



## Clinical trial results:

**A single arm, open-label, phase II, multicentre study to assess the safety of vismodegib (GDC-0449) in patients with locally advanced or metastatic basal cell carcinoma (BCC).**

### Summary

|                          |  |
|--------------------------|--|
| EudraCT number           | 2011-000195-34   |
| Trial protocol           | SE AT DE BG GB BE IT ES NL SI DK HU CZ GR SK IE PT PL NO |
| Global end of trial date | <del>11 June 2017</del><br>14 June 2017                  |

### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v2 (current)   |
| This version publication date  | 24 June 2018   |
| First version publication date | 08 August 2015 |

Version creation reason

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | MO25616 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01367665 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | F. Hoffmann-La Roche AG   |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070  |
| Public contact               | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.com |
| Scientific contact           | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.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                       | 14 June 2017 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 14 June 2017 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

This single-arm, open-label, multi-center study will evaluate the safety and efficacy of vismodegib (GDC-0449) in patients with locally advanced or metastatic basal cell carcinoma. Patients will receive oral doses of vismodegib 150 mg once daily until disease progression or unacceptable toxicity.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 01 July 2011 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | France: 302            |
| Country: Number of subjects enrolled | Italy: 182             |
| Country: Number of subjects enrolled | Germany: 111           |
| Country: Number of subjects enrolled | Spain: 94              |
| Country: Number of subjects enrolled | Austria: 76            |
| Country: Number of subjects enrolled | Canada: 50             |
| Country: Number of subjects enrolled | United Kingdom: 41     |
| Country: Number of subjects enrolled | Czech Republic: 33     |
| Country: Number of subjects enrolled | Australia: 30          |
| Country: Number of subjects enrolled | Russian Federation: 30 |
| Country: Number of subjects enrolled | Sweden: 25             |
| Country: Number of subjects enrolled | Switzerland: 23        |
| Country: Number of subjects enrolled | Netherlands: 20        |
| Country: Number of subjects enrolled | Greece: 18             |
| Country: Number of subjects enrolled | Portugal: 17           |
| Country: Number of subjects enrolled | Brazil: 15             |
| Country: Number of subjects enrolled | Bulgaria: 15           |
| Country: Number of subjects enrolled | Poland: 13             |
| Country: Number of subjects enrolled | Colombia: 12           |
| Country: Number of subjects enrolled | Hungary: 12            |
| Country: Number of subjects enrolled | Turkey: 10             |

|                                      |                           |
|--------------------------------------|---------------------------|
| Country: Number of subjects enrolled | Romania: 9                |
| Country: Number of subjects enrolled | Belgium: 8                |
| Country: Number of subjects enrolled | Finland: 8                |
| Country: Number of subjects enrolled | Israel: 8                 |
| Country: Number of subjects enrolled | Serbia: 7                 |
| Country: Number of subjects enrolled | Ireland: 6                |
| Country: Number of subjects enrolled | Slovenia: 6               |
| Country: Number of subjects enrolled | Argentina: 5              |
| Country: Number of subjects enrolled | Croatia: 5                |
| Country: Number of subjects enrolled | Denmark: 5                |
| Country: Number of subjects enrolled | Lithuania: 5              |
| Country: Number of subjects enrolled | Slovakia: 5               |
| Country: Number of subjects enrolled | New Zealand: 4            |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 3 |
| Country: Number of subjects enrolled | Norway: 2                 |
| Worldwide total number of subjects   | 1215                      |
| EEA total number of subjects         | 1018                      |

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)                      | 425 |
| From 65 to 84 years                       | 553 |
| 85 years and over                         | 237 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 1232 participants were enrolled in the study, but only 1215 participants received at least one dose of any study treatment. Results include only the treated 1215 participants.

### Period 1

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

### Arms

|                              |                               |
|------------------------------|-------------------------------|
| Are arms mutually exclusive? | Yes                           |
| <b>Arm title</b>             | Vismodegib - Locally Advanced |

Arm description:

Participants received vismodegib 150 mg orally once a day until one of the following occurred: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator.

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

Dosage and administration details:

Participants received vismodegib 150 mg orally once a day until one of the following occurs: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator.

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Vismodegib - Metastatic |
|------------------|-------------------------|

Arm description:

Participants received vismodegib 150 mg orally once a day until one of the following occurred: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator.

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

Dosage and administration details:

Participants received vismodegib 150 mg orally once a day until one of the following occurs: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator.

| <b>Number of subjects in period 1</b> | Vismodegib - Locally Advanced | Vismodegib - Metastatic |
|---------------------------------------|-------------------------------|-------------------------|
| Started                               | 1119                          | 96                      |
| Completed                             | 677                           | 41                      |
| Not completed                         | 442                           | 55                      |
| Adverse event, serious fatal          | 102                           | 19                      |
| Not Done                              | 118                           | 14                      |
| Lost to follow-up                     | 222                           | 22                      |

## Baseline characteristics

### Reporting groups

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Vismodegib - Locally Advanced |
|-----------------------|-------------------------------|

Reporting group description:

Participants received vismodegib 150 mg orally once a day until one of the following occurred: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Vismodegib - Metastatic |
|-----------------------|-------------------------|

Reporting group description:

Participants received vismodegib 150 mg orally once a day until one of the following occurred: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator.

| Reporting group values                             | Vismodegib - Locally Advanced | Vismodegib - Metastatic | Total |
|--|-------------------------------|-------------------------|-------|
| Number of subjects                                 | 1119                          | 96                      | 1215  |
| Age categorical                                    |                               |                         |       |
| 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)                               | 382                           | 43                      | 425   |
| From 65-84 years                                   | 511                           | 42                      | 553   |
| 85 years and over                                  | 226                           | 11                      | 237   |
| Age Continuous                                     |                               |                         |       |
| Units: years                                       |                               |                         |       |
| arithmetic mean                                    | 69.7                          | 66.6                    |       |
| standard deviation                                 | ± 16.1                        | ± 13.0                  | -     |
| Sex: Female, Male                                  |                               |                         |       |
| Units: Subjects                                    |                               |                         |       |
| Female   | 485                           | 36                      | 521   |
| Male   | 634                           | 60                      | 694   |
| Race/Ethnicity, Customized                         |                               |                         |       |
| Units: Subjects                                    |                               |                         |       |
| Race: Asian  | 1                             | 0                       | 1     |
| Race: Black or African American                    | 1                             | 1                       | 2     |
| Race: White  | 787                           | 92                      | 879   |
| Race: Other  | 15                            | 0                       | 15    |
| Race: Not Applicable/Missing                       | 315                           | 3                       | 318   |

## End points

### End points reporting groups

|   |                               |
|---|-------------------------------|
| Reporting group title   | Vismodegib - Locally Advanced |
| Reporting group description:<br>Participants received vismodegib 150 mg orally once a day until one of the following occurred: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator. |                               |
| Reporting group title   | Vismodegib - Metastatic       |
| Reporting group description:<br>Participants received vismodegib 150 mg orally once a day until one of the following occurred: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator. |                               |

### Primary: Percentage of Participants who Experienced any Adverse Events (AEs), AEs Grade 3 or 4, AEs Leading to Drug Interruptions or Discontinuations and any Serious Adverse Events (SAEs)

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants who Experienced any Adverse Events (AEs), AEs Grade 3 or 4, AEs Leading to Drug Interruptions or Discontinuations and any Serious Adverse Events (SAEs) <sup>[1]</sup> |
|-----------------|---|

#### End point description:

Adverse events were graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activity of daily living with inability to perform bathing, dressing and undressing, feeding self, using the toilet, taking medications but not bedridden. Grade 4: An immediate threat to life. Urgent medical intervention is required in order to maintain survival.

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

#### End point timeframe:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this end point.

| End point values                                 | Vismodegib -<br>Locally<br>Advanced | Vismodegib -<br>Metastatic |  |  |
|--|-------------------------------------|----------------------------|--|--|
| Subject group type                               | Reporting group                     | Reporting group            |  |  |
| Number of subjects analysed                      | 1119                                | 96                         |  |  |
| Units: percentage of participants                |                                     |                            |  |  |
| number (not applicable)                          |                                     |                            |  |  |
| Any AEs  | 98.4                                | 99.0                       |  |  |
| Any AEs with maximum severity of<br>Grade 3 or 4 | 43.4                                | 52.1                       |  |  |
| Any Serious AEs                                  | 24.3                                | 32.3                       |  |  |
| Any AEs leading to study drug<br>interruption    | 40.5                                | 35.4                       |  |  |
| Any AEs leading to study drug<br>discontinuation | 33.8                                | 17.7                       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Participants who Died due to Adverse Events, Disease Progression or Other reasons

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants who Died due to Adverse Events, Disease Progression or Other reasons <sup>[2]</sup> |
|-----------------|--|

End point description:

Reasons for "other" included "unknown," "natural causes," "cardiac decompensation," "general state alteration," "deterioration of general state," "clinical deterioration taking into consideration patient's age," "old age," and "disease progression of mediastinal squamous cell carcinoma (SCC)."

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

End point timeframe:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this end point.

| End point values                  | Vismodegib -<br>Locally<br>Advanced | Vismodegib -<br>Metastatic |  |  |
|-----------------------------------|-------------------------------------|----------------------------|--|--|
| Subject group type                | Reporting group                     | Reporting group            |  |  |
| Number of subjects analysed       | 1119                                | 96                         |  |  |
| Units: percentage of participants |                                     |                            |  |  |
| number (not applicable)           |                                     |                            |  |  |
| Adverse Event                     | 6.1                                 | 6.3                        |  |  |
| Disease Progression               | 1.9                                 | 13.5                       |  |  |
| Other                             | 1.3                                 | 0                          |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Participants who Report a Shift in NCI CTCAE Grades to 3/4 in Hematology and Biochemistry Laboratory Parameters

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants who Report a Shift in NCI CTCAE Grades to 3/4 in Hematology and Biochemistry Laboratory Parameters <sup>[3]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)



Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this end point.

| End point values                                | Vismodegib -<br>Locally<br>Advanced | Vismodegib -<br>Metastatic |  |  |
|---|-------------------------------------|----------------------------|--|--|
| Subject group type                              | Reporting group                     | Reporting group            |  |  |
| Number of subjects analysed                     | 1119                                | 96                         |  |  |
| Units: percentage of participants               |                                     |                            |  |  |
| number (not applicable)                         |                                     |                            |  |  |
| Hemoglobin (High)                               | 0.1                                 | 0                          |  |  |
| Hemoglobin (Low)                                | 1.3                                 | 2.1                        |  |  |
| Neutrophils, Total, Abs (Low)                   | 0.5                                 | 0                          |  |  |
| Platelet (Low)                                  | 0.2                                 | 0                          |  |  |
| White Blood Cell Count (High)                   | 0.2                                 | 1.0                        |  |  |
| White Blood Cell Count (Low)                    | 0.2                                 | 0                          |  |  |
| Alkaline Phosphatase (High)                     | 0.6                                 | 0                          |  |  |
| SGPT/ALT (alanine aminotransferase) -<br>High   | 2.2                                 | 4.2                        |  |  |
| SGOT/AST (aspartate aminotransferase) -<br>High | 1.5                                 | 3.1                        |  |  |
| Creatine Kinase (High)                          | 0.1                                 | 0                          |  |  |
| Creatinine (High)                               | 1.3                                 | 2.1                        |  |  |
| Glucose (Low)                                   | 0.4                                 | 0                          |  |  |
| Potassium (High)                                | 1.1                                 | 4.2                        |  |  |
| Potassium (Low)                                 | 0.8                                 | 1.0                        |  |  |
| Sodium (High)                                   | 0.2                                 | 0                          |  |  |
| Sodium (Low)                                    | 2.6                                 | 4.2                        |  |  |
| Total Bilirubin (High)                          | 0.5                                 | 0                          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Exposure to Study Treatment: Duration on Treatment

|                 |   |
|-----------------|---|
| End point title | Exposure to Study Treatment: Duration on Treatment <sup>[4]</sup> |
|-----------------|---|

End point description:

Duration on treatment was the number of days between first and last dose of study treatment.

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

End point timeframe:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this end point.

| End point values              | Vismodegib - Locally Advanced | Vismodegib - Metastatic |  |  |
|-------------------------------|-------------------------------|-------------------------|--|--|
| Subject group type            | Reporting group               | Reporting group         |  |  |
| Number of subjects analysed   | 1119                          | 96                      |  |  |
| Units: days                   |                               |                         |  |  |
| median (full range (min-max)) | 256.0 (2 to 1904)             | 337.0 (2 to 1932)       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Exposure to Study Treatment - Dose Intensity

|                 |   |
|-----------------|---|
| End point title | Exposure to Study Treatment - Dose Intensity <sup>[5]</sup> |
|-----------------|---|

End point description:

Dose intensity was defined as the percentage of actual number of doses received versus planned.

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

End point timeframe:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this end point.

| End point values              | Vismodegib - Locally Advanced | Vismodegib - Metastatic |  |  |
|-------------------------------|-------------------------------|-------------------------|--|--|
| Subject group type            | Reporting group               | Reporting group         |  |  |
| Number of subjects analysed   | 1119                          | 96                      |  |  |
| Units: percentage             |                               |                         |  |  |
| median (full range (min-max)) | 97.62 (44.9 to 100.0)         | 98.51 (67.8 to 100.0)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Best Overall Response Rate (BORR)

|                 |                                   |
|-----------------|-----------------------------------|
| End point title | Best Overall Response Rate (BORR) |
|-----------------|-----------------------------------|

End point description:

BORR was defined as the percentage of participants achieving either a complete response (CR) or a partial response (PR) as assessed by the Investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. CR was defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) required a reduction in short axis to <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

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

End point timeframe:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)

| End point values                  | Vismodegib -<br>Locally<br>Advanced | Vismodegib -<br>Metastatic |  |  |
|-----------------------------------|-------------------------------------|----------------------------|--|--|
| Subject group type                | Reporting group                     | Reporting group            |  |  |
| Number of subjects analysed       | 1103                                | 89                         |  |  |
| Units: percentage of participants |                                     |                            |  |  |
| number (not applicable)           |                                     |                            |  |  |
| CR                                | 33.9                                | 4.8                        |  |  |
| PR                                | 35.3                                | 32.5                       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Response

|                 |                      |
|-----------------|----------------------|
| End point title | Duration of Response |
|-----------------|----------------------|

End point description:

Duration of response was defined as the time interval between the date of the earliest qualifying response (CR or PR) and the date of disease progression or death for any cause. Median duration of response was estimated using Kaplan-Meier estimates.

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

End point timeframe:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)

| End point values                 | Vismodegib -<br>Locally<br>Advanced | Vismodegib -<br>Metastatic |  |  |
|----------------------------------|-------------------------------------|----------------------------|--|--|
| Subject group type               | Reporting group                     | Reporting group            |  |  |
| Number of subjects analysed      | 745                                 | 31                         |  |  |
| Units: months                    |                                     |                            |  |  |
| median (confidence interval 95%) | 18.89 (17.64<br>to 22.57)           | 13.93 (9.23 to<br>18.50)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Response

|                 |                  |
|-----------------|------------------|
| End point title | Time to Response |
|-----------------|------------------|

End point description:

Time to response was defined as the interval between the date of first treatment and the date of first documentation of confirmed CR or PR (whichever occur first). 99999 represented data that was not estimable due to insufficient number of events.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Baseline to the data cut-off of 14 June 2017 (up to 6 years) |           |

| End point values                 | Vismodegib - Locally Advanced | Vismodegib - Metastatic |  |  |
|----------------------------------|-------------------------------|-------------------------|--|--|
| Subject group type               | Reporting group               | Reporting group         |  |  |
| Number of subjects analysed      | 1076                          | 83                      |  |  |
| Units: months                    |                               |                         |  |  |
| median (confidence interval 95%) | 3.65 (2.92 to 3.71)           | 99999 (5.49 to 99999)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-Free Survival (PFS)

|   |                                 |
|---|---------------------------------|
| End point title   | Progression-Free Survival (PFS) |
| End point description:  |                                 |
| PFS was defined as the time interval between the date of the first therapy and the date of progression or death for any causes, whichever occurs first. Disease progression was assessed by the investigator. |                                 |
| End point type  | Secondary                       |
| End point timeframe:  |                                 |
| Baseline to the data cut-off of 14 June 2017 (up to 6 years)  |                                 |

| End point values                 | Vismodegib - Locally Advanced | Vismodegib - Metastatic |  |  |
|----------------------------------|-------------------------------|-------------------------|--|--|
| Subject group type               | Reporting group               | Reporting group         |  |  |
| Number of subjects analysed      | 1103                          | 89                      |  |  |
| Units: months                    |                               |                         |  |  |
| median (confidence interval 95%) | 20.30 (19.38 to 21.82)        | 12.85 (11.30 to 17.68)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS)

|   |                       |
|---|-----------------------|
| End point title   | Overall Survival (OS) |
| End point description:  |                       |
| OS was defined as the time from the date of first treatment to the date of death, regardless of the cause |                       |

of death. 99999 represented data that was not estimable. The median OS was not reached in both the metastatic BCC and locally advanced BCC cohorts.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Baseline to the data cut-off of 14 June 2017 (up to 6 years) |           |

| End point values                 | Vismodegib -<br>Locally<br>Advanced | Vismodegib -<br>Metastatic |  |  |
|----------------------------------|-------------------------------------|----------------------------|--|--|
| Subject group type               | Reporting group                     | Reporting group            |  |  |
| Number of subjects analysed      | 1103                                | 89                         |  |  |
| Units: months                    |                                     |                            |  |  |
| median (confidence interval 95%) | 99999 (99999<br>to 99999)           | 99999 (99999<br>to 99999)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline Scores of Skindex-16 Questionnaire Domains of Emotion, Function and Symptom

|                 |  |
|-----------------|--|
| End point title | Change from Baseline Scores of Skindex-16 Questionnaire Domains of Emotion, Function and Symptom |
|-----------------|--|

End point description:

The Skindex-16 questionnaire includes three domains for the assessment of the effects of skin disease on participants' quality of life: symptoms, emotions and function. Responses from the questionnaire were transformed to a linear scale of 100 varying from 0 (never bothered, i.e., best) to 100 (always bothers, i.e., worst).

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

End point timeframe:

Baseline to the data cut-off date of 14 June 2017 (up to 6 years).

| End point values                          | Vismodegib -<br>Locally<br>Advanced | Vismodegib -<br>Metastatic |  |  |
|---|-------------------------------------|----------------------------|--|--|
| Subject group type                        | Reporting group                     | Reporting group            |  |  |
| Number of subjects analysed               | 1111                                | 89                         |  |  |
| Units: Skindex-16 Composite Domain Scores |                                     |                            |  |  |
| arithmetic mean (standard deviation)      |                                     |                            |  |  |
| Emotion: C2D1 (Cycle 2 Day 1)             | -18.02 (±<br>26.12)                 | -8.68 (±<br>23.50)         |  |  |
| Emotion: C7D1                             | -26.04 (±<br>30.80)                 | -13.14 (±<br>33.25)        |  |  |
| Emotion: End of Study                     | -24.66 (±<br>33.13)                 | 7.76 (± 27.61)             |  |  |
| Function: C2D1                            | -7.43 (±<br>22.18)                  | -1.71 (±<br>16.31)         |  |  |

|                        |                  |                  |  |  |
|------------------------|------------------|------------------|--|--|
| Function: C7D1         | -11.09 (± 26.49) | -10.00 (± 24.74) |  |  |
| Function: End of Study | -9.84 (± 28.03)  | 4.81 (± 29.80)   |  |  |
| Symptom: C2D1          | -9.92 (± 22.02)  | -5.06 (± 23.10)  |  |  |
| Symptom: C7D1          | -12.03 (± 24.95) | -6.73 (± 28.92)  |  |  |
| Symptom: End of Study  | -11.85 (± 27.05) | 1.85 (± 22.15)   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with a ≥ 30% Reduction in Disease-Related Symptoms According to MDASI Scale

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with a ≥ 30% Reduction in Disease-Related Symptoms According to MDASI Scale <sup>[6]</sup> |
|-----------------|---|

End point description:

M.D. Anderson Symptom Inventory (MDASI) scale. The MDASI core instrument is a 19-item patient self-report questionnaire whose items comprise two scales, symptom severity and symptom interference. For 13 items (i.e., pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, difficulty remembering things, lack of appetite, drowsiness, dry mouth, sadness, vomiting, and numbness or tingling), participants were asked to rate how severe the symptoms were when "at their worst" in the last 24 hours. For the remaining 6 items, participants were asked to rate how much the symptoms have interfered with 6 areas of functioning (i.e., general activity, walking, work, mood, relations with other people, and enjoyment of life) in the last 24 hours.

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

End point timeframe:

08-May-2013 (Protocol Version ≥ 4) to the data cut-off date of 14 June 2017 (approximately 4 years and 1 month).

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, the MDASI measurements were measured in Metastatic patients only.

|                                   |                         |  |  |  |
|-----------------------------------|-------------------------|--|--|--|
| <b>End point values</b>           | Vismodegib - Metastatic |  |  |  |
| Subject group type                | Reporting group         |  |  |  |
| Number of subjects analysed       | 16                      |  |  |  |
| Units: Percentage of participants |                         |  |  |  |
| number (not applicable)           | 60.0                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of participants with a ≥ 30% Reduction in Composite Symptom Severity Score According to MDASI Scale

|                 |   |
|-----------------|---|
| End point title | Percentage of participants with a ≥ 30% Reduction in Composite Symptom Severity Score According to MDASI Scale <sup>[7]</sup> |
|-----------------|---|

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**End point description:**

M.D. Anderson Symptom Inventory (MDASI) scale. The MDASI core instrument is a 19-item patient self-report questionnaire whose items comprise two scales, symptom severity and symptom interference. For 13 items (i.e., pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, difficulty remembering things, lack of appetite, drowsiness, dry mouth, sadness, vomiting, and numbness or tingling), participants were asked to rate how severe the symptoms were when "at their worst" in the last 24 hours. For the remaining 6 items, participants were asked to rate how much the symptoms have interfered with 6 areas of functioning (i.e., general activity, walking, work, mood, relations with other people, and enjoyment of life) in the last 24 hours.

---

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

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**End point timeframe:**

08-May-2013 (Protocol Version  $\geq 4$ ) to the data cut-off date of 14 June 2017 (approximately 4 years and 1 month).

**Notes:**

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol, the MDASI measurements were measured in Metastatic patients only.

|                                   |                         |  |  |  |
|-----------------------------------|-------------------------|--|--|--|
| <b>End point values</b>           | Vismodegib - Metastatic |  |  |  |
| Subject group type                | Reporting group         |  |  |  |
| Number of subjects analysed       | 16                      |  |  |  |
| Units: Percentage of participants |                         |  |  |  |
| number (not applicable)           | 33.3                    |  |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline to the data cut-off of 14 June 2017 (up to 6 years)

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

### Reporting groups

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Vismodegib - Metastatic |
|-----------------------|-------------------------|

Reporting group description:

Participants received vismodegib 150 mg orally once a day until one of the following occurred: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator.

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Vismodegib - Locally Advanced |
|-----------------------|-------------------------------|

Reporting group description:

Participants received vismodegib 150 mg orally once a day until one of the following occurred: Disease progression, intolerable toxicity most probably attributable to vismodegib, consent withdrawal, death, study termination by the Sponsor, or other reason deemed by the Investigator.

| Serious adverse events  | Vismodegib - Metastatic | Vismodegib - Locally Advanced |  |
|---|-------------------------|-------------------------------|--|
| Total subjects affected by serious adverse events                   |                         |                               |  |
| subjects affected / exposed   | 31 / 96 (32.29%)        | 272 / 1119 (24.31%)           |  |
| number of deaths (all causes)                                       | 19                      | 103                           |  |
| number of deaths resulting from adverse events                      |                         |                               |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                         |                               |  |
| BREAST CANCER RECURRENT   |                         |                               |  |
| subjects affected / exposed   | 0 / 96 (0.00%)          | 1 / 1119 (0.09%)              |  |
| occurrences causally related to treatment / all                     | 0 / 0                   | 0 / 1                         |  |
| deaths causally related to treatment / all                          | 0 / 0                   | 0 / 0                         |  |
| HEPATIC CANCER  |                         |                               |  |
| subjects affected / exposed   | 0 / 96 (0.00%)          | 1 / 1119 (0.09%)              |  |
| occurrences causally related to treatment / all                     | 0 / 0                   | 0 / 1                         |  |
| deaths causally related to treatment / all                          | 0 / 0                   | 0 / 0                         |  |
| INFECTED NEOPLASM   |                         |                               |  |
| subjects affected / exposed   | 0 / 96 (0.00%)          | 3 / 1119 (0.27%)              |  |
| occurrences causally related to treatment / all                     | 0 / 0                   | 0 / 4                         |  |
| deaths causally related to treatment / all                          | 0 / 0                   | 0 / 0                         |  |



|   |                |                   |  |
|---|----------------|-------------------|--|
| LIP SQUAMOUS CELL CARCINOMA                     |                |                   |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0             |  |
| LUNG NEOPLASM MALIGNANT                         |                |                   |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0             |  |
| METASTASES TO CENTRAL NERVOUS SYSTEM            |                |                   |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0             |  |
| METASTATIC SQUAMOUS CELL CARCINOMA              |                |                   |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0             |  |
| NON-SMALL CELL LUNG CANCER METASTATIC           |                |                   |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1             |  |
| RECTAL ADENOCARCINOMA                           |                |                   |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1             |  |
| SQUAMOUS CELL CARCINOMA                         |                |                   |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 4 / 1119 (0.36%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 3 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0             |  |
| SQUAMOUS CELL CARCINOMA OF SKIN                 |                |                   |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 10 / 1119 (0.89%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 5 / 10            |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 2             |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| ADENOCARCINOMA OF COLON                         |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| MALIGNANT NEOPLASM OF EYELID                    |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| METASTATIC MALIGNANT MELANOMA                   |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| BASAL CELL CARCINOMA                            |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| BENIGN NEOPLASM OF ADRENAL GLAND                |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| COLON CANCER                                    |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| GASTRIC CANCER                                  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| INTESTINAL ADENOCARCINOMA                       |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| INVASIVE LOBULAR BREAST                         |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| CARCINOMA                                       |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| LUNG ADENOCARCINOMA                             |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| MARGINAL ZONE LYMPHOMA                          |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| METASTASES TO BONE                              |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| NASAL CAVITY CANCER                             |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| PAPILLARY RENAL CELL CARCINOMA                  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| PARATHYROID TUMOUR BENIGN                       |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| RECTAL CANCER                                   |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            |  |
| RECTAL CANCER STAGE III                         |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| SKIN NEOPLASM BLEEDING                          |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| SQUAMOUS CELL BREAST CARCINOMA                  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| TUMOUR HAEMORRHAGE                              |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Vascular disorders                              |                |                  |  |
| ARTERIAL HAEMORRHAGE                            |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ARTERIAL OCCLUSIVE DISEASE                      |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| DEEP VEIN THROMBOSIS                            |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 3 / 1119 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| HYPOTENSION                                     |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (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           |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ORTHOSTATIC HYPOTENSION                         |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| AORTIC ANEURYSM                                 |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| CIRCULATORY COLLAPSE                            |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            |  |
| HAEMORRHAGE                                     |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0            |  |
| HYPERTENSION                                    |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| PERIPHERAL ISCHAEMIA                            |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| SHOCK HAEMORRHAGIC                              |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| THROMBOSIS                                      |                |                  |  |

|  |                |                   |  |
|--|----------------|-------------------|--|
| subjects affected / exposed                          | 0 / 96 (0.00%) | 1 / 1119 (0.09%)  |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1             |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0             |  |
| Surgical and medical procedures                      |                |                   |  |
| EYELID OPERATION                                     |                |                   |  |
| subjects affected / exposed                          | 0 / 96 (0.00%) | 1 / 1119 (0.09%)  |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1             |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0             |  |
| General disorders and administration site conditions |                |                   |  |
| ASTHENIA   |                |                   |  |
| subjects affected / exposed                          | 0 / 96 (0.00%) | 4 / 1119 (0.36%)  |  |
| occurrences causally related to treatment / all      | 0 / 0          | 3 / 4             |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 1             |  |
| CHEST PAIN   |                |                   |  |
| subjects affected / exposed                          | 0 / 96 (0.00%) | 2 / 1119 (0.18%)  |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 2             |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0             |  |
| GENERAL PHYSICAL HEALTH DETERIORATION                |                |                   |  |
| subjects affected / exposed                          | 1 / 96 (1.04%) | 11 / 1119 (0.98%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 5 / 11            |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 4             |  |
| MULTIPLE ORGAN DYSFUNCTION SYNDROME                  |                |                   |  |
| subjects affected / exposed                          | 0 / 96 (0.00%) | 1 / 1119 (0.09%)  |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1             |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 1             |  |
| SUDDEN DEATH   |                |                   |  |
| subjects affected / exposed                          | 1 / 96 (1.04%) | 2 / 1119 (0.18%)  |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 2             |  |
| deaths causally related to treatment / all           | 0 / 1          | 0 / 2             |  |
| TERMINAL STATE                                       |                |                   |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            |  |
| ILL-DEFINED DISORDER                            |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| PYREXIA   |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| CYST  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| DEATH   |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            |  |
| GAIT DISTURBANCE                                |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| HERNIA  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| IMPAIRED HEALING                                |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| OEDEMA PERIPHERAL                               |                |                  |  |

|  |                |                  |  |
|--|----------------|------------------|--|
| subjects affected / exposed                            | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0            |  |
| <b>PAIN</b>  |                |                  |  |
| subjects affected / exposed                            | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0            |  |
| <b>PERFORMANCE STATUS DECREASED</b>                    |                |                  |  |
| subjects affected / exposed                            | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 1            |  |
| <b>Reproductive system and breast disorders</b>        |                |                  |  |
| <b>BENIGN PROSTATIC HYPERPLASIA</b>                    |                |                  |  |
| subjects affected / exposed                            | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0            |  |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                |                  |  |
| <b>ACUTE PULMONARY OEDEMA</b>                          |                |                  |  |
| subjects affected / exposed                            | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 1            |  |
| <b>CHRONIC OBSTRUCTIVE PULMONARY DISEASE</b>           |                |                  |  |
| subjects affected / exposed                            | 0 / 96 (0.00%) | 4 / 1119 (0.36%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 4            |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 1            |  |
| <b>PNEUMONIA ASPIRATION</b>                            |                |                  |  |
| subjects affected / exposed                            | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 2            |  |
| <b>PNEUMONITIS</b>                                     |                |                  |  |



|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            |  |
| <b>PULMONARY EMBOLISM</b>                       |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 3 / 1119 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1            |  |
| <b>DYSпноEA</b>                                 |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>EPISTAXIS</b>                                |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>ASTHMATIC CRISIS</b>                         |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>PULMONARY OEDEMA</b>                         |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>SINUS POLYP</b>                              |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>TACHYPNOEA</b>                               |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>Psychiatric disorders</b>                    |                |                  |  |
| <b>DEPRESSION</b>                               |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| DISORIENTATION                                  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ANXIETY   |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| SOMATIC SYMPTOM DISORDER                        |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| SUICIDE ATTEMPT                                 |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Product issues                                  |                |                  |  |
| DEVICE DISLOCATION                              |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Investigations                                  |                |                  |  |
| ALANINE AMINOTRANSFERASE INCREASED              |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ASPARTATE AMINOTRANSFERASE INCREASED            |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| BLOOD ALKALINE PHOSPHATASE INCREASED            |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| HEPATIC ENZYME INCREASED                        |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 5 / 1119 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 5 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| TRANSAMINASES INCREASED                         |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| WEIGHT DECREASED                                |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| BLOOD BILIRUBIN INCREASED                       |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| BLOOD CREATINE PHOSPHOKINASE INCREASED          |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| BLOOD TEST ABNORMAL                             |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| EJECTION FRACTION DECREASED                     |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| LIVER FUNCTION TEST INCREASED                   |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| 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  |                |                  |  |
| EYEBALL AVULSION                                |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| FALL  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 8 / 1119 (0.71%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| FEMORAL NECK FRACTURE                           |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| FEMUR FRACTURE                                  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| FOREIGN BODY                                    |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| HIP FRACTURE                                    |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 6 / 1119 (0.54%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| INCISIONAL HERNIA                               |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| PROCEDURAL INTESTINAL PERFORATION               |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| TRAUMATIC HAEMATOMA                             |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| SUBDURAL HAEMATOMA                              |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ABDOMINAL WOUND DEHISCENCE                      |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| BONE CONTUSION                                  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| CARTILAGE INJURY                                |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| CERVICAL VERTEBRAL FRACTURE                     |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| CHEST INJURY                                    |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| CONCUSSION                                      |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| LACERATION                                      |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| LIMB INJURY                                     |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| LUMBAR VERTEBRAL FRACTURE                       |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| POST PROCEDURAL HAEMORRHAGE                     |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| RADIUS FRACTURE                                 |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| RIB FRACTURE                                    |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ROAD TRAFFIC ACCIDENT                           |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| SPINAL COMPRESSION FRACTURE                     |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>TIBIA FRACTURE</b>                           |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>UPPER LIMB FRACTURE</b>                      |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>WOUND SECRETION</b>                          |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>WRIST FRACTURE</b>                           |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>Cardiac disorders</b>                        |                |                  |  |
| <b>ATRIAL FIBRILLATION</b>                      |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 3 / 1119 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>ATRIOVENTRICULAR BLOCK FIRST DEGREE</b>      |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>CARDIAC ARREST</b>                           |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            |  |
| <b>CARDIAC FAILURE CONGESTIVE</b>               |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            |  |
| LEFT VENTRICULAR DILATION                       |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| MYOCARDIAL INFARCTION                           |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 8 / 1119 (0.71%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 3 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0          | 2 / 6            |  |
| MYOCARDIAL ISCHAEMIA                            |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| SINUS NODE DYSFUNCTION                          |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| CARDIAC FAILURE                                 |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 3 / 1119 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            |  |
| ACUTE LEFT VENTRICULAR FAILURE                  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            |  |
| ACUTE MYOCARDIAL INFARCTION                     |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ATRIOVENTRICULAR BLOCK COMPLETE                 |                |                  |  |



|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ATRIOVENTRICULAR BLOCK SECOND DEGREE            |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| CARDIO-RESPIRATORY ARREST                       |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1            |  |
| CARDIOPULMONARY FAILURE                         |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            |  |
| CONGESTIVE CARDIOMYOPATHY                       |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Nervous system disorders                        |                |                  |  |
| CEREBROVASCULAR ACCIDENT                        |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 3 / 1119 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 2            |  |
| DIZZINESS                                       |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| DYSGEUSIA                                       |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| EMBOLIC STROKE                                  |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| HAEMORRHAGE INTRACRANIAL                        |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ISCHAEMIC STROKE                                |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1            |  |
| NERVOUS SYSTEM DISORDER                         |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| SYNCOPE   |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 6 / 1119 (0.54%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| SPINAL CORD COMPRESSION                         |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| BRAIN OEDEMA                                    |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| CEREBROSPINAL FISTULA                           |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| CEREBROVASCULAR DISORDER                        |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            |  |
| DEMENTIA  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| FACIAL PARALYSIS                                |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| FACIAL PARESIS                                  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| FOCAL DYSCOGNITIVE SEIZURES                     |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| GENERALISED TONIC-CLONIC SEIZURE                |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| LETHARGY  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| LOSS OF CONSCIOUSNESS                           |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| PARAESTHESIA                                    |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>PARTIAL SEIZURES</b>                         |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>PRESYNCOPE</b>                               |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>SEIZURE</b>                                  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>TRANSIENT ISCHAEMIC ATTACK</b>               |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>TRIGEMINAL NEURALGIA</b>                     |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>Blood and lymphatic system disorders</b>     |                |                  |  |
| <b>ANAEMIA</b>                                  |                |                  |  |
| alternative dictionary used: MedDRA 17.0        |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 4 / 1119 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>PANCYTOPENIA</b>                             |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| NORMOCHROMATIC NORMOCYTIC ANAEMIA               |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| THROMBOCYTOMPENIA                               |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Ear and labyrinth disorders                     |                |                  |  |
| VERTIGO   |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| VERTIGO POSITIONAL                              |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Eye disorders                                   |                |                  |  |
| DIPLOPIA  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| LAGOPHTHALMOS                                   |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| RETINAL ARTERY OCCLUSION                        |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Gastrointestinal disorders                      |                |                  |  |
| ABDOMINAL PAIN                                  |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| DIARRHOEA                                       |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| GASTRIC ULCER HAEMORRHAGE                       |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 3 / 1119 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| GASTRITIS EROSIVE                               |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| INGUINAL HERNIA                                 |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 3 / 1119 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| INTESTINAL OBSTRUCTION                          |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 3 / 1119 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| VOLVULUS  |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| PHARYNGO-OESOPHAGEAL DIVERTICULUM               |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| NAUSEA  |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| PANCREATITIS                                    |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| VOMITING  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ABDOMINAL INCARCERATED HERNIA                   |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| CONSTIPATION                                    |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| DUODENAL ULCER                                  |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| DUODENAL ULCER HAEMORRHAGE                      |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| GASTRIC PERFORATION                             |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| GASTRIC ULCER                                   |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| GASTRITIS                                       |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| GASTROINTESTINAL HAEMORRHAGE                    |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ILEUS   |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| INTESTINAL ISCHAEMIA                            |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| LOWER GASTROINTESTINAL HAEMORRHAGE              |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| PANCREATITIS ACUTE                              |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Hepatobiliary disorders                         |                |                  |  |
| CHOLELITHIASIS                                  |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| CHOLESTASIS                                     |                |                  |  |



|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| HEPATITIS                                       |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| HEPATOTOXICITY                                  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| CHOLECYSTITIS ACUTE                             |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 4 / 1119 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1            |  |
| BILE DUCT OBSTRUCTION                           |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| BILIARY COLIC                                   |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| BILIARY CYST                                    |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| CHOLANGITIS ACUTE                               |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| CHOLECYSTITIS                                   |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| DRUG-INDUCED LIVER INJURY                       |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| HEPATIC MASS                                    |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| HEPATITIS TOXIC                                 |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| HEPATOCELLULAR INJURY                           |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Skin and subcutaneous tissue disorders          |                |                  |  |
| ANGIOEDEMA                                      |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| DERMATITIS                                      |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| RASH  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| SKIN ULCER                                      |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| DECUBITUS ULCER                                 |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| DERMAL CYST                                     |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| LICHEN SCLEROSUS                                |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Renal and urinary disorders                     |                |                  |  |
| RENAL FAILURE                                   |                |                  |  |
| subjects affected / exposed                     | 2 / 96 (2.08%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 1 / 2          | 2 / 2            |  |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0            |  |
| URETHRAL STENOSIS                               |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| URINARY RETENTION                               |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| CHRONIC KIDNEY DISEASE                          |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 3 / 1119 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ACUTE KIDNEY INJURY                             |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ACUTE PRERENAL FAILURE                          |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| HAEMORRHAGE URINARY TRACT                       |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Musculoskeletal and connective tissue disorders |                |                  |  |
| MUSCULOSKELETAL DISORDER                        |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| PATHOLOGICAL FRACTURE                           |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ARTHRALGIA                                      |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| BACK PAIN                                       |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| MUSCLE SPASMS                                   |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| OSTEOPOROTIC FRACTURE                           |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ROTATOR CUFF SYNDROME                           |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| SOFT TISSUE MASS                                |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Infections and infestations                     |                |                  |  |
| ABSCCESS  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| APPENDICITIS                                    |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| BACTERIAL INFECTION                             |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| BRAIN ABSCESS                                   |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| CELLULITIS                                      |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| CLOSTRIDIUM COLITIS                             |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 1 / 96 (1.04%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>CYSTITIS</b>                                 |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>DIVERTICULITIS</b>                           |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>ENDOCARDITIS BACTERIAL</b>                   |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>ENTEROCOCCAL SEPSIS</b>                      |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>GASTROENTERITIS</b>                          |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 5 / 1119 (0.45%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>GASTROENTERITIS CLOSTRIDIAL</b>              |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>GASTROENTERITIS VIRAL</b>                    |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>GROIN ABSCESS</b>                            |                |                  |  |

|   |                |                   |  |
|---|----------------|-------------------|--|
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 1119 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0             |  |
| HERPES ZOSTER                                   |                |                   |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 3 / 1119 (0.27%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0             |  |
| INFECTED SKIN ULCER                             |                |                   |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0             |  |
| LOCALISED INFECTION                             |                |                   |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0             |  |
| LOWER RESPIRATORY TRACT INFECTION               |                |                   |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0             |  |
| PNEUMONIA                                       |                |                   |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 17 / 1119 (1.52%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 18            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 2             |  |
| PYELONEPHRITIS ACUTE                            |                |                   |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0             |  |
| SEPSIS  |                |                   |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 3 / 1119 (0.27%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 3             |  |
| SOFT TISSUE INFECTION                           |                |                   |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                                   | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all               | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all                    | 0 / 0          | 0 / 0            |  |
| BRONCHITIS  |                |                  |  |
| subjects affected / exposed                                   | 0 / 96 (0.00%) | 5 / 1119 (0.45%) |  |
| occurrences causally related to treatment / all               | 0 / 0          | 1 / 5            |  |
| deaths causally related to treatment / all                    | 0 / 0          | 0 / 0            |  |
| PYELONEPHRITIS  |                |                  |  |
| subjects affected / exposed                                   | 0 / 96 (0.00%) | 4 / 1119 (0.36%) |  |
| occurrences causally related to treatment / all               | 0 / 0          | 0 / 5            |  |
| deaths causally related to treatment / all                    | 0 / 0          | 0 / 0            |  |
| CLOSTRIDIUM DIFFICILE COLITIS                                 |                |                  |  |
| subjects affected / exposed                                   | 0 / 96 (0.00%) | 3 / 1119 (0.27%) |  |
| occurrences causally related to treatment / all               | 0 / 0          | 0 / 3            |  |
| deaths causally related to treatment / all                    | 0 / 0          | 0 / 0            |  |
| URINARY TRACT INFECTION                                       |                |                  |  |
| subjects affected / exposed                                   | 0 / 96 (0.00%) | 3 / 1119 (0.27%) |  |
| occurrences causally related to treatment / all               | 0 / 0          | 0 / 3            |  |
| deaths causally related to treatment / all                    | 0 / 0          | 0 / 0            |  |
| INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE |                |                  |  |
| subjects affected / exposed                                   | 1 / 96 (1.04%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all               | 0 / 1          | 0 / 1            |  |
| deaths causally related to treatment / all                    | 0 / 1          | 0 / 0            |  |
| LUNG INFECTION  |                |                  |  |
| subjects affected / exposed                                   | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all               | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all                    | 0 / 0          | 0 / 1            |  |
| UROSEPSIS   |                |                  |  |
| subjects affected / exposed                                   | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all               | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all                    | 0 / 0          | 0 / 0            |  |
| ABSCESS LIMB  |                |                  |  |



|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ACTINOMYCOSIS                                   |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ACUTE SINUSITIS                                 |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ENDOPHTHALMITIS                                 |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ERYSIPELAS                                      |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| GANGRENE  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| INFECTION                                       |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| MENINGITIS BACTERIAL                            |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| MORGANELLA INFECTION                            |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| ORBITAL INFECTION                               |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| PERIORBITAL CELLULITIS                          |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| PNEUMONIA BACTERIAL                             |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| SUBCUTANEOUS ABSCESS                            |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| Metabolism and nutrition disorders              |                |                  |  |
| CACHEXIA  |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 2            |  |
| DECREASED APPETITE                              |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| DEHYDRATION                                     |                |                  |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 4 / 1119 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 2 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| HYPERKALAEMIA                                   |                |                  |  |

|   |                |                  |  |
|---|----------------|------------------|--|
| subjects affected / exposed                     | 1 / 96 (1.04%) | 1 / 1119 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>HYPOGLYCAEMIA</b>                            |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 1119 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>HYPOKALAEMIA</b>                             |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 3 / 1119 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>HYPONATRAEMIA</b>                            |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 3 / 1119 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |
| <b>HYPERCALCAEMIA</b>                           |                |                  |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 3 / 1119 (0.27%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0            |  |

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

| <b>Non-serious adverse events</b>                     | Vismodegib - Metastatic | Vismodegib - Locally Advanced |  |
|---|-------------------------|-------------------------------|--|
| Total subjects affected by non-serious adverse events |                         |                               |  |
| subjects affected / exposed                           | 90 / 96 (93.75%)        | 1065 / 1119 (95.17%)          |  |
| <b>Investigations</b>                                 |                         |                               |  |
| <b>WEIGHT DECREASED</b>                               |                         |                               |  |
| subjects affected / exposed                           | 38 / 96 (39.58%)        | 471 / 1119 (42.09%)           |  |
| occurrences (all)                                     | 63                      | 774                           |  |
| <b>ALANINE AMINOTRANSFERASE INCREASED</b>             |                         |                               |  |
| subjects affected / exposed                           | 6 / 96 (6.25%)          | 54 / 1119 (4.83%)             |  |
| occurrences (all)                                     | 15                      | 69                            |  |
| <b>ASPARTATE AMINOTRANSFERASE INCREASED</b>           |                         |                               |  |

|  |                  |                     |  |
|--|------------------|---------------------|--|
| subjects affected / exposed                          | 7 / 96 (7.29%)   | 52 / 1119 (4.65%)   |  |
| occurrences (all)                                    | 15               | 66                  |  |
| BLOOD CREATINE PHOSPHOKINASE INCREASED               |                  |                     |  |
| subjects affected / exposed                          | 10 / 96 (10.42%) | 59 / 1119 (5.27%)   |  |
| occurrences (all)                                    | 23               | 129                 |  |
| GAMMA-GLUTAMYLTRANSFERASE INCREASED                  |                  |                     |  |
| subjects affected / exposed                          | 5 / 96 (5.21%)   | 55 / 1119 (4.92%)   |  |
| occurrences (all)                                    | 11               | 85                  |  |
| BLOOD CREATININE INCREASED                           |                  |                     |  |
| subjects affected / exposed                          | 6 / 96 (6.25%)   | 31 / 1119 (2.77%)   |  |
| occurrences (all)                                    | 8                | 43                  |  |
| Vascular disorders                                   |                  |                     |  |
| HYPERTENSION   |                  |                     |  |
| subjects affected / exposed                          | 6 / 96 (6.25%)   | 58 / 1119 (5.18%)   |  |
| occurrences (all)                                    | 6                | 86                  |  |
| Nervous system disorders                             |                  |                     |  |
| AGEUSIA  |                  |                     |  |
| subjects affected / exposed                          | 12 / 96 (12.50%) | 201 / 1119 (17.96%) |  |
| occurrences (all)                                    | 13               | 264                 |  |
| DIZZINESS  |                  |                     |  |
| subjects affected / exposed                          | 9 / 96 (9.38%)   | 66 / 1119 (5.90%)   |  |
| occurrences (all)                                    | 17               | 71                  |  |
| DYSGEUSIA  |                  |                     |  |
| subjects affected / exposed                          | 47 / 96 (48.96%) | 620 / 1119 (55.41%) |  |
| occurrences (all)                                    | 80               | 1007                |  |
| HEADACHE   |                  |                     |  |
| subjects affected / exposed                          | 9 / 96 (9.38%)   | 87 / 1119 (7.77%)   |  |
| occurrences (all)                                    | 12               | 109                 |  |
| General disorders and administration site conditions |                  |                     |  |
| ASTHENIA   |                  |                     |  |
| subjects affected / exposed                          | 19 / 96 (19.79%) | 276 / 1119 (24.66%) |  |
| occurrences (all)                                    | 29               | 411                 |  |
| FATIGUE  |                  |                     |  |

|   |                  |                        |  |
|---|------------------|------------------------|--|
| subjects affected / exposed                     | 16 / 96 (16.67%) | 185 / 1119<br>(16.53%) |  |
| occurrences (all)                               | 27               | 287                    |  |
| OEDEMA PERIPHERAL                               |                  |                        |  |
| subjects affected / exposed                     | 5 / 96 (5.21%)   | 34 / 1119 (3.04%)      |  |
| occurrences (all)                               | 7                | 36                     |  |
| Blood and lymphatic system disorders            |                  |                        |  |
| ANAEMIA   |                  |                        |  |
| subjects affected / exposed                     | 14 / 96 (14.58%) | 81 / 1119 (7.24%)      |  |
| occurrences (all)                               | 23               | 112                    |  |
| Gastrointestinal disorders                      |                  |                        |  |
| ABDOMINAL PAIN                                  |                  |                        |  |
| alternative dictionary used:<br>MedDRA 17.0     |                  |                        |  |
| subjects affected / exposed                     | 8 / 96 (8.33%)   | 78 / 1119 (6.97%)      |  |
| occurrences (all)                               | 10               | 101                    |  |
| ABDOMINAL PAIN UPPER                            |                  |                        |  |
| subjects affected / exposed                     | 6 / 96 (6.25%)   | 64 / 1119 (5.72%)      |  |
| occurrences (all)                               | 8                | 79                     |  |
| DIARRHOEA                                       |                  |                        |  |
| subjects affected / exposed                     | 18 / 96 (18.75%) | 183 / 1119<br>(16.35%) |  |
| occurrences (all)                               | 37               | 301                    |  |
| CONSTIPATION                                    |                  |                        |  |
| subjects affected / exposed                     | 14 / 96 (14.58%) | 107 / 1119 (9.56%)     |  |
| occurrences (all)                               | 18               | 152                    |  |
| NAUSEA  |                  |                        |  |
| subjects affected / exposed                     | 24 / 96 (25.00%) | 197 / 1119<br>(17.61%) |  |
| occurrences (all)                               | 38               | 290                    |  |
| VOMITING  |                  |                        |  |
| subjects affected / exposed                     | 6 / 96 (6.25%)   | 96 / 1119 (8.58%)      |  |
| occurrences (all)                               | 10               | 138                    |  |
| Respiratory, thoracic and mediastinal disorders |                  |                        |  |
| COUGH   |                  |                        |  |
| subjects affected / exposed                     | 12 / 96 (12.50%) | 64 / 1119 (5.72%)      |  |
| occurrences (all)                               | 19               | 71                     |  |
| DYSPNOEA  |                  |                        |  |

|  |                         |                             |  |
|--|-------------------------|-----------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 12 / 96 (12.50%)<br>16  | 26 / 1119 (2.32%)<br>29     |  |
| Skin and subcutaneous tissue disorders<br>ALOPECIA<br>subjects affected / exposed<br>occurrences (all)                     | 50 / 96 (52.08%)<br>78  | 700 / 1119 (62.56%)<br>972  |  |
| PRURITUS<br>subjects affected / exposed<br>occurrences (all)   | 9 / 96 (9.38%)<br>13    | 61 / 1119 (5.45%)<br>73     |  |
| ACTINIC KERATOSIS<br>subjects affected / exposed<br>occurrences (all)  | 5 / 96 (5.21%)<br>6     | 46 / 1119 (4.11%)<br>60     |  |
| Musculoskeletal and connective tissue disorders<br>ARTHRALGIA<br>subjects affected / exposed<br>occurrences (all)          | 9 / 96 (9.38%)<br>13    | 117 / 1119 (10.46%)<br>160  |  |
| BACK PAIN<br>subjects affected / exposed<br>occurrences (all)  | 7 / 96 (7.29%)<br>9     | 53 / 1119 (4.74%)<br>60     |  |
| MUSCLE SPASMS<br>subjects affected / exposed<br>occurrences (all)  | 62 / 96 (64.58%)<br>147 | 754 / 1119 (67.38%)<br>1801 |  |
| MUSCULOSKELETAL PAIN<br>subjects affected / exposed<br>occurrences (all)   | 8 / 96 (8.33%)<br>8     | 31 / 1119 (2.77%)<br>35     |  |
| PAIN IN EXTREMITY<br>subjects affected / exposed<br>occurrences (all)  | 9 / 96 (9.38%)<br>9     | 49 / 1119 (4.38%)<br>66     |  |
| MYALGIA<br>subjects affected / exposed<br>occurrences (all)  | 7 / 96 (7.29%)<br>10    | 78 / 1119 (6.97%)<br>111    |  |
| Infections and infestations<br>VIRAL UPPER RESPIRATORY TRACT INFECTION<br>subjects affected / exposed<br>occurrences (all) | 6 / 96 (6.25%)<br>8     | 55 / 1119 (4.92%)<br>77     |  |

|                                    |                  |                        |  |
|------------------------------------|------------------|------------------------|--|
| Metabolism and nutrition disorders |                  |                        |  |
| DECREASED APPETITE                 |                  |                        |  |
| subjects affected / exposed        | 23 / 96 (23.96%) | 283 / 1119<br>(25.29%) |  |
| occurrences (all)                  | 27               | 415                    |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 27 January 2012  | Key changes to the protocol included increasing the number of patients to be enrolled from 150 to 550 patients. The length of study was amended to include an end of treatment phase visit when a patient received their last dose of vismodegib and thereafter discontinued vismodegib (regardless of when it occurred), and one Safety Follow-Up Visit 30 days after the last dose of vismodegib.   |
| 08 November 2012 | Key changes to the protocol included increasing the number of patients to be enrolled from 550 to 800 patients. The length of study was amended to include five safety follow-up visits 1 month, 3 months, 6 months, 9 months and 12 months after the last dose of vismodegib (+/-5 days). Clarification was added regarding use of contraceptive methods during the study. Further details on the frequency of interim analyses and Data Safety Monitoring Board (DSMB) Committee reviews were also added to this version of the protocol.   |
| 08 May 2013      | Key changes to the protocol included increasing the number of patients to be enrolled from 800 to approximately 1200 patients. In addition, this amendment included increased number of interim analyses and increased stringency of contraception requirements. Following a request by the EMA, disease symptoms and tumor tissue of patients with metastatic disease were to be assessed following approval of this version of the protocol.  |
| 03 October 2013  | (EU) Key changes to the protocol included extension of enrollment to accrue additional patients with metastatic BCC to allow for an extension of enrollment above the 1200 patients previously planned in order to ensure that 10 – 15 patients with metastatic BCC were evaluated according to Protocol Amendment version 4 (dated 8 May 2013), which included additional assessments for metastatic BCC patients. In addition, post-treatment PK testing in a sub cohort of patients for a period of 12 months to further characterize the PK profile of vismodegib up to 12 months after dosing cessation, and PK testing for patients with persistent vismodegib related AEs (6 months after discontinuation of vismodegib) to further assess vismodegib exposure in these patients, were added during this amendment.                |
| 20 November 2013 | (Rest of the world) Key changes to the protocol included extension of enrollment to accrue additional patients with metastatic BCC to allow for an extension of enrollment above the 1200 patients previously planned in order to ensure that 10 – 15 patients with metastatic BCC were evaluated according to Protocol Amendment version 4 (dated 8 May 2013), which included additional assessments for metastatic BCC patients. In addition, post-treatment PK testing in a sub cohort of patients for a period of 12 months to further characterize the PK profile of vismodegib up to 12 months after dosing cessation, and PK testing for patients with persistent vismodegib related AEs (6 months after discontinuation of vismodegib) to further assess vismodegib exposure in these patients, were added during this amendment. |
| 04 April 2016    | Key changes to the protocol included revised pregnancy prevention duration and the waiting time for blood donations after vismodegib discontinuation from 7 to 9 months after the last dose of vismodegib.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No



## Limitations and caveats

None reported