>subjects affected / exposed<br>occurrences (all)<br><br>Diabetic nephropathy<br>subjects affected / exposed<br>occurrences (all)<br><br>Dysuria<br>subjects affected / exposed<br>occurrences (all)<br><br>Haematuria<br>subjects affected / exposed<br>occurrences (all)<br><br>Leukocyturia           |  |                 |  |
|  | Additional description: Calculus urinary       |                 |  |
|  | 3 / 127 (2.36%)                                | 1 / 127 (0.79%) |  |
|  | 7  | 1               |  |
|  | Additional description: Chronic kidney disease |                 |  |
|  | 1 / 127 (0.79%)                                | 1 / 127 (0.79%) |  |
|  | 1  | 1               |  |
|  | Additional description: Diabetic nephropathy   |                 |  |
|  | 1 / 127 (0.79%)                                | 0 / 127 (0.00%) |  |
|  | 2  | 0               |  |
|  | Additional description: Dysuria                |                 |  |
|  | 2 / 127 (1.57%)                                | 3 / 127 (2.36%) |  |
|  | 2  | 3               |  |
|  | Additional description: Haematuria             |                 |  |
|  | 1 / 127 (0.79%)                                | 3 / 127 (2.36%) |  |
|  | 2  | 3               |  |
|  | Additional description: Leukocyturia           |                 |  |

|                              |  |                 |  |
|------------------------------|--|-----------------|--|
| subjects affected / exposed  | 2 / 127 (1.57%)                                      | 3 / 127 (2.36%) |  |
| occurrences (all)            | 2  | 3               |  |
| Micturition urgency          | Additional description: Micturition urgency          |                 |  |
| subjects affected / exposed  | 2 / 127 (1.57%)                                      | 0 / 127 (0.00%) |  |
| occurrences (all)            | 2  | 0               |  |
| Nephrolithiasis              | Additional description: Nephrolithiasis              |                 |  |
| subjects affected / exposed  | 1 / 127 (0.79%)                                      | 2 / 127 (1.57%) |  |
| occurrences (all)            | 1  | 2               |  |
| Nephropathy                  | Additional description: Nephropathy                  |                 |  |
| subjects affected / exposed  | 0 / 127 (0.00%)                                      | 1 / 127 (0.79%) |  |
| occurrences (all)            | 0  | 1               |  |
| Nephropathy toxic            | Additional description: Nephropathy toxic            |                 |  |
| subjects affected / exposed  | 1 / 127 (0.79%)                                      | 0 / 127 (0.00%) |  |
| occurrences (all)            | 1  | 0               |  |
| Nephroptosis                 | Additional description: Nephroptosis                 |                 |  |
| subjects affected / exposed  | 0 / 127 (0.00%)                                      | 1 / 127 (0.79%) |  |
| occurrences (all)            | 0  | 2               |  |
| Nocturia                     | Additional description: Nocturia                     |                 |  |
| subjects affected / exposed  | 1 / 127 (0.79%)                                      | 0 / 127 (0.00%) |  |
| occurrences (all)            | 1  | 0               |  |
| Proteinuria                  | Additional description: Proteinuria                  |                 |  |
| subjects affected / exposed  | 1 / 127 (0.79%)                                      | 1 / 127 (0.79%) |  |
| occurrences (all)            | 1  | 3               |  |
| Pyelocaliectasis             | Additional description: Pyelocaliectasis             |                 |  |
| subjects affected / exposed  | 1 / 127 (0.79%)                                      | 1 / 127 (0.79%) |  |
| occurrences (all)            | 1  | 1               |  |
| Renal cyst                   | Additional description: Renal cyst                   |                 |  |
| subjects affected / exposed  | 2 / 127 (1.57%)                                      | 7 / 127 (5.51%) |  |
| occurrences (all)            | 2  | 7               |  |
| Renal colic                  | Additional description: Renal colic                  |                 |  |
| subjects affected / exposed  | 1 / 127 (0.79%)                                      | 2 / 127 (1.57%) |  |
| occurrences (all)            | 1  | 2               |  |
| Tubulointerstitial nephritis | Additional description: Tubulointerstitial nephritis |                 |  |
| subjects affected / exposed  | 0 / 127 (0.00%)                                      | 1 / 127 (0.79%) |  |
| occurrences (all)            | 0  | 1               |  |
| Urinary incontinence         | Additional description: Urinary incontinence         |                 |  |

|   |  |                 |  |
|---|--|-----------------|--|
| subjects affected / exposed                     | 1 / 127 (0.79%)                                | 0 / 127 (0.00%) |  |
| occurrences (all)                               | 1  | 0               |  |
| Urinary retention                               | Additional description: Urinary retention      |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                | 0 / 127 (0.00%) |  |
| occurrences (all)                               | 1  | 0               |  |
| Urinary tract disorder                          | Additional description: Urinary tract disorder |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                | 1 / 127 (0.79%) |  |
| occurrences (all)                               | 0  | 1               |  |
| Endocrine disorders                             |  |                 |  |
| Autoimmune thyroiditis                          | Additional description: Autoimmune thyroiditis |                 |  |
| subjects affected / exposed                     | 4 / 127 (3.15%)                                | 1 / 127 (0.79%) |  |
| occurrences (all)                               | 4  | 1               |  |
| Goitre  | Additional description: Goitre                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                | 1 / 127 (0.79%) |  |
| occurrences (all)                               | 1  | 1               |  |
| Hyperthyroidism                                 | Additional description: Hyperthyroidism        |                 |  |
| subjects affected / exposed                     | 4 / 127 (3.15%)                                | 0 / 127 (0.00%) |  |
| occurrences (all)                               | 4  | 0               |  |
| Hypothyroidism                                  | Additional description: Hypothyroidism         |                 |  |
| subjects affected / exposed                     | 7 / 127 (5.51%)                                | 2 / 127 (1.57%) |  |
| occurrences (all)                               | 7  | 2               |  |
| Thyroiditis                                     | Additional description: Thyroiditis            |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                | 0 / 127 (0.00%) |  |
| occurrences (all)                               | 1  | 0               |  |
| Musculoskeletal and connective tissue disorders |  |                 |  |
| Arthralgia                                      | Additional description: Arthralgia             |                 |  |
| subjects affected / exposed                     | 18 / 127 (14.17%)                              | 6 / 127 (4.72%) |  |
| occurrences (all)                               | 39   | 10              |  |
| Arthritis                                       | Additional description: Arthritis              |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%)                                | 2 / 127 (1.57%) |  |
| occurrences (all)                               | 0  | 2               |  |
| Arthritis reactive                              | Additional description: Arthritis reactive     |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%)                                | 0 / 127 (0.00%) |  |
| occurrences (all)                               | 2  | 0               |  |
| Back pain                                       | Additional description: Back pain              |                 |  |

|  |  |                 |  |
|--|--|-----------------|--|
| subjects affected / exposed              | 13 / 127 (10.24%)  | 7 / 127 (5.51%) |  |
| occurrences (all)                        | 18   | 10              |  |
| Bone pain                                | Additional description: Bone pain                                |                 |  |
| subjects affected / exposed              | 3 / 127 (2.36%)  | 3 / 127 (2.36%) |  |
| occurrences (all)                        | 3  | 3               |  |
| Bursitis                                 | Additional description: Bursitis                                 |                 |  |
| subjects affected / exposed              | 0 / 127 (0.00%)  | 2 / 127 (1.57%) |  |
| occurrences (all)                        | 0  | 2               |  |
| Diffuse idiopathic skeletal hyperostosis | Additional description: Diffuse idiopathic skeletal hyperostosis |                 |  |
| subjects affected / exposed              | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                        | 1  | 0               |  |
| Gouty arthritis                          | Additional description: Gouty arthritis                          |                 |  |
| subjects affected / exposed              | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                        | 1  | 0               |  |
| Groin pain                               | Additional description: Groin pain                               |                 |  |
| subjects affected / exposed              | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                        | 1  | 0               |  |
| Haemarthrosis                            | Additional description: Haemarthrosis                            |                 |  |
| subjects affected / exposed              | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                        | 0  | 1               |  |
| Intervertebral disc protrusion           | Additional description: Intervertebral disc protrusion           |                 |  |
| subjects affected / exposed              | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                        | 1  | 0               |  |
| Joint swelling                           | Additional description: Joint swelling                           |                 |  |
| subjects affected / exposed              | 1 / 127 (0.79%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                        | 1  | 3               |  |
| Muscle spasms                            | Additional description: Muscle spasms                            |                 |  |
| subjects affected / exposed              | 4 / 127 (3.15%)  | 3 / 127 (2.36%) |  |
| occurrences (all)                        | 4  | 3               |  |
| Muscular weakness                        | Additional description: Muscular weakness                        |                 |  |
| subjects affected / exposed              | 4 / 127 (3.15%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                        | 5  | 0               |  |
| Musculoskeletal chest pain               | Additional description: Musculoskeletal chest pain               |                 |  |
| subjects affected / exposed              | 3 / 127 (2.36%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                        | 8  | 1               |  |

|   |   |                       |
|---|---|-----------------------|
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)      | Additional description: Musculoskeletal pain      |                       |
|   | 5 / 127 (3.94%)<br>14                             | 0 / 127 (0.00%)<br>0  |
| Musculoskeletal stiffness<br>subjects affected / exposed<br>occurrences (all) | Additional description: Musculoskeletal stiffness |                       |
|   | 1 / 127 (0.79%)<br>1                              | 0 / 127 (0.00%)<br>0  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                   | Additional description: Myalgia                   |                       |
|   | 12 / 127 (9.45%)<br>20                            | 6 / 127 (4.72%)<br>11 |
| Neck pain<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Neck pain                 |                       |
|   | 2 / 127 (1.57%)<br>2                              | 1 / 127 (0.79%)<br>1  |
| Osteoarthritis<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Osteoarthritis            |                       |
|   | 7 / 127 (5.51%)<br>8                              | 2 / 127 (1.57%)<br>3  |
| Osteochondrosis<br>subjects affected / exposed<br>occurrences (all)           | Additional description: Osteochondrosis           |                       |
|   | 1 / 127 (0.79%)<br>1                              | 1 / 127 (0.79%)<br>1  |
| Osteopenia<br>subjects affected / exposed<br>occurrences (all)                | Additional description: Osteopenia                |                       |
|   | 1 / 127 (0.79%)<br>1                              | 0 / 127 (0.00%)<br>0  |
| Osteoporosis<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Osteoporosis              |                       |
|   | 1 / 127 (0.79%)<br>1                              | 0 / 127 (0.00%)<br>0  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Pain in extremity         |                       |
|   | 10 / 127 (7.87%)<br>16                            | 6 / 127 (4.72%)<br>6  |
| Rotator cuff syndrome<br>subjects affected / exposed<br>occurrences (all)     | Additional description: Rotator cuff syndrome     |                       |
|   | 2 / 127 (1.57%)<br>2                              | 0 / 127 (0.00%)<br>0  |
| Scoliosis<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Scoliosis                 |                       |
|   | 1 / 127 (0.79%)<br>1                              | 0 / 127 (0.00%)<br>0  |
| Sjogren's syndrome<br>subjects affected / exposed<br>occurrences (all)        | Additional description: Sjogren's syndrome        |                       |
|   | 1 / 127 (0.79%)<br>1                              | 1 / 127 (0.79%)<br>1  |

|  |  |                        |
|--|--|------------------------|
| Spinal osteoarthritis<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Spinal osteoarthritis            |                        |
|  | 1 / 127 (0.79%)<br>2                                     | 1 / 127 (0.79%)<br>1   |
| Spinal retrolisthesis<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Spinal retrolisthesis            |                        |
|  | 1 / 127 (0.79%)<br>1                                     | 0 / 127 (0.00%)<br>0   |
| Spinal pain<br>subjects affected / exposed<br>occurrences (all)                      | Additional description: Spinal pain                      |                        |
|  | 4 / 127 (3.15%)<br>4                                     | 5 / 127 (3.94%)<br>5   |
| Spondylolisthesis<br>subjects affected / exposed<br>occurrences (all)                | Additional description: Spondylolisthesis                |                        |
|  | 1 / 127 (0.79%)<br>1                                     | 0 / 127 (0.00%)<br>0   |
| Temporomandibular joint syndrome<br>subjects affected / exposed<br>occurrences (all) | Additional description: Temporomandibular joint syndrome |                        |
|  | 1 / 127 (0.79%)<br>1                                     | 0 / 127 (0.00%)<br>0   |
| Tendonitis<br>subjects affected / exposed<br>occurrences (all)                       | Additional description: Tendonitis                       |                        |
|  | 2 / 127 (1.57%)<br>2                                     | 1 / 127 (0.79%)<br>1   |
| Infections and infestations  |  |                        |
|  | Additional description: Alveolar osteitis                |                        |
|  | 1 / 127 (0.79%)<br>1                                     | 0 / 127 (0.00%)<br>0   |
|  | Additional description: Acute sinusitis                  |                        |
|  | 2 / 127 (1.57%)<br>3                                     | 2 / 127 (1.57%)<br>2   |
|  | Additional description: Borrelia infection               |                        |
|  | 0 / 127 (0.00%)<br>0                                     | 1 / 127 (0.79%)<br>1   |
|  | Additional description: Bronchitis                       |                        |
|  | 6 / 127 (4.72%)<br>10                                    | 12 / 127 (9.45%)<br>13 |
|  | Additional description: COVID-19                         |                        |
| COVID-19<br>subjects affected / exposed<br>occurrences (all)                         | 3 / 127 (2.36%)<br>3                                     | 3 / 127 (2.36%)<br>3   |
|  | Additional description: COVID-19 pneumonia               |                        |
| COVID-19 pneumonia   |  |                        |

|                                  |  |                 |  |
|----------------------------------|--|-----------------|--|
| subjects affected / exposed      | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                | 0  | 1               |  |
| Conjunctivitis                   | Additional description: Conjunctivitis                   |                 |  |
| subjects affected / exposed      | 3 / 127 (2.36%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                | 3  | 2               |  |
| Chronic sinusitis                | Additional description: Chronic sinusitis                |                 |  |
| subjects affected / exposed      | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                | 1  | 0               |  |
| Cystitis                         | Additional description: Cystitis                         |                 |  |
| subjects affected / exposed      | 2 / 127 (1.57%)  | 3 / 127 (2.36%) |  |
| occurrences (all)                | 7  | 6               |  |
| Ear infection                    | Additional description: Ear infection                    |                 |  |
| subjects affected / exposed      | 2 / 127 (1.57%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                | 2  | 0               |  |
| Erysipelas                       | Additional description: Erysipelas                       |                 |  |
| subjects affected / exposed      | 2 / 127 (1.57%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                | 2  | 0               |  |
| Folliculitis                     | Additional description: Folliculitis                     |                 |  |
| subjects affected / exposed      | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                | 0  | 2               |  |
| Fungal infection                 | Additional description: Fungal infection                 |                 |  |
| subjects affected / exposed      | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                | 1  | 0               |  |
| Fungal skin infection            | Additional description: Fungal skin infection            |                 |  |
| subjects affected / exposed      | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                | 3  | 0               |  |
| Furuncle                         | Additional description: Furuncle                         |                 |  |
| subjects affected / exposed      | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)                | 0  | 1               |  |
| Gastroenteritis                  | Additional description: Gastroenteritis                  |                 |  |
| subjects affected / exposed      | 0 / 127 (0.00%)  | 2 / 127 (1.57%) |  |
| occurrences (all)                | 0  | 2               |  |
| Gastrointestinal viral infection | Additional description: Gastrointestinal viral infection |                 |  |
| subjects affected / exposed      | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)                | 1  | 0               |  |
| Herpes zoster                    | Additional description: Herpes zoster                    |                 |  |

|  |   |                         |  |
|--|---|-------------------------|--|
| subjects affected / exposed<br>occurrences (all) | 5 / 127 (3.94%)<br>5                                      | 2 / 127 (1.57%)<br>2    |  |
| Hordeolum  | Additional description: Hordeolum                         |                         |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                                      | 1 / 127 (0.79%)<br>1    |  |
| Infected dermal cyst                             | Additional description: Infected dermal cyst              |                         |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 127 (0.79%)<br>1                                      | 0 / 127 (0.00%)<br>0    |  |
| Infection  | Additional description: Infection                         |                         |  |
| subjects affected / exposed<br>occurrences (all) | 2 / 127 (1.57%)<br>2                                      | 1 / 127 (0.79%)<br>1    |  |
| Influenza  | Additional description: Influenza                         |                         |  |
| subjects affected / exposed<br>occurrences (all) | 6 / 127 (4.72%)<br>7                                      | 15 / 127 (11.81%)<br>15 |  |
| Laryngitis                                       | Additional description: Laryngitis                        |                         |  |
| subjects affected / exposed<br>occurrences (all) | 2 / 127 (1.57%)<br>3                                      | 0 / 127 (0.00%)<br>0    |  |
| Lower respiratory tract infection                | Additional description: Lower respiratory tract infection |                         |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 127 (0.00%)<br>0                                      | 1 / 127 (0.79%)<br>1    |  |
| Lyme disease                                     | Additional description: Lyme disease                      |                         |  |
| subjects affected / exposed<br>occurrences (all) | 3 / 127 (2.36%)<br>3                                      | 0 / 127 (0.00%)<br>0    |  |
| Nasopharyngitis                                  | Additional description: Nasopharyngitis                   |                         |  |
| subjects affected / exposed<br>occurrences (all) | 9 / 127 (7.09%)<br>20                                     | 14 / 127 (11.02%)<br>24 |  |
| Oesophageal candidiasis                          | Additional description: Oesophageal candidiasis           |                         |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 127 (0.79%)<br>1                                      | 0 / 127 (0.00%)<br>0    |  |
| Onychomycosis                                    | Additional description: Onychomycosis                     |                         |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 127 (0.79%)<br>1                                      | 0 / 127 (0.00%)<br>0    |  |
| Oral candidiasis                                 | Additional description: Oral candidiasis                  |                         |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 127 (0.79%)<br>1                                      | 0 / 127 (0.00%)<br>0    |  |
| Oral fungal infection                            | Additional description: Oral fungal infection             |                         |  |



|                                |  |                 |  |
|--------------------------------|--|-----------------|--|
| subjects affected / exposed    | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)              | 1  | 0               |  |
| Oral herpes                    | Additional description: Oral herpes                    |                 |  |
| subjects affected / exposed    | 5 / 127 (3.94%)  | 3 / 127 (2.36%) |  |
| occurrences (all)              | 5  | 4               |  |
| Oral infection                 | Additional description: Oral infection                 |                 |  |
| subjects affected / exposed    | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)              | 0  | 1               |  |
| Otitis externa                 | Additional description: Otitis externa                 |                 |  |
| subjects affected / exposed    | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)              | 0  | 1               |  |
| Parainfluenzae virus infection | Additional description: Parainfluenzae virus infection |                 |  |
| subjects affected / exposed    | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)              | 0  | 1               |  |
| Paronychia                     | Additional description: Paronychia                     |                 |  |
| subjects affected / exposed    | 1 / 127 (0.79%)  | 1 / 127 (0.79%) |  |
| occurrences (all)              | 1  | 1               |  |
| Periodontitis                  | Additional description: Periodontitis                  |                 |  |
| subjects affected / exposed    | 1 / 127 (0.79%)  | 1 / 127 (0.79%) |  |
| occurrences (all)              | 1  | 1               |  |
| Pharyngitis                    | Additional description: Pharyngitis                    |                 |  |
| subjects affected / exposed    | 1 / 127 (0.79%)  | 3 / 127 (2.36%) |  |
| occurrences (all)              | 1  | 7               |  |
| Pharyngotonsillitis            | Additional description: Pharyngotonsillitis            |                 |  |
| subjects affected / exposed    | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)              | 1  | 0               |  |
| Pneumonia                      | Additional description: Pneumonia                      |                 |  |
| subjects affected / exposed    | 2 / 127 (1.57%)  | 1 / 127 (0.79%) |  |
| occurrences (all)              | 2  | 4               |  |
| Pulpitis dental                | Additional description: Pulpitis dental                |                 |  |
| subjects affected / exposed    | 1 / 127 (0.79%)  | 0 / 127 (0.00%) |  |
| occurrences (all)              | 1  | 0               |  |
| Pyelonephritis acute           | Additional description: Pyelonephritis acute           |                 |  |
| subjects affected / exposed    | 0 / 127 (0.00%)  | 1 / 127 (0.79%) |  |
| occurrences (all)              | 0  | 1               |  |
| Pyelonephritis chronic         | Additional description: Pyelonephritis chronic         |                 |  |

|                                   |   |                 |  |
|-----------------------------------|---|-----------------|--|
| subjects affected / exposed       | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences (all)                 | 1   | 0               |  |
| Respiratory tract infection       | Additional description: Respiratory tract infection       |                 |  |
| subjects affected / exposed       | 4 / 127 (3.15%)   | 4 / 127 (3.15%) |  |
| occurrences (all)                 | 4   | 4               |  |
| Respiratory tract infection viral | Additional description: Respiratory tract infection viral |                 |  |
| subjects affected / exposed       | 1 / 127 (0.79%)   | 1 / 127 (0.79%) |  |
| occurrences (all)                 | 1   | 1               |  |
| Rhinitis                          | Additional description: Rhinitis                          |                 |  |
| subjects affected / exposed       | 7 / 127 (5.51%)   | 3 / 127 (2.36%) |  |
| occurrences (all)                 | 9   | 4               |  |
| Rhinotracheitis                   | Additional description: Rhinotracheitis                   |                 |  |
| subjects affected / exposed       | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences (all)                 | 2   | 0               |  |
| Sinusitis                         | Additional description: Sinusitis                         |                 |  |
| subjects affected / exposed       | 2 / 127 (1.57%)   | 4 / 127 (3.15%) |  |
| occurrences (all)                 | 2   | 5               |  |
| Staphylococcal infection          | Additional description: Staphylococcal infection          |                 |  |
| subjects affected / exposed       | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences (all)                 | 1   | 0               |  |
| Tinea versicolour                 | Additional description: Tinea versicolour                 |                 |  |
| subjects affected / exposed       | 0 / 127 (0.00%)   | 1 / 127 (0.79%) |  |
| occurrences (all)                 | 0   | 1               |  |
| Tonsillitis                       | Additional description: Tonsillitis                       |                 |  |
| subjects affected / exposed       | 2 / 127 (1.57%)   | 1 / 127 (0.79%) |  |
| occurrences (all)                 | 2   | 1               |  |
| Tooth infection                   | Additional description: Tooth infection                   |                 |  |
| subjects affected / exposed       | 1 / 127 (0.79%)   | 1 / 127 (0.79%) |  |
| occurrences (all)                 | 2   | 1               |  |
| Tracheitis                        | Additional description: Tracheitis                        |                 |  |
| subjects affected / exposed       | 0 / 127 (0.00%)   | 1 / 127 (0.79%) |  |
| occurrences (all)                 | 0   | 1               |  |
| Urinary tract infection           | Additional description: Urinary tract infection           |                 |  |
| subjects affected / exposed       | 8 / 127 (6.30%)   | 8 / 127 (6.30%) |  |
| occurrences (all)                 | 17  | 11              |  |
| Upper respiratory tract infection | Additional description: Upper respiratory tract infection |                 |  |

|                                    |   |                 |  |
|------------------------------------|---|-----------------|--|
| subjects affected / exposed        | 11 / 127 (8.66%)  | 7 / 127 (5.51%) |  |
| occurrences (all)                  | 18  | 12              |  |
| Viraemia                           | Additional description: Viraemia                          |                 |  |
| subjects affected / exposed        | 1 / 127 (0.79%)   | 2 / 127 (1.57%) |  |
| occurrences (all)                  | 1   | 2               |  |
| Viral infection                    | Additional description: Viral infection                   |                 |  |
| subjects affected / exposed        | 6 / 127 (4.72%)   | 0 / 127 (0.00%) |  |
| occurrences (all)                  | 6   | 0               |  |
| Vulvovaginal mycotic infection     | Additional description: Vulvovaginal mycotic infection    |                 |  |
| subjects affected / exposed        | 0 / 127 (0.00%)   | 2 / 127 (1.57%) |  |
| occurrences (all)                  | 0   | 2               |  |
| Metabolism and nutrition disorders |   |                 |  |
| Decreased appetite                 | Additional description: Decreased appetite                |                 |  |
| subjects affected / exposed        | 3 / 127 (2.36%)   | 2 / 127 (1.57%) |  |
| occurrences (all)                  | 3   | 3               |  |
| Dehydration                        | Additional description: Dehydration                       |                 |  |
| subjects affected / exposed        | 0 / 127 (0.00%)   | 1 / 127 (0.79%) |  |
| occurrences (all)                  | 0   | 1               |  |
| Diabetes mellitus                  | Additional description: Diabetes mellitus                 |                 |  |
| subjects affected / exposed        | 2 / 127 (1.57%)   | 0 / 127 (0.00%) |  |
| occurrences (all)                  | 2   | 0               |  |
| Diabetic metabolic decompensation  | Additional description: Diabetic metabolic decompensation |                 |  |
| subjects affected / exposed        | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences (all)                  | 1   | 0               |  |
| Dyslipidaemia                      | Additional description: Dyslipidaemia                     |                 |  |
| subjects affected / exposed        | 2 / 127 (1.57%)   | 1 / 127 (0.79%) |  |
| occurrences (all)                  | 2   | 1               |  |
| Folate deficiency                  | Additional description: Folate deficiency                 |                 |  |
| subjects affected / exposed        | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences (all)                  | 1   | 0               |  |
| Gout                               | Additional description: Gout                              |                 |  |
| subjects affected / exposed        | 1 / 127 (0.79%)   | 0 / 127 (0.00%) |  |
| occurrences (all)                  | 1   | 0               |  |
| Hypercalcaemia                     | Additional description: Hypercalcaemia                    |                 |  |
| subjects affected / exposed        | 0 / 127 (0.00%)   | 1 / 127 (0.79%) |  |
| occurrences (all)                  | 0   | 1               |  |

|                             |   |                 |
|-----------------------------|---|-----------------|
| Hyperchloraemia             | Additional description: Hyperchloraemia       |                 |
| subjects affected / exposed | 1 / 127 (0.79%)                               | 0 / 127 (0.00%) |
| occurrences (all)           | 1   | 0               |
| Hypercholesterolaemia       | Additional description: Hypercholesterolaemia |                 |
| subjects affected / exposed | 1 / 127 (0.79%)                               | 2 / 127 (1.57%) |
| occurrences (all)           | 1   | 3               |
| Hyperglycaemia              | Additional description: Hyperglycaemia        |                 |
| subjects affected / exposed | 5 / 127 (3.94%)                               | 1 / 127 (0.79%) |
| occurrences (all)           | 6   | 1               |
| Hyperkalaemia               | Additional description: Hyperkalaemia         |                 |
| subjects affected / exposed | 1 / 127 (0.79%)                               | 3 / 127 (2.36%) |
| occurrences (all)           | 2   | 5               |
| Hyperlipidaemia             | Additional description: Hyperlipidaemia       |                 |
| subjects affected / exposed | 1 / 127 (0.79%)                               | 2 / 127 (1.57%) |
| occurrences (all)           | 1   | 2               |
| Hypernatraemia              | Additional description: Hypernatraemia        |                 |
| subjects affected / exposed | 0 / 127 (0.00%)                               | 1 / 127 (0.79%) |
| occurrences (all)           | 0   | 1               |
| Hypertriglyceridaemia       | Additional description: Hypertriglyceridaemia |                 |
| subjects affected / exposed | 1 / 127 (0.79%)                               | 4 / 127 (3.15%) |
| occurrences (all)           | 1   | 4               |
| Hyperuricaemia              | Additional description: Hyperuricaemia        |                 |
| subjects affected / exposed | 4 / 127 (3.15%)                               | 3 / 127 (2.36%) |
| occurrences (all)           | 6   | 4               |
| Hypoalbuminaemia            | Additional description: Hypoalbuminaemia      |                 |
| subjects affected / exposed | 3 / 127 (2.36%)                               | 0 / 127 (0.00%) |
| occurrences (all)           | 3   | 0               |
| Hypocalcaemia               | Additional description: Hypocalcaemia         |                 |
| subjects affected / exposed | 5 / 127 (3.94%)                               | 2 / 127 (1.57%) |
| occurrences (all)           | 10  | 6               |
| Hypoglycaemia               | Additional description: Hypoglycaemia         |                 |
| subjects affected / exposed | 0 / 127 (0.00%)                               | 1 / 127 (0.79%) |
| occurrences (all)           | 0   | 1               |
| Hypokalaemia                | Additional description: Hypokalaemia          |                 |
| subjects affected / exposed | 2 / 127 (1.57%)                               | 1 / 127 (0.79%) |
| occurrences (all)           | 4   | 2               |

|  |  |                       |
|--|--|-----------------------|
| Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Hypomagnesaemia          |                       |
|  | 0 / 127 (0.00%)<br>0                             | 1 / 127 (0.79%)<br>1  |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)            | Additional description: Hyponatraemia            |                       |
|  | 2 / 127 (1.57%)<br>2                             | 0 / 127 (0.00%)<br>0  |
| Hypoproteinaemia<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Hypoproteinaemia         |                       |
|  | 0 / 127 (0.00%)<br>0                             | 1 / 127 (0.79%)<br>1  |
| Iron deficiency<br>subjects affected / exposed<br>occurrences (all)          | Additional description: Iron deficiency          |                       |
|  | 8 / 127 (6.30%)<br>14                            | 4 / 127 (3.15%)<br>10 |
| Magnesium deficiency<br>subjects affected / exposed<br>occurrences (all)     | Additional description: Magnesium deficiency     |                       |
|  | 0 / 127 (0.00%)<br>0                             | 1 / 127 (0.79%)<br>1  |
| Steroid diabetes<br>subjects affected / exposed<br>occurrences (all)         | Additional description: Steroid diabetes         |                       |
|  | 0 / 127 (0.00%)<br>0                             | 1 / 127 (0.79%)<br>1  |
| Type 2 diabetes mellitus<br>subjects affected / exposed<br>occurrences (all) | Additional description: Type 2 diabetes mellitus |                       |
|  | 1 / 127 (0.79%)<br>1                             | 1 / 127 (0.79%)<br>1  |
| Vitamin D deficiency<br>subjects affected / exposed<br>occurrences (all)     | Additional description: Vitamin D deficiency     |                       |
|  | 3 / 127 (2.36%)<br>3                             | 1 / 127 (0.79%)<br>1  |

## 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

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32014125>

<http://www.ncbi.nlm.nih.gov/pubmed/32814349>

<http://www.ncbi.nlm.nih.gov/pubmed/33134869>