



## Clinical trial results:

**A double-blind, randomized, placebo-controlled Phase III study to assess the efficacy of recMAGE-A3 + AS15 Antigen-Specific Cancer Immunotherapeutic as adjuvant therapy in patients with resectable MAGE-A3-positive Non-Small Cell Lung Cancer**

### Summary

|                          |  |
|--------------------------|--|
| EudraCT number           | 2007-001283-73                                     |
| Trial protocol           | BE DE IE FI ES SI FR SE GR IT LV AT NL HU CZ EE GB |
| Global end of trial date | 23 September 2014                                  |

### Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)  |
| This version publication date  | 13 December 2020  |
| First version publication date | 03 March 2016   |
| Version creation reason        | <ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Results have been amended to account for consistency with other registries. |

### Trial information

#### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 109493 |
|-----------------------|--------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00480025 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | GlaxoSmithKline Biologicals   |
| Sponsor organisation address | Rue de l'Institut 89, Rixensart, Belgium, B-1330  |
| Public contact               | Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.com |
| Scientific contact           | Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.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                       | 08 May 2015       |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 06 December 2013  |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 23 September 2014 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this Phase III study is to demonstrate the clinical efficacy (in terms of disease-free survival) of recMAGE-A3 + AS15 versus placebo in NSCLC after complete surgical resection.

three co-primary objectives are considered:

- Objective A: Efficacy in the overall population;
- Objective B: Efficacy in the population of patients who did not receive adjuvant chemotherapy (no-CT population).
- Objective C: Efficacy in the population of patients presenting the potentially favourable gene signature.

Protection of trial subjects:

Patients were observed closely for at least 30 minutes following treatment, with appropriate medical treatment readily available in case of a rare anaphylactic reaction. MAGE-A3 ASCI/placebo were administered by qualified and trained personnel, only to eligible subjects with no contraindications to any components of these products. During treatment, the following was checked to assess need to postpone treatment: acute disease at time of administration; any systemic grade  $\geq 2$  Common Terminology Criteria Adverse Event related or possibly related to treatment; fever, defined as an oral, axillary or tympanic temperature  $\leq 38^{\circ}\text{C}$ ; need for influenza vaccine, immunoglobulins and/or any blood products; any medical reason exposing the patient to unacceptable risk. Patients were required to discontinue treatment in case of evidence of disease relapse/occurrence of second primary lung cancer; treatment with either investigational or non-registered product other than MAGE-A3 ASCI study product or other anticancer treatments; anaphylactic reaction following treatment administration; any intolerable adverse event; clinical signs or symptoms indicative of any autoimmune disorder, except vitiligo; appearance of any confirmed or suspected immunosuppressive or immunodeficient condition, or any condition requiring use of any immunosuppressive agent or systemic corticosteroids prescribed for chronic use; inability of the patient to complete study evaluations due to unforeseen circumstances; other conditions indicating the patient's best interest to be withdrawn from treatment. In addition, between the end of the 120-weeks treatment phase, the following follow-up (FU) of patients was also planned: 1) an active FU for survival, recurrence, serious adverse events related to treatment & SAEs related to study participation and concurrent GSK medication of up to 5 years from the 1st treatment, and 2) annual contacts up to 10 years after 1st treatment.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 04 October 2007  |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 8 Years          |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |               |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Argentina: 10 |
|--------------------------------------|---------------|

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Australia: 25           |
| Country: Number of subjects enrolled | Brazil: 21              |
| Country: Number of subjects enrolled | Canada: 37              |
| Country: Number of subjects enrolled | Netherlands: 24         |
| Country: Number of subjects enrolled | Norway: 22              |
| Country: Number of subjects enrolled | Poland: 166             |
| Country: Number of subjects enrolled | Spain: 86               |
| Country: Number of subjects enrolled | Sweden: 12              |
| Country: Number of subjects enrolled | United Kingdom: 83      |
| Country: Number of subjects enrolled | Austria: 26             |
| Country: Number of subjects enrolled | Belgium: 35             |
| Country: Number of subjects enrolled | Czech Republic: 50      |
| Country: Number of subjects enrolled | Estonia: 57             |
| Country: Number of subjects enrolled | Finland: 9              |
| Country: Number of subjects enrolled | France: 107             |
| Country: Number of subjects enrolled | Germany: 268            |
| Country: Number of subjects enrolled | Greece: 97              |
| Country: Number of subjects enrolled | Hungary: 57             |
| Country: Number of subjects enrolled | Ireland: 8              |
| Country: Number of subjects enrolled | Italy: 113              |
| Country: Number of subjects enrolled | China: 159              |
| Country: Number of subjects enrolled | Hong Kong: 10           |
| Country: Number of subjects enrolled | India: 13               |
| Country: Number of subjects enrolled | Israel: 16              |
| Country: Number of subjects enrolled | Japan: 210              |
| Country: Number of subjects enrolled | Korea, Republic of: 108 |
| Country: Number of subjects enrolled | Russian Federation: 55  |
| Country: Number of subjects enrolled | Singapore: 1            |
| Country: Number of subjects enrolled | Switzerland: 11         |
| Country: Number of subjects enrolled | Taiwan: 31              |
| Country: Number of subjects enrolled | Thailand: 20            |
| Country: Number of subjects enrolled | Ukraine: 22             |
| Country: Number of subjects enrolled | United States: 343      |
| Worldwide total number of subjects   | 2312                    |
| EEA total number of subjects         | 1220                    |
| Notes:                               |                         |

### Subjects enrolled per age group

|   |      |
|---|------|
| In utero                                  | 0    |
| Preterm newborn - gestational age < 37 wk | 0    |
| Newborns (0-27 days)                      | 0    |
| Infants and toddlers (28 days-23 months)  | 0    |
| Children (2-11 years)                     | 0    |
| Adolescents (12-17 years)                 | 0    |
| Adults (18-64 years)                      | 1251 |
| From 65 to 84 years                       | 1055 |
| 85 years and over                         | 6    |

## Subject disposition

### Recruitment

Recruitment details:

A total of 2315 patients were screened towards participation in the study. For 3 of these subjects informed consent forms issues were reported, and thus only 2312 subjects were considered for analyses/results. Out of these 2312 subjects, 2278 were enrolled in the study.

### Pre-assignment

Screening details:

Out of the 2278 enrolled patients, only 2272 patients received at least one dose of study treatment (1515 received MAGE-A3 ASCI and 757 received placebo).

### Pre-assignment period milestones

|                              |      |
|------------------------------|------|
| Number of subjects started   | 2312 |
| Number of subjects completed | 2272 |

### Pre-assignment subject non-completion reasons

|                            |                 |
|----------------------------|-----------------|
| Reason: Number of subjects | Not treated: 40 |
|----------------------------|-----------------|

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Entire Study Period (overall period)         |
| Is this the baseline period? | Yes  |
| Allocation method            | Randomised - controlled                      |
| Blinding used                | Double blind                                 |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst |

Blinding implementation details:

Because the final establishment of the gene expression signature classifier by testing the samples on the training set was to only start after a positive interim analysis or after the final analysis of DFS in the overall/no-CT population, Disease Free Survival (DFS) in the GS+ population was to be analyzed at a later time point. Therefore, the Sponsor, investigators and patients should remain blinded to the treatment assignment until analysis of DFS in the GS+ population.

### Arms

|                              |                     |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes                 |
| Arm title                    | MAGE-A3 Total Group |

Arm description:

Patients received up to 13 doses (D) of MAGE-A3 ASCI, 5 Ds every 3 weeks followed by 8 Ds every 12 weeks.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | recMAGE-A3 recombinant protein formulated in AS15 adjuvant |
| Investigational medicinal product code | recMAGE-A3 + AS15  |
| Other name                             | MAGE-A3 ASCI, MAGE-A3 ASCI product, GSK1572932A            |
| Pharmaceutical forms                   | Powder and suspension for suspension for injection         |
| Routes of administration               | Intramuscular use  |

Dosage and administration details:

Up to 13 doses via intramuscular injections in the deltoid or lateral region of the thigh preferably alternating on right and left side.

|           |                     |
|-----------|---------------------|
| Arm title | Placebo Total Group |
|-----------|---------------------|

Arm description:

Patients received up to 13 doses (D) of placebo, 5 Ds every 3 weeks followed by 8 Ds every 12 weeks.

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|  |   |
|--|---|
| Investigational medicinal product name | Placebo   |
| Investigational medicinal product code |   |
| Other name                             | Sucrose reconstituted with an oil-in-water emulsion |
| Pharmaceutical forms                   | Powder and suspension for suspension for injection  |
| Routes of administration               | Intramuscular use                                   |

Dosage and administration details:

Up to 13 doses via intramuscular injections in the deltoid or lateral region of the thigh preferably alternating on right and left side.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | <b>MAGE-A3 Total Group</b> | <b>Placebo Total Group</b> |
|---|----------------------------|----------------------------|
| Started   | 1515                       | 757                        |
| Completed   | 763                        | 388                        |
| Not completed                                       | 752                        | 369                        |
| Adverse event, non-fatal                            | 44                         | 12                         |
| Disease Progression / Recurrence                    | 449                        | 224                        |
| SAE including intercurrent illness                  | 76                         | 42                         |
| Unspecified   | 70                         | 29                         |
| Protocol deviation                                  | 12                         | 7                          |
| Patients remaining ongoing at Data Lock Point       | 101                        | 55                         |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Out of the 2312 enrolled patients, not all started treatment, only 2272 patients started the trial.

## Baseline characteristics

### Reporting groups

|   |                     |
|---|---------------------|
| Reporting group title   | MAGE-A3 Total Group |
| Reporting group description:  |                     |
| Patients received up to 13 doses (D) of MAGE-A3 ASCI, 5 Ds every 3 weeks followed by 8 Ds every 12 weeks. |                     |
| Reporting group title   | Placebo Total Group |
| Reporting group description:  |                     |
| Patients received up to 13 doses (D) of placebo, 5 Ds every 3 weeks followed by 8 Ds every 12 weeks.      |                     |

| Reporting group values                             | MAGE-A3 Total Group | Placebo Total Group | Total |
|--|---------------------|---------------------|-------|
| Number of subjects                                 | 1515                | 757                 | 2272  |
| Age categorical                                    |                     |                     |       |
| Units: Subjects                                    |                     |                     |       |
| In utero   |                     |                     | 0     |
| Preterm newborn infants (gestational age < 37 wks) |                     |                     | 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)                               |                     |                     | 0     |
| From 65-84 years                                   |                     |                     | 0     |
| 85 years and over                                  |                     |                     | 0     |
| Age continuous                                     |                     |                     |       |
| Units: years                                       |                     |                     |       |
| arithmetic mean                                    | 63.1                | 63.4                |       |
| standard deviation                                 | ± 8.96              | ± 9.15              | -     |
| Gender categorical                                 |                     |                     |       |
| Units: Subjects                                    |                     |                     |       |
| Female   | 370                 | 179                 | 549   |
| Male   | 1145                | 578                 | 1723  |

### Subject analysis sets

|  |                     |
|--|---------------------|
| Subject analysis set title   | MAGE-A3 CT Group    |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:  |                     |
| Patients received up to 13 doses (D) of MAGE-A3 ASCI, 5 Ds every 3 weeks followed by 8 Ds every 12 weeks. Patients in this sub-group consisted solely of patients who had received adjuvant chemotherapy prior to randomization (CT Population). |                     |
| Subject analysis set title   | Placebo CT Group    |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:  |                     |
| Patients received up to 13 doses (D) of placebo, 5 Ds every 3 weeks followed by 8 Ds every 12 weeks. Patients in this sub-group consisted solely of patients who had received adjuvant chemotherapy prior to randomization (CT Population).      |                     |
| Subject analysis set title   | MAGE-A3 No-CT Group |
| Subject analysis set type  | Sub-group analysis  |

Subject analysis set description:

Patients received up to 13 doses (D) of MAGE-A3 ASCI, 5 Ds every 3 weeks followed by 8 Ds every 12 weeks. Patients in this sub-group consisted solely of patients who had not received adjuvant chemotherapy prior to randomization (No-CT Population).

|                            |                     |
|----------------------------|---------------------|
| Subject analysis set title | Placebo No-CT Group |
| Subject analysis set type  | Sub-group analysis  |

Subject analysis set description:

Patients received up to 13 doses (D) of placebo, 5 Ds every 3 weeks followed by 8 Ds every 12 weeks. Patients in this sub-group consisted solely of patients who had not received adjuvant chemotherapy prior to randomization (No-CT Population).

| Reporting group values  | MAGE-A3 CT Group | Placebo CT Group | MAGE-A3 No-CT Group |
|---|------------------|------------------|---------------------|
| Number of subjects  | 784              | 392              | 731                 |
| Age categorical<br>Units: Subjects  |                  |                  |                     |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                  |                  |                     |
| Age continuous<br>Units: years  |                  |                  |                     |
| arithmetic mean   | 61.1             | 61.1             | 65.3                |
| standard deviation  | ± 8.27           | ± 8.65           | ± 9.16              |
| Gender categorical<br>Units: Subjects   |                  |                  |                     |
| Female  | 185              | 97               | 185                 |
| Male  | 599              | 295              | 546                 |

| Reporting group values  | Placebo No-CT Group |  |  |
|---|---------------------|--|--|
| Number of subjects  | 365                 |  |  |
| Age categorical<br>Units: Subjects  |                     |  |  |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                     |  |  |
| Age continuous<br>Units: years  |                     |  |  |
| arithmetic mean   | 65.8                |  |  |

|                    |            |  |  |
|--------------------|------------|--|--|
| standard deviation | $\pm 9.07$ |  |  |
|--------------------|------------|--|--|

|                    |     |  |  |
|--------------------|-----|--|--|
| Gender categorical |     |  |  |
| Units: Subjects    |     |  |  |
| Female             | 82  |  |  |
| Male               | 283 |  |  |



## End points

### End points reporting groups

|  |                     |
|--|---------------------|
| Reporting group title  | MAGE-A3 Total Group |
| Reporting group description:<br>Patients received up to 13 doses (D) of MAGE-A3 ASCI, 5 Ds every 3 weeks followed by 8 Ds every 12 weeks.  |                     |
| Reporting group title  | Placebo Total Group |
| Reporting group description:<br>Patients received up to 13 doses (D) of placebo, 5 Ds every 3 weeks followed by 8 Ds every 12 weeks.   |                     |
| Subject analysis set title   | MAGE-A3 CT Group    |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:<br>Patients received up to 13 doses (D) of MAGE-A3 ASCI, 5 Ds every 3 weeks followed by 8 Ds every 12 weeks. Patients in this sub-group consisted solely of patients who had received adjuvant chemotherapy prior to randomization (CT Population).        |                     |
| Subject analysis set title   | Placebo CT Group    |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:<br>Patients received up to 13 doses (D) of placebo, 5 Ds every 3 weeks followed by 8 Ds every 12 weeks. Patients in this sub-group consisted solely of patients who had received adjuvant chemotherapy prior to randomization (CT Population).             |                     |
| Subject analysis set title   | MAGE-A3 No-CT Group |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:<br>Patients received up to 13 doses (D) of MAGE-A3 ASCI, 5 Ds every 3 weeks followed by 8 Ds every 12 weeks. Patients in this sub-group consisted solely of patients who had not received adjuvant chemotherapy prior to randomization (No-CT Population). |                     |
| Subject analysis set title   | Placebo No-CT Group |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:<br>Patients received up to 13 doses (D) of placebo, 5 Ds every 3 weeks followed by 8 Ds every 12 weeks. Patients in this sub-group consisted solely of patients who had not received adjuvant chemotherapy prior to randomization (No-CT Population).      |                     |

### Primary: Person year rate (PYAR) as regards disease-free survival (DFS) in the overall population

|   |  |
|---|--|
| End point title   | Person year rate (PYAR) as regards disease-free survival (DFS) in the overall population |
| End point description:<br>DFS = time interval from randomization to 1st evidence of recurrence/death, if occurring before. All recurrence types were included, including local, regional & distant metastasis & 2nd primary lung cancer (i.e. local recurrence, defined as a tumor within same lung or at bronchial stump; regional recurrence, involving a clinically or radiologically manifest disease in mediastinum or supraclavicular nodes; & distant recurrence [any tumor arising in contralateral lung or outside hemithorax]). Deaths occurring without prior documentation of recurrence were considered as event & not censored. If no event occurred by time of analysis, time to event was censored at last assessment date of patient. New 1ry cancers outside lungs were not considered as event. $PYAR = n$ (=number of subjects reported with at least 1 event) divided by $T$ (=sum of follow-up period [in years] censored at 1st occurrence of event in group). Median DFS estimates were obtained non-parametrically by Kaplan-Meier method. |  |
| End point type  | Primary  |
| End point timeframe:<br>Period of follow-up was from administration of first dose of MAGE-A3 ASCI study product/placebo solution to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)  |  |

| <b>End point values</b>       | MAGE-A3 Total Group | Placebo Total Group |  |  |
|-------------------------------|---------------------|---------------------|--|--|
| Subject group type            | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed   | 1515                | 757                 |  |  |
| Units: events/person-years    |                     |                     |  |  |
| number (not applicable)       |                     |                     |  |  |
| DFS PYAR – Overall Population | 0.17                | 0.168               |  |  |

## Statistical analyses

| <b>Statistical analysis title</b> | DFS Comparing MAGE-A3 vs placebo – All Patients |
|-----------------------------------|---|
|-----------------------------------|---|

Statistical analysis description:

Analysis compared DFS PYAR between groups for period from 1st treatment dose to DLP. A Cox model was used to evaluate treatment efficacy (TE). TE was calculated as PYAR in MAGE-A3 Total Group (PYAR1) divided by PYAR in Placebo Total Group (PYAR2), and weighed for adjustment factors. This comparison in all patients (overall population) also included taking into account stratification by previous CT vs. No-CT treatment and weighing using randomization-minimization factors (RMF) as regressors.

|   |   |
|---|---|
| Comparison groups                       | MAGE-A3 Total Group v Placebo Total Group |
| Number of subjects included in analysis | 2272                                      |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority <sup>[1]</sup>                |
| P-value                                 | = 0.7379 <sup>[2]</sup>                   |
| Method                                  | Regression, Cox                           |
| Parameter estimate                      | TE  |
| Point estimate                          | 1.024                                     |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | 0.891                                     |
| upper limit                             | 1.177                                     |

Notes:

[1] - RMF taken into account included: 1) Number of chemotherapy cycles received (1, 2 vs. 3, 4), if any; 2) Pathological stage of the disease (IB vs. II vs. IIIA); 3) Type of lymph-node sampling (minimal lymph-node sampling vs. systematic radical mediastinal lymphadenectomy); 4) ECOG performance status randomization (0, 1 vs. 2); 5) Smoking status ( 100 cigarettes a lifetime vs. > 100 cigarettes and current smoker vs. > 100 cigarettes and past smoker).

[2] - 2-sided p-value of Likelihood Ratio test from RMF-adjusted Cox regression, Efron method used to handle ties. Overall population objective reached if p-value < 2%/4% in absence/presence of statistically significant effect in the No-CT population.

## Primary: Person year rate (PYAR) as regards disease-free survival (DFS) in the No-CT population

|                 |  |
|-----------------|--|
| End point title | Person year rate (PYAR) as regards disease-free survival (DFS) in the No-CT population |
|-----------------|--|

End point description:

DFS = time interval from randomization to 1st evidence of recurrence/death, if occurring before. All recurrence types were included, including local, regional & distant metastasis & 2nd primary lung cancer (i.e. local recurrence, defined as a tumor within same lung or at bronchial stump; regional recurrence, involving a clinically or radiologically manifest disease in mediastinum or supraclavicular nodes; & distant recurrence [any tumor arising in contralateral lung or outside hemithorax]). Deaths occurring without prior documentation of recurrence were considered as event & not censored. If no event

occurred by time of analysis, time to event was censored at last assessment date of patient. New 1ry cancers outside lungs were not considered as event.  $PYAR = n$  (=number of subjects reported with at least 1 event) divided by  $T$  (=sum of follow-up period [in years] censored at 1st occurrence of event in group). Median DFS estimates were obtained non-parametrically by Kaplan-Meier method.

|  |         |
|--|---------|
| End point type   | Primary |
| End point timeframe:   |         |
| Period of follow-up was from administration of first dose of MAGE-A3 ASCI study product/placebo solution to data lock point (DLP) on 23 January 2014 (up to 5 years per patient) |         |

| End point values            | MAGE-A3 No-CT Group  | Placebo No-CT Group  |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 731                  | 365                  |  |  |
| Units: events/person-years  |                      |                      |  |  |
| number (not applicable)     |                      |                      |  |  |
| DFS PYAR – No-CT Population | 0.169                | 0.178                |  |  |

## Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | DFS Comparing MAGE-A3 vs placebo – No-CT Patients |
|----------------------------|---|

Statistical analysis description:

Analysis compared DFS PYAR between groups for the period from 1st treatment dose to DLP. A Cox model was used to evaluate treatment efficacy (TE). TE was calculated as PYAR in MAGE-A3 No-CT Group (PYAR1) divided by PYAR in Placebo No-CT Group (PYAR2) and weighed for adjustment factors. This comparison in all patients (overall population) also included taking into account weighing using randomization-minimization factors (RMF) as regressors.

|   |   |
|---|---|
| Comparison groups                       | MAGE-A3 No-CT Group v Placebo No-CT Group |
| Number of subjects included in analysis | 1096                                      |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority <sup>[3]</sup>                |
| P-value                                 | = 0.7572 <sup>[4]</sup>                   |
| Method                                  | Regression, Cox                           |
| Parameter estimate                      | TE  |
| Point estimate                          | 0.97                                      |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | 0.797                                     |
| upper limit                             | 1.179                                     |

Notes:

[3] - RMF included: 1) Number of chemotherapy cycles received (1, 2 vs. 3, 4), if any; 2) Pathological stage of the disease (IB vs. II vs. IIIA); 3) Type of lymph-node sampling (minimal lymph-node sampling vs. systematic radical mediastinal lymphadenectomy); 4) ECOG performance status randomization (0, 1 vs. 2); 5) Smoking status ( 100 cigarettes a lifetime vs. > 100 cigarettes and current smoker vs. > 100 cigarettes and past smoker).

[4] - 2-sided p-value of Likelihood Ratio test from RMF-adjusted Cox regression, Efron method used to handle ties. No-CT population objective reached if p-value < 2.56%/4% in absence/presence of statistically significant effect in the No-CT population.

## Secondary: Person year rate (PYAR) as regards disease-free survival (DFS) in the CT population

|   |   |
|---|---|
| End point title   | Person year rate (PYAR) as regards disease-free survival (DFS) in the CT population |
| End point description:  |   |
| DFS = time interval from randomization to 1st evidence of recurrence/death, if occurring before. All recurrence types were included, including local, regional & distant metastasis & 2nd primary lung cancer (i.e. local recurrence, defined as a tumor within same lung or at bronchial stump; regional recurrence, involving a clinically or radiologically manifest disease in mediastinum or supraclavicular nodes; & distant recurrence [any tumor arising in contralateral lung or outside hemithorax]). Deaths occurring without prior documentation of recurrence were considered as event & not censored. If no event occurred by time of analysis, time to event was censored at last assessment date of patient. New 1ry cancers outside lungs were not considered as event. PYAR = n (=number of subjects reported with at least 1 event) divided by T (=sum of follow-up period [in years] censored at 1st occurrence of event in group). Median DFS estimates were obtained non-parametrically by Kaplan-Meier method. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Period of follow-up was from administration of first dose of MAGE-A3 ASCI study product/placebo solution to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)  |   |

| End point values            | MAGE-A3 CT Group     | Placebo CT Group     |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 784                  | 392                  |  |  |
| Units: events/person-years  |                      |                      |  |  |
| number (not applicable)     |                      |                      |  |  |
| DFS PYAR – CT Population    | 0.172                | 0.158                |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Person year rate (PYAR) as regards overall-survival (OS) in the overall population

|  |  |
|--|--|
| End point title  | Person year rate (PYAR) as regards overall-survival (OS) in the overall population |
| End point description:   |  |
| OS was defined as the time interval from randomization to the date of death, irrespective of the cause of death. Patients still alive were censored at the last visit they were known to be alive. PYAR = n (=number of subjects reported with at least 1 event) divided by T (=sum of follow-up period [in years] censored at 1st occurrence of event in group). Median OS estimates were obtained non-parametrically by Kaplan-Meier method. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Period of follow-up was from administration of first dose of MAGE-A3 ASCI study product/placebo solution to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)   |  |

| End point values             | MAGE-A3 Total Group | Placebo Total Group |  |  |
|------------------------------|---------------------|---------------------|--|--|
| Subject group type           | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed  | 1515                | 757                 |  |  |
| Units: events/person-years   |                     |                     |  |  |
| number (not applicable)      |                     |                     |  |  |
| OS PYAR – Overall Population | 0.082               | 0.081               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Person year rate (PYAR) as regards overall-survival (OS) in the No-CT population

|                 |  |
|-----------------|--|
| End point title | Person year rate (PYAR) as regards overall-survival (OS) in the No-CT population |
|-----------------|--|

End point description:

OS was defined as the time interval from randomization to the date of death, irrespective of the cause of death. Patients still alive were censored at the last visit they were known to be alive.  $PYAR = n$  (=number of subjects reported with at least 1 event) divided by  $T$  (=sum of follow-up period [in years] censored at 1st occurrence of event in group). Median OS estimates were obtained non-parametrically by Kaplan-Meier method.

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

End point timeframe:

Period of follow-up was from administration of first dose of MAGE-A3 ASCI study product/placebo solution to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

| End point values            | MAGE-A3 No-CT Group  | Placebo No-CT Group  |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 731                  | 365                  |  |  |
| Units: events/person-years  |                      |                      |  |  |
| number (not applicable)     |                      |                      |  |  |
| OS PYAR – No-CT Population  | 0.084                | 0.086                |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Person year rate (PYAR) as regards overall-survival (OS) in the CT population

|                 |   |
|-----------------|---|
| End point title | Person year rate (PYAR) as regards overall-survival (OS) in the CT population |
|-----------------|---|

End point description:

OS was defined as the time interval from randomization to the date of death, irrespective of the cause of death. Patients still alive were censored at the last visit they were known to be alive.  $PYAR = n$  (=number of subjects reported with at least 1 event) divided by  $T$  (=sum of follow-up period [in years] censored at 1st occurrence of event in group). Median OS estimates were obtained non-parametrically

by Kaplan-Meier method.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Period of follow-up was from administration of first dose of MAGE-A3 ASCI study product/placebo solution to data lock point (DLP) on 23 January 2014 (up to 5 years per patient) |           |

| End point values            | MAGE-A3 CT Group     | Placebo CT Group     |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 784                  | 392                  |  |  |
| Units: events/person-years  |                      |                      |  |  |
| number (not applicable)     |                      |                      |  |  |
| OS PYAR – CT Population     | 0.08                 | 0.076                |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Person year rate (PYAR) as regards lung-cancer specific survival (LCSS) in the Overall population

|                 |   |
|-----------------|---|
| End point title | Person year rate (PYAR) as regards lung-cancer specific survival (LCSS) in the Overall population |
|-----------------|---|

End point description:

LCSS was defined as the time interval from randomization to the date of death due to lung cancer. Deaths due to other or unknown causes were censored at the date of death.  $PYAR = n$  (=number of subjects reported with at least 1 event) divided by  $T$  (=sum of follow-up period [in years] censored at 1st occurrence of event in group). Median OS estimates were obtained non-parametrically by Kaplan-Meier method.

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

End point timeframe:

Period of follow-up was from administration of first dose of MAGE-A3 ASCI study product/placebo solution to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

| End point values               | MAGE-A3 Total Group | Placebo Total Group |  |  |
|--------------------------------|---------------------|---------------------|--|--|
| Subject group type             | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed    | 1515                | 757                 |  |  |
| Units: events/person-years     |                     |                     |  |  |
| number (not applicable)        |                     |                     |  |  |
| LCSS PYAR – Overall Population | 0.064               | 0.061               |  |  |

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Person year rate (PYAR) as regards lung-cancer specific survival (LCSS) in the No-CT population**

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|                 |   |
|-----------------|---|
| End point title | Person year rate (PYAR) as regards lung-cancer specific survival (LCSS) in the No-CT population |
|-----------------|---|

End point description:

LCSS was defined as the time interval from randomization to the date of death due to lung cancer. Deaths due to other or unknown causes were censored at the date of death.  $PYAR = n$  (=number of subjects reported with at least 1 event) divided by  $T$  (=sum of follow-up period [in years] censored at 1st occurrence of event in group). Median OS estimates were obtained non-parametrically by Kaplan-Meier method.

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

End point timeframe:

Period of follow-up was from administration of first dose of MAGE-A3 ASCI study product/placebo solution to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

---

| End point values             | MAGE-A3 No-CT Group  | Placebo No-CT Group  |  |  |
|------------------------------|----------------------|----------------------|--|--|
| Subject group type           | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed  | 731                  | 365                  |  |  |
| Units: events/person-years   |                      |                      |  |  |
| number (not applicable)      |                      |                      |  |  |
| LCSS PYAR – No-CT Population | 0.064                | 0.06                 |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Person year rate (PYAR) as regards lung-cancer specific survival (LCSS) in the CT population**

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|                 |  |
|-----------------|--|
| End point title | Person year rate (PYAR) as regards lung-cancer specific survival (LCSS) in the CT population |
|-----------------|--|

End point description:

LCSS was defined as the time interval from randomization to the date of death due to lung cancer. Deaths due to other or unknown causes were censored at the date of death.  $PYAR = n$  (=number of subjects reported with at least 1 event) divided by  $T$  (=sum of follow-up period [in years] censored at 1st occurrence of event in group). Median OS estimates were obtained non-parametrically by Kaplan-Meier method.

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

End point timeframe:

Period of follow-up was from administration of first dose of MAGE-A3 ASCI study product/placebo solution to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

---

| End point values            | MAGE-A3 CT Group     | Placebo CT Group     |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 784                  | 392                  |  |  |
| Units: events/person-years  |                      |                      |  |  |
| number (not applicable)     |                      |                      |  |  |
| LCSS PYAR – CT Population   | 0.063                | 0.063                |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Kaplan-Meier estimate (KME) of 2, 3, 4 and 5-year as regards disease-free survival (DFS) in the overall population

|                 |  |
|-----------------|--|
| End point title | Kaplan-Meier estimate (KME) of 2, 3, 4 and 5-year as regards disease-free survival (DFS) in the overall population |
|-----------------|--|

End point description:

DFS = time interval from randomization to 1st evidence of recurrence/death, if occurring before. All recurrence types were included, including local, regional & distant metastasis & 2nd primary lung cancer (i.e. local recurrence, defined as a tumor within same lung or at bronchial stump; regional recurrence, involving a clinically or radiologically manifest disease in mediastinum or supraclavicular nodes; & distant recurrence [any tumor arising in contralateral lung or outside hemithorax]). Deaths occurring without prior documentation of recurrence were considered as event & not censored. If no event occurred by time of analysis, time to event was censored at last assessment date of patient. New 1ry cancers outside lungs were not considered as event. Median DFS KMEs in % were obtained non-parametrically by Kaplan-Meier method and confidence intervals (CIs) calculated using the Greenwood formula for standard error computation.

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

End point timeframe:

KME assessed at 2, 3, 4 and 5-year (Y) post Dose 1 of treatment. Follow-up period was from administration of 1st dose of MAGE-A3 ASCI study product/placebo solution to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

| End point values                   | MAGE-A3 Total Group    | Placebo Total Group    |  |  |
|------------------------------------|------------------------|------------------------|--|--|
| Subject group type                 | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed        | 1515                   | 757                    |  |  |
| Units: percent probability         |                        |                        |  |  |
| median (confidence interval 95%)   |                        |                        |  |  |
| DFS KME at 2Y – Overall Population | 65.57 (63.08 to 67.95) | 65.5 (61.94 to 68.81)  |  |  |
| DFS KME at 3Y – Overall Population | 59.97 (57.3 to 62.53)  | 60.42 (56.62 to 64)    |  |  |
| DFS KME at 4Y – Overall Population | 56.72 (53.8 to 59.54)  | 57.19 (53.07 to 61.1)  |  |  |
| DFS KME at 5Y – Overall Population | 51.73 (47.66 to 55.64) | 49.56 (42.87 to 55.88) |  |  |

## Statistical analyses



**Secondary: Kaplan-Meier estimate (KME) of 2, 3, 4 and 5-year as regards disease-free survival (DFS) in the No-CT population**

|                 |  |
|-----------------|--|
| End point title | Kaplan-Meier estimate (KME) of 2, 3, 4 and 5-year as regards disease-free survival (DFS) in the No-CT population |
|-----------------|--|

## End point description:

DFS = time interval from randomization to 1st evidence of recurrence/death, if occurring before. All recurrence types were included, including local, regional & distant metastasis & 2nd primary lung cancer (i.e. local recurrence, defined as a tumor within same lung or at bronchial stump; regional recurrence, involving a clinically or radiologically manifest disease in mediastinum or supraclavicular nodes; & distant recurrence [any tumor arising in contralateral lung or outside hemithorax]). Deaths occurring without prior documentation of recurrence were considered as event & not censored. If no event occurred by time of analysis, time to event was censored at last assessment date of patient. New 1ry cancers outside lungs were not considered as event. Median DFS KMEs in % were obtained non-parametrically by Kaplan-Meier method and confidence intervals (CIs) calculated using the Greenwood formula for standard error computation.

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

## End point timeframe:

KME assessed at 2, 3, 4 and 5-year (Y) post Dose 1 of treatment. Follow-up period was from administration of 1st dose of MAGE-A3 ASCI study product/placebo solution to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

| End point values                 | MAGE-A3 No-CT Group    | Placebo No-CT Group    |  |  |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type               | Subject analysis set   | Subject analysis set   |  |  |
| Number of subjects analysed      | 731                    | 365                    |  |  |
| Units: percent probability       |                        |                        |  |  |
| median (confidence interval 95%) |                        |                        |  |  |
| DFS KME at 2Y – No-CT Population | 66.03 (62.39 to 69.4)  | 63.96 (58.72 to 68.72) |  |  |
| DFS KME at 3Y – No-CT Population | 59.6 (55.7 to 63.27)   | 57.62 (52.02 to 62.81) |  |  |
| DFS KME at 4Y – No-CT Population | 55.4 (51.06 to 59.52)  | 54.85 (48.98 to 60.33) |  |  |
| DFS KME at 5Y – No-CT Population | 49.72 (43.44 to 55.67) | 44.59 (34.64 to 54.05) |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Kaplan-Meier estimate (KME) of 2, 3, 4 and 5-year as regards disease-free survival (DFS) in the CT population**

|                 |   |
|-----------------|---|
| End point title | Kaplan-Meier estimate (KME) of 2, 3, 4 and 5-year as regards disease-free survival (DFS) in the CT population |
|-----------------|---|

## End point description:

DFS = time interval from randomization to 1st evidence of recurrence/death, if occurring before. All recurrence types were included, including local, regional & distant metastasis & 2nd primary lung cancer (i.e. local recurrence, defined as a tumor within same lung or at bronchial stump; regional recurrence, involving a clinically or radiologically manifest disease in mediastinum or supraclavicular nodes; & distant recurrence [any tumor arising in contralateral lung or outside hemithorax]). Deaths occurring without prior documentation of recurrence were considered as event & not censored. If no event

occurred by time of analysis, time to event was censored at last assessment date of patient. New 1ry cancers outside lungs were not considered as event. Median DFS KMEs in % were obtained non-parametrically by Kaplan-Meier method and confidence intervals (CIs) calculated using the Greenwood formula for standard error computation.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| KME assessed at 2, 3, 4 and 5-year (Y) post Dose 1 of treatment. Follow-up period was from administration of 1st dose of MAGE-A3 ASCI study product/placebo solution to data lock point (DLP) on 23 January 2014 (up to 5 years per patient) |           |

| End point values                 | MAGE-A3 CT Group       | Placebo CT Group       |  |  |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type               | Subject analysis set   | Subject analysis set   |  |  |
| Number of subjects analysed      | 784                    | 392                    |  |  |
| Units: percent probability       |                        |                        |  |  |
| median (confidence interval 95%) |                        |                        |  |  |
| DFS KME at 2Y – CT Population    | 65.17 (61.67 to 68.43) | 66.94 (61.98 to 71.41) |  |  |
| DFS KME at 3Y – CT Population    | 60.39 (56.68 to 63.89) | 63.09 (57.84 to 67.87) |  |  |
| DFS KME at 4Y – CT Population    | 58.17 (54.22 to 61.9)  | 59.3 (53.33 to 64.76)  |  |  |
| DFS KME at 5Y – CT Population    | 53.64 (48.28 to 58.7)  | 54.8 (46.44 to 62.39)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Person year rate (PYAR) as regards disease-free specific survival (DFSS) in the overall population

|                 |  |
|-----------------|--|
| End point title | Person year rate (PYAR) as regards disease-free specific survival (DFSS) in the overall population |
|-----------------|--|

End point description:

DFSS was defined as the interval from randomization to the date of disease recurrence or death due to lung cancer. Patients who had died due to another cause than lung cancer were censored on their date of death and patients alive at the time of analysis were censored on the date of last assessment. Patients with no assessment post-randomization were censored on the date of randomization.  $PYAR = n$  (=number of subjects reported with at least 1 event) divided by T (=sum of follow-up period [in years] censored at 1st occurrence of event in group). Median DFS estimates were obtained non-parametrically by Kaplan-Meier method.

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

End point timeframe:

Period of follow-up was from administration of first dose of MAGE-A3 ASCI study product/placebo solution to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

| End point values               | MAGE-A3 Total Group | Placebo Total Group |  |  |
|--------------------------------|---------------------|---------------------|--|--|
| Subject group type             | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed    | 1515                | 757                 |  |  |
| Units: events/person-years     |                     |                     |  |  |
| number (not applicable)        |                     |                     |  |  |
| DFSS PYAR – Overall Population | 0.159               | 0.154               |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Person year rate (PYAR) as regards disease-free specific survival (DFSS) in the No-CT population

|                 |  |
|-----------------|--|
| End point title | Person year rate (PYAR) as regards disease-free specific survival (DFSS) in the No-CT population |
|-----------------|--|

End point description:

DFSS was defined as the interval from randomization to the date of disease recurrence or death due to lung cancer. Patients who had died due to another cause than lung cancer were censored on their date of death and patients alive at the time of analysis were censored on the date of last assessment. Patients with no assessment post-randomization were censored on the date of randomization.  $PYAR = n$  (=number of subjects reported with at least 1 event) divided by T (=sum of follow-up period [in years] censored at 1st occurrence of event in group). Median DFS estimates were obtained non-parametrically by Kaplan-Meier method.

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

End point timeframe:

Period of follow-up was from administration of first dose of MAGE-A3 ASCI study product/placebo solution to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

| End point values             | MAGE-A3 No-CT Group  | Placebo No-CT Group  |  |  |
|------------------------------|----------------------|----------------------|--|--|
| Subject group type           | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed  | 731                  | 365                  |  |  |
| Units: events/person-years   |                      |                      |  |  |
| number (not applicable)      |                      |                      |  |  |
| DFSS PYAR – No-CT Population | 0.155                | 0.159                |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Person year rate (PYAR) as regards disease-free specific survival (DFSS) in the CT population

|                 |   |
|-----------------|---|
| End point title | Person year rate (PYAR) as regards disease-free specific survival (DFSS) in the CT population |
|-----------------|---|

End point description:

DFSS was defined as the interval from randomization to the date of disease recurrence or death due to lung cancer. Patients who had died due to another cause than lung cancer were censored on their date

of death and patients alive at the time of analysis were censored on the date of last assessment. Patients with no assessment post-randomization were censored on the date of randomization. PYAR = n (=number of subjects reported with at least 1 event) divided by T (=sum of follow-up period [in years] censored at 1st occurrence of event in group). Median DFS estimates were obtained non-parametrically by Kaplan-Meier method.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Period of follow-up was from administration of first dose of MAGE-A3 ASCI study product/placebo solution to data lock point (DLP) on 23 January 2014 (up to 5 years per patient) |           |

| End point values            | MAGE-A3 CT Group     | Placebo CT Group     |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 784                  | 392                  |  |  |
| Units: events/person-years  |                      |                      |  |  |
| number (not applicable)     |                      |                      |  |  |
| DFSS PYAR – CT Population   | 0.162                | 0.149                |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects seropositive for anti-Melanoma AntiGen (MAGE)-A3 antibodies (Anti-MAGE-A3 S+)

|                 |  |
|-----------------|--|
| End point title | Number of subjects seropositive for anti-Melanoma AntiGen (MAGE)-A3 antibodies (Anti-MAGE-A3 S+) |
|-----------------|--|

End point description:

A seropositive subject for anti-MAGE-A3 antibodies was a subject with anti-MAGE-A3 antibodies  $\geq$  the seropositivity cut-off of 27 Enzyme-linked immunosorbent assay (ELISA) units per millilitre (EL.U/mL).

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Pre-treatment (PRE), at Weeks (W) 6 and 12, at Months (M) 9, 12, 18 and 30 and at one year after treatment concluding time point, i.e. at follow-up visit 2 at W120 added of one year (At 12M post W120) |           |

| End point values                  | MAGE-A3 Total Group | Placebo Total Group |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 1184                | 614                 |  |  |
| Units: Subjects                   |                     |                     |  |  |
| Anti-MAGE-A3 S+, PRE (N=1184;614) | 105                 | 53                  |  |  |
| Anti-MAGE-A3 S+, W6 (N=945;548)   | 929                 | 43                  |  |  |
| Anti-MAGE-A3 S+, W12 (N=925;491)  | 921                 | 42                  |  |  |
| Anti-MAGE-A3 S+, M9 (N=633;352)   | 631                 | 30                  |  |  |
| Anti-MAGE-A3 S+, M12 (N=538;279)  | 536                 | 19                  |  |  |
| Anti-MAGE-A3 S+, M18 (N=420;229)  | 419                 | 15                  |  |  |
| Anti-MAGE-A3 S+, M30 (N=384;222)  | 383                 | 17                  |  |  |

|  |    |   |  |  |
|--|----|---|--|--|
| Anti-MAGE-A3 S+, at 12M post W120<br>(N=76;47) | 75 | 5 |  |  |
|--|----|---|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of humoral responders as regards anti-Melanoma AntiGen (MAGE)-A3 antibodies (Anti-MAGE-A3 HR)

|                 |  |
|-----------------|--|
| End point title | Number of humoral responders as regards anti-Melanoma AntiGen (MAGE)-A3 antibodies (Anti-MAGE-A3 HR) |
|-----------------|--|

End point description:

A seropositive/seronegative subject for anti-MAGE-A3 antibodies was a subject with anti-MAGE-A3 antibodies  $\geq$ / $<$  the seropositivity cut-off of 27 Enzyme-linked immunosorbent assay (ELISA) units per millilitre (EL.U/mL). A humoral responder as regards anti-MAGE-A3 antibodies was defined as 1) for initially seronegative patients, a patient with post-administration Anti-MAGE-A3 antibody concentration  $\geq$  27 EL.U/mL; 2) for initially seropositive patients: post-treatment administration antibody concentration  $\geq$  2 fold the pre-treatment antibody concentration.

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

End point timeframe:

At Weeks (W) 6 and 12, at Months (M) 9, 12, 18 and 30 and at one year after treatment concluding time point, i.e. at follow-up visit 2 at W120 added of one year (at 12M post W120)

| End point values                               | MAGE-A3 Total Group | Placebo Total Group |  |  |
|--|---------------------|---------------------|--|--|
| Subject group type                             | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed                    | 942                 | 548                 |  |  |
| Units: Subjects                                |                     |                     |  |  |
| Anti-MAGE-A3 HR, W6 (N=942;548)                | 922                 | 10                  |  |  |
| Anti-MAGE-A3 HR, W12 (N=920;491)               | 916                 | 15                  |  |  |
| Anti-MAGE-A3 HR, M9 (N=630;352)                | 627                 | 13                  |  |  |
| Anti-MAGE-A3 HR, M12 (N=537;279)               | 534                 | 6                   |  |  |
| Anti-MAGE-A3 HR, M18 (N=420;229)               | 417                 | 7                   |  |  |
| Anti-MAGE-A3 HR, M30 (N=382;222)               | 380                 | 8                   |  |  |
| Anti-MAGE-A3 HR, at 12M post W120<br>(N=76;47) | 75                  | 3                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects seropositive for anti-protein D (PD) antibodies (Anti-PD S+)

|                 |   |
|-----------------|---|
| End point title | Number of subjects seropositive for anti-protein D (PD) antibodies (Anti-PD S+) |
|-----------------|---|

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**End point description:**

A seropositive subject for anti-PD antibodies was a subject with anti-PD antibodies  $\geq$  the seropositivity cut-off of 100 Enzyme-linked immunosorbent assay (ELISA) units per millilitre (EL.U/mL).

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

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**End point timeframe:**

Pre-treatment (PRE), at Weeks (W) 6 and 12, at Months (M) 9, 12, 18 and 30 and at one year after treatment concluding time point, i.e. at follow-up visit 2 at W120 added of one year (at 12M post W120)

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| End point values                       | MAGE-A3 Total Group | Placebo Total Group |  |  |
|--|---------------------|---------------------|--|--|
| Subject group type                     | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed            | 1096                | 554                 |  |  |
| Units: Subjects                        |                     |                     |  |  |
| Anti-PD S+, PRE (N=1096;554)           | 381                 | 210                 |  |  |
| Anti-PD S+, W6 (N=967;493)             | 958                 | 195                 |  |  |
| Anti-PD S+, W12 (N=864;436)            | 860                 | 176                 |  |  |
| Anti-PD S+, M9 (N=582;311)             | 580                 | 133                 |  |  |
| Anti-PD S+, M12 (N=485;243)            | 483                 | 101                 |  |  |
| Anti-PD S+, M18 (N=376;197)            | 375                 | 77                  |  |  |
| Anti-PD S+, M30 (N=358;189)            | 357                 | 75                  |  |  |
| Anti-PD S+, at 12M post W120 (N=78;46) | 77                  | 17                  |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Number of humoral responders as regards anti-protein D (PD) antibodies (Anti-PD HR)**

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|                 |   |
|-----------------|---|
| End point title | Number of humoral responders as regards anti-protein D (PD) antibodies (Anti-PD HR) |
|-----------------|---|

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**End point description:**

A seropositive/seronegative subject for anti-PD antibodies was a subject with anti-PD antibodies  $\geq$ / $<$  the seropositivity cut-off of 100 Enzyme-linked immunosorbent assay (ELISA) units per millilitre (EL.U/mL). A humoral responder as regards anti-PD antibodies was defined as 1) for initially seronegative patients, a patient with post-administration anti-PD antibody concentration  $\geq$  100 EL.U/mL; 2) for initially seropositive patients: post-administration antibody concentration  $\geq$  2 fold the pre-vaccination antibody concentration.

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

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**End point timeframe:**

At Weeks (W) 6 and 12, at Months (M) 9, 12, 18 and 30 and at one year after treatment concluding time point, i.e. at follow-up visit 2 at W120 added of one year (at 12M post W120)

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| End point values                       | MAGE-A3 Total Group | Placebo Total Group |  |  |
|--|---------------------|---------------------|--|--|
| Subject group type                     | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed            | 962                 | 490                 |  |  |
| Units: Subjects                        |                     |                     |  |  |
| Anti-PD HR, W6 (N=962;490)             | 945                 | 27                  |  |  |
| Anti-PD HR, W12 (N=859;432)            | 853                 | 35                  |  |  |
| Anti-PD HR, M9 (N=579;307)             | 575                 | 26                  |  |  |
| Anti-PD HR, M12 (N=482;240)            | 479                 | 19                  |  |  |
| Anti-PD HR, M18 (N=374;194)            | 370                 | 21                  |  |  |
| Anti-PD HR, M30 (N=354;186)            | 352                 | 17                  |  |  |
| Anti-PD HR, at 12M post W120 (N=78;46) | 77                  | 4                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Health-related quality of life (HQL) scores

|   |   |
|---|---|
| End point title   | Health-related quality of life (HQL) scores |
| End point description:  |   |
| HQL was assessed using the EQ-5D generic health state classification and valuation system. The number and percentage of patients with each score within each dimension of the EQ-5D questionnaire (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) were tabulated at each assessment for each group. Each of these scores can take 3 levels: no problem (level 1), moderate problem (level 2) or extreme problem (level 3). Resulting descriptive mean and standard deviation (SD) for the EQ-5D Utility Value (EQ-5D UV) were tabulated. Valid EQ-5D data were defined as questionnaires assessed 1) on day of and before treatment administration; or 2) on day after treatment administration for W0, W6, W12; or 3) during follow-up visits or at time of recurrence. The EQ-5D total score ranges from -0.016 (worst health state) to 1.000 (best health state). |   |
| End point type  | Secondary                                   |
| End point timeframe:  |   |
| At Week (W) 0 on day of treatment (DoT) (W0 DoT), W0 on day post treatment (DpT) (W0 DpT), W6 DoT, W6 DpT, W12 DoT, W12 DpT, Month (M) 6, M9, M12, M24, 6M post W120, at recurrence, and at 12M post W120   |   |

| End point values                     | MAGE-A3 Total Group | Placebo Total Group |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 226                 | 103                 |  |  |
| Units: Score on a scale              |                     |                     |  |  |
| arithmetic mean (standard deviation) |                     |                     |  |  |
| EQ-5D UV, At W0 DoT (N=226;103)      | 0.83 (± 0.152)      | 0.823 (± 0.189)     |  |  |
| EQ-5D UV, At W0 DpT (N=206;93)       | 0.788 (± 0.182)     | 0.838 (± 0.177)     |  |  |
| EQ-5D UV, At W6 DoT (N=215;99)       | 0.837 (± 0.182)     | 0.825 (± 0.191)     |  |  |
| EQ-5D UV, At W6 DpT (N=188;94)       | 0.798 (± 0.205)     | 0.835 (± 0.176)     |  |  |
| EQ-5D UV, At W12 DoT (N=201;97)      | 0.848 (± 0.158)     | 0.811 (± 0.236)     |  |  |

|                                     |                 |                 |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| EQ-5D UV, At W12 DpT (N=186;87)     | 0.841 (± 0.152) | 0.831 (± 0.211) |  |  |
| EQ-5D UV, At M6 (N=176;84)          | 0.847 (± 0.182) | 0.825 (± 0.236) |  |  |
| EQ-5D UV, At M9 (N=173;81)          | 0.84 (± 0.197)  | 0.81 (± 0.219)  |  |  |
| EQ-5D UV, At M12 (N=146;69)         | 0.857 (± 0.166) | 0.824 (± 0.214) |  |  |
| EQ-5D UV, At M24 (N=102;50)         | 0.855 (± 0.179) | 0.865 (± 0.145) |  |  |
| EQ-5D UV, At 6M post W120 (N=7;3)   | 0.723 (± 0.298) | 0.679 (± 0.073) |  |  |
| EQ-5D UV, At recurrence (N=41;14)   | 0.662 (± 0.343) | 0.785 (± 0.159) |  |  |
| EQ-5D UV, At 12M post W120 (N=16;5) | 0.753 (± 0.199) | 0.777 (± 0.395) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of patients with abnormal alanine aminotransferase (ALT) values by maximum grade

|                 |   |
|-----------------|---|
| End point title | Number of patients with abnormal alanine aminotransferase (ALT) values by maximum grade |
|-----------------|---|

End point description:

The status of each patient as regards ALT laboratory values at baseline (SCR) up to DLP was collected and graded according to the Common Terminology Criteria (CTC) Adverse event terminology, version 3.0. The post-treatment values were presented by worst grade versus baseline grade. SCR CTC grade statuses reported were unknown (UNK), Grade 0 (G0), G1 and G2. CTC grade statuses reported at DLP were G0, G1, G2, G3, G4, and UNK.

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

End point timeframe:

Period of follow-up was from screening (SCR) to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

| End point values            | MAGE-A3 Total Group | Placebo Total Group |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 1515                | 757                 |  |  |
| Units: Subjects             |                     |                     |  |  |
| ALT - SCR UNK; DLP G0       | 1                   | 0                   |  |  |
| ALT - SCR UNK; DLP G1       | 1                   | 1                   |  |  |
| ALT - SCR UNK; DLP G2       | 0                   | 0                   |  |  |
| ALT - SCR UNK; DLP G3       | 0                   | 0                   |  |  |
| ALT - SCR UNK; DLP G4       | 0                   | 0                   |  |  |
| ALT - SCR UNK; DLP UNK      | 3                   | 1                   |  |  |
| ALT - SCR G0; DLP G0        | 1133                | 588                 |  |  |
| ALT - SCR G0; DLP G1        | 162                 | 77                  |  |  |
| ALT - SCR G0; DLP G2        | 17                  | 8                   |  |  |
| ALT - SCR G0; DLP G3        | 7                   | 7                   |  |  |
| ALT - SCR G0; DLP G4        | 1                   | 1                   |  |  |



|                       |     |    |  |  |
|-----------------------|-----|----|--|--|
| ALT - SCR G0; DLP UNK | 113 | 37 |  |  |
| ALT - SCR G1; DLP G0  | 34  | 14 |  |  |
| ALT - SCR G1; DLP G1  | 32  | 17 |  |  |
| ALT - SCR G1; DLP G2  | 4   | 3  |  |  |
| ALT - SCR G1; DLP G3  | 1   | 2  |  |  |
| ALT - SCR G1; DLP G4  | 0   | 0  |  |  |
| ALT - SCR G1; DLP UNK | 4   | 1  |  |  |
| ALT - SCR G2; DLP G0  | 0   | 0  |  |  |
| ALT - SCR G2; DLP G1  | 1   | 0  |  |  |
| ALT - SCR G2; DLP G2  | 1   | 0  |  |  |
| ALT - SCR G2; DLP G3  | 0   | 0  |  |  |
| ALT - SCR G2; DLP G4  | 0   | 0  |  |  |
| ALT - SCR G2; DLP UNK | 0   | 0  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of patients with abnormal alanine aspartate aminotransferase (AST) values by maximum grade

|                 |   |
|-----------------|---|
| End point title | Number of patients with abnormal alanine aspartate aminotransferase (AST) values by maximum grade |
|-----------------|---|

End point description:

The status of each patient as regards AST laboratory values at baseline (SCR) up to DLP was collected and graded according to the Common Terminology Criteria (CTC) Adverse event terminology, version 3.0. The post-treatment values were presented by worst grade versus baseline grade. SCR CTC grade statuses reported were unknown (UNK), Grade 0 (G0), G1 and G2. CTC grade statuses reported at DLP were G0, G1, G2, G3, G4, and UNK.

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

End point timeframe:

Period of follow-up was from screening (SCR) to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

| End point values            | MAGE-A3 Total Group | Placebo Total Group |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 1515                | 757                 |  |  |
| Units: Subjects             |                     |                     |  |  |
| AST - SCR UNK; DLP G0       | 12                  | 4                   |  |  |
| AST - SCR UNK; DLP G1       | 5                   | 2                   |  |  |
| AST - SCR UNK; DLP G2       | 0                   | 0                   |  |  |
| AST - SCR UNK; DLP G3       | 0                   | 0                   |  |  |
| AST - SCR UNK; DLP G4       | 0                   | 0                   |  |  |
| AST - SCR UNK; DLP UNK      | 5                   | 2                   |  |  |
| AST - SCR G0; DLP G0        | 1170                | 579                 |  |  |
| AST - SCR G0; DLP G1        | 136                 | 84                  |  |  |
| AST - SCR G0; DLP G2        | 6                   | 4                   |  |  |
| AST - SCR G0; DLP G3        | 8                   | 5                   |  |  |
| AST - SCR G0; DLP G4        | 2                   | 1                   |  |  |

|                       |     |    |  |  |
|-----------------------|-----|----|--|--|
| AST - SCR G0; DLP UNK | 111 | 37 |  |  |
| AST - SCR G1; DLP G0  | 26  | 19 |  |  |
| AST - SCR G1; DLP G1  | 25  | 16 |  |  |
| AST - SCR G1; DLP G2  | 5   | 2  |  |  |
| AST - SCR G1; DLP G3  | 0   | 1  |  |  |
| AST - SCR G1; DLP G4  | 0   | 0  |  |  |
| AST - SCR G1; DLP UNK | 2   | 1  |  |  |
| AST - SCR G2; DLP G0  | 0   | 0  |  |  |
| AST - SCR G2; DLP G1  | 0   | 0  |  |  |
| AST - SCR G2; DLP G2  | 0   | 0  |  |  |
| AST - SCR G2; DLP G3  | 1   | 0  |  |  |
| AST - SCR G2; DLP G4  | 0   | 0  |  |  |
| AST - SCR G2; DLP UNK | 1   | 0  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of patients with abnormal alkaline phosphatase (ALKP) values by maximum grade

|                 |  |
|-----------------|--|
| End point title | Number of patients with abnormal alkaline phosphatase (ALKP) values by maximum grade |
|-----------------|--|

End point description:

The status of each patient as regards ALKP laboratory values at baseline (SCR) up to DLP was collected and graded according to the Common Terminology Criteria (CTC) Adverse event terminology, version 3.0. The post-treatment values were presented by worst grade versus baseline grade. SCR CTC grade statuses reported were unknown (UNK), Grade 0 (G0), G1 and G2. CTC grade statuses reported at DLP were G0, G1, G2, G3, G4, and UNK.

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

End point timeframe:

Period of follow-up was from screening (SCR) to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

| End point values            | MAGE-A3 Total Group | Placebo Total Group |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 1515                | 757                 |  |  |
| Units: Subjects             |                     |                     |  |  |
| ALKP - SCR UNK; DLP G0      | 21                  | 3                   |  |  |
| ALKP - SCR UNK; DLP G1      | 0                   | 0                   |  |  |
| ALKP - SCR UNK; DLP G2      | 0                   | 0                   |  |  |
| ALKP - SCR UNK; DLP G3      | 1                   | 0                   |  |  |
| ALKP - SCR UNK; DLP G4      | 0                   | 0                   |  |  |
| ALKP - SCR UNK; DLP UNK     | 5                   | 3                   |  |  |
| ALKP - SCR G0; DLP G0       | 1121                | 569                 |  |  |
| ALKP - SCR G0; DLP G1       | 99                  | 63                  |  |  |
| ALKP - SCR G0; DLP G2       | 3                   | 2                   |  |  |
| ALKP - SCR G0; DLP G3       | 1                   | 0                   |  |  |
| ALKP - SCR G0; DLP G4       | 0                   | 0                   |  |  |

|                        |     |    |  |  |
|------------------------|-----|----|--|--|
| ALKP - SCR G0; DLP UNK | 107 | 39 |  |  |
| ALKP - SCR G1; DLP G0  | 63  | 35 |  |  |
| ALKP - SCR G1; DLP G1  | 79  | 38 |  |  |
| ALKP - SCR G1; DLP G2  | 1   | 0  |  |  |
| ALKP - SCR G1; DLP G3  | 1   | 0  |  |  |
| ALKP - SCR G1; DLP G4  | 0   | 0  |  |  |
| ALKP - SCR G1; DLP UNK | 11  | 4  |  |  |
| ALKP - SCR G2; DLP G0  | 0   | 0  |  |  |
| ALKP - SCR G2; DLP G1  | 2   | 1  |  |  |
| ALKP - SCR G2; DLP G2  | 0   | 0  |  |  |
| ALKP - SCR G2; DLP G3  | 0   | 0  |  |  |
| ALKP - SCR G2; DLP G4  | 0   | 0  |  |  |
| ALKP - SCR G2; DLP UNK | 0   | 0  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of patients with abnormal bilirubin (BIL) values by maximum grade

|                 |  |
|-----------------|--|
| End point title | Number of patients with abnormal bilirubin (BIL) values by maximum grade |
|-----------------|--|

End point description:

The status of each patient as regards BIL laboratory values at baseline (SCR) up to DLP was collected and graded according to the Common Terminology Criteria (CTC) Adverse event terminology, version 3.0. The post-treatment values were presented by worst grade versus baseline grade. SCR CTC grade statuses reported were unknown (UNK), Grade 0 (G0) and G1. CTC grade statuses reported at DLP were G0, G1, G2, G3, G4, and UNK.

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

End point timeframe:

Period of follow-up was from screening (SCR) to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

| End point values            | MAGE-A3 Total Group | Placebo Total Group |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 1515                | 757                 |  |  |
| Units: Subjects             |                     |                     |  |  |
| BIL - SCR UNK; DLP G0       | 9                   | 2                   |  |  |
| BIL - SCR UNK; DLP G1       | 1                   | 0                   |  |  |
| BIL - SCR UNK; DLP G2       | 0                   | 0                   |  |  |
| BIL - SCR UNK; DLP G3       | 0                   | 0                   |  |  |
| BIL - SCR UNK; DLP G4       | 0                   | 0                   |  |  |
| BIL - SCR UNK; DLP UNK      | 4                   | 2                   |  |  |
| BIL - SCR G0; DLP G0        | 1275                | 661                 |  |  |
| BIL - SCR G0; DLP G1        | 74                  | 28                  |  |  |
| BIL - SCR G0; DLP G2        | 11                  | 9                   |  |  |
| BIL - SCR G0; DLP G3        | 1                   | 2                   |  |  |
| BIL - SCR G0; DLP G4        | 1                   | 0                   |  |  |

|                       |     |    |  |  |
|-----------------------|-----|----|--|--|
| BIL - SCR G0; DLP UNK | 114 | 37 |  |  |
| BIL - SCR G1; DLP G0  | 10  | 5  |  |  |
| BIL - SCR G1; DLP G1  | 8   | 9  |  |  |
| BIL - SCR G1; DLP G2  | 5   | 1  |  |  |
| BIL - SCR G1; DLP G3  | 1   | 0  |  |  |
| BIL - SCR G1; DLP G4  | 0   | 0  |  |  |
| BIL - SCR G1; DLP UNK | 1   | 1  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of patients with abnormal creatinine (CREA) values by maximum grade

|                 |  |
|-----------------|--|
| End point title | Number of patients with abnormal creatinine (CREA) values by maximum grade |
|-----------------|--|

End point description:

The status of each patient as regards CREA laboratory values at baseline (SCR) up to DLP was collected and graded according to the Common Terminology Criteria (CTC) Adverse event terminology, version 3.0. The post-treatment values were presented by worst grade versus baseline grade. SCR CTC grade statuses reported were unknown (UNK), Grade 0 (G0), G1 and G2. CTC grade statuses reported at DLP were G0, G1, G2, G3, G4, and UNK.

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

End point timeframe:

Period of follow-up was from screening (SCR) to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

| End point values            | MAGE-A3 Total Group | Placebo Total Group |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 1515                | 757                 |  |  |
| Units: Subjects             |                     |                     |  |  |
| CREA - SCR UNK; DLP G0      | 2                   | 0                   |  |  |
| CREA - SCR UNK; DLP G1      | 0                   | 0                   |  |  |
| CREA - SCR UNK; DLP G2      | 0                   | 0                   |  |  |
| CREA - SCR UNK; DLP G3      | 0                   | 0                   |  |  |
| CREA - SCR UNK; DLP G4      | 2                   | 0                   |  |  |
| CREA - SCR UNK; DLP UNK     | 1139                | 577                 |  |  |
| CREA - SCR G0; DLP G0       | 126                 | 74                  |  |  |
| CREA - SCR G0; DLP G1       | 9                   | 3                   |  |  |
| CREA - SCR G0; DLP G2       | 3                   | 1                   |  |  |
| CREA - SCR G0; DLP G3       | 1                   | 0                   |  |  |
| CREA - SCR G0; DLP G4       | 103                 | 32                  |  |  |
| CREA - SCR G0; DLP UNK      | 27                  | 14                  |  |  |
| CREA - SCR G1; DLP G0       | 72                  | 44                  |  |  |
| CREA - SCR G1; DLP G1       | 11                  | 6                   |  |  |
| CREA - SCR G1; DLP G2       | 0                   | 0                   |  |  |
| CREA - SCR G1; DLP G3       | 1                   | 0                   |  |  |
| CREA - SCR G1; DLP G4       | 6                   | 4                   |  |  |

|                        |   |   |  |  |
|------------------------|---|---|--|--|
| CREA - SCR G1; DLP UNK | 0 | 0 |  |  |
| CREA - SCR G2; DLP G0  | 7 | 2 |  |  |
| CREA - SCR G2; DLP G1  | 6 | 0 |  |  |
| CREA - SCR G2; DLP G2  | 0 | 0 |  |  |
| CREA - SCR G2; DLP G3  | 0 | 0 |  |  |
| CREA - SCR G2; DLP G4  | 0 | 0 |  |  |
| CREA - SCR G2; DLP UNK | 0 | 0 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of patients with abnormal haemoglobin (HGB) values by maximum grade

|                 |  |
|-----------------|--|
| End point title | Number of patients with abnormal haemoglobin (HGB) values by maximum grade |
|-----------------|--|

End point description:

The status of each patient as regards HGB laboratory values at baseline (SCR) up to DLP was collected and graded according to the Common Terminology Criteria (CTC) Adverse event terminology, version 3.0. The post-treatment values were presented by worst grade versus baseline grade. SCR CTC grade statuses reported were unknown (UNK), Grade 0 (G0), G1, G2 and G3. CTC grade statuses reported at DLP were G0, G1, G2, G3, G4, and UNK.

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

End point timeframe:

Period of follow-up was from screening (SCR) to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

| End point values            | MAGE-A3 Total Group | Placebo Total Group |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 1515                | 757                 |  |  |
| Units: Subjects             |                     |                     |  |  |
| HGB - SCR UNK; DLP G0       | 3                   | 0                   |  |  |
| HGB - SCR UNK; DLP G1       | 1                   | 0                   |  |  |
| HGB - SCR UNK; DLP G2       | 0                   | 0                   |  |  |
| HGB - SCR UNK; DLP G3       | 0                   | 0                   |  |  |
| HGB - SCR UNK; DLP G4       | 0                   | 0                   |  |  |
| HGB - SCR UNK; DLP UNK      | 3                   | 0                   |  |  |
| HGB - SCR G0; DLP G0        | 534                 | 274                 |  |  |
| HGB - SCR G0; DLP G1        | 70                  | 26                  |  |  |
| HGB - SCR G0; DLP G2        | 9                   | 5                   |  |  |
| HGB - SCR G0; DLP G3        | 1                   | 1                   |  |  |
| HGB - SCR G0; DLP G4        | 0                   | 2                   |  |  |
| HGB - SCR G0; DLP UNK       | 50                  | 19                  |  |  |
| HGB - SCR G1; DLP G0        | 342                 | 187                 |  |  |
| HGB - SCR G1; DLP G1        | 310                 | 142                 |  |  |
| HGB - SCR G1; DLP G2        | 17                  | 14                  |  |  |
| HGB - SCR G1; DLP G3        | 6                   | 3                   |  |  |
| HGB - SCR G1; DLP G4        | 2                   | 0                   |  |  |

|                       |    |    |  |  |
|-----------------------|----|----|--|--|
| HGB - SCR G1; DLP UNK | 49 | 15 |  |  |
| HGB - SCR G2; DLP G0  | 29 | 30 |  |  |
| HGB - SCR G2; DLP G1  | 63 | 31 |  |  |
| HGB - SCR G2; DLP G3  | 12 | 3  |  |  |
| HGB - SCR G2; DLP G4  | 1  | 3  |  |  |
| HGB - SCR G2; DLP UNK | 1  | 0  |  |  |
| HGB - SCR G3; DLP G0  | 6  | 0  |  |  |
| HGB - SCR G3; DLP G1  | 2  | 1  |  |  |
| HGB - SCR G3; DLP G2  | 3  | 1  |  |  |
| HGB - SCR G3; DLP G3  | 1  | 0  |  |  |
| HGB - SCR G3; DLP G4  | 0  | 0  |  |  |
| HGB - SCR G3; DLP UNK | 0  | 0  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of patients with abnormal leukocytes (LEU) values by maximum grade

|                 |   |
|-----------------|---|
| End point title | Number of patients with abnormal leukocytes (LEU) values by maximum grade |
|-----------------|---|

End point description:

The status of each patient as regards LEU laboratory values at baseline (SCR) up to DLP was collected and graded according to the Common Terminology Criteria (CTC) Adverse event terminology, version 3.0. The post-treatment values were presented by worst grade versus baseline grade. SCR CTC grade statuses reported were unknown (UNK), Grade 0 (G0), G1, G2 and G3. CTC grade statuses reported at DLP were G0, G1, G2, G3, G4, and UNK.

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

End point timeframe:

Period of follow-up was from screening (SCR) to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

| End point values            | MAGE-A3 Total Group | Placebo Total Group |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 1515                | 757                 |  |  |
| Units: Subjects             |                     |                     |  |  |
| LEU - SCR UNK; DLP G0       | 1                   | 0                   |  |  |
| LEU - SCR UNK; DLP G1       | 0                   | 0                   |  |  |
| LEU - SCR UNK; DLP G2       | 0                   | 0                   |  |  |
| LEU - SCR UNK; DLP G3       | 0                   | 0                   |  |  |
| LEU - SCR UNK; DLP G4       | 0                   | 0                   |  |  |
| LEU - SCR UNK; DLP UNK      | 1                   | 0                   |  |  |
| LEU - SCR G0; DLP G0        | 1259                | 652                 |  |  |
| LEU - SCR G0; DLP G1        | 45                  | 29                  |  |  |
| LEU - SCR G0; DLP G2        | 4                   | 2                   |  |  |
| LEU - SCR G0; DLP G3        | 2                   | 0                   |  |  |
| LEU - SCR G0; DLP G4        | 6                   | 2                   |  |  |
| LEU - SCR G0; DLP UNK       | 98                  | 32                  |  |  |

|                       |    |    |  |  |
|-----------------------|----|----|--|--|
| LEU - SCR G1; DLP G0  | 54 | 24 |  |  |
| LEU - SCR G1; DLP G1  | 21 | 5  |  |  |
| LEU - SCR G1; DLP G2  | 2  | 1  |  |  |
| LEU - SCR G1; DLP G3  | 0  | 0  |  |  |
| LEU - SCR G1; DLP G4  | 0  | 1  |  |  |
| LEU - SCR G1; DLP UNK | 4  | 0  |  |  |
| LEU - SCR G2; DLP G0  | 13 | 6  |  |  |
| LEU - SCR G2; DLP G1  | 3  | 2  |  |  |
| LEU - SCR G2; DLP G2  | 2  | 0  |  |  |
| LEU - SCR G2; DLP G3  | 0  | 0  |  |  |
| LEU - SCR G2; DLP G4  | 0  | 0  |  |  |
| LEU - SCR G2; DLP UNK | 0  | 0  |  |  |
| LEU - SCR G3; DLP G0  | 0  | 1  |  |  |
| LEU - SCR G3; DLP G1  | 0  | 0  |  |  |
| LEU - SCR G3; DLP G2  | 0  | 0  |  |  |
| LEU - SCR G3; DLP G3  | 0  | 0  |  |  |
| LEU - SCR G3; DLP G4  | 0  | 0  |  |  |
| LEU - SCR G3; DLP UNK | 0  | 0  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of patients with abnormal lymphocytes (LYM) values by maximum grade

|                 |  |
|-----------------|--|
| End point title | Number of patients with abnormal lymphocytes (LYM) values by maximum grade |
|-----------------|--|

End point description:

The status of each patient as regards LYM laboratory values at baseline (SCR) up to DLP was collected and graded according to the Common Terminology Criteria (CTC) Adverse event terminology, version 3.0. The post-treatment values were presented by worst grade versus baseline grade. SCR CTC grade statuses reported were unknown (UNK), Grade 0 (G0), G1, G2 and G3. CTC grade statuses reported at DLP were G0, G1, G2, G3, G4, and UNK.

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

End point timeframe:

Period of follow-up was from screening (SCR) to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

| End point values            | MAGE-A3 Total Group | Placebo Total Group |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 1515                | 757                 |  |  |
| Units: Subjects             |                     |                     |  |  |
| LYM - SCR UNK; DLP G0       | 12                  | 3                   |  |  |
| LYM - SCR UNK; DLP G1       | 3                   | 1                   |  |  |
| LYM - SCR UNK; DLP G2       | 0                   | 0                   |  |  |
| LYM - SCR UNK; DLP G3       | 0                   | 0                   |  |  |
| LYM - SCR UNK; DLP G4       | 0                   | 0                   |  |  |
| LYM - SCR UNK; DLP UNK      | 4                   | 2                   |  |  |

|                       |     |     |  |  |
|-----------------------|-----|-----|--|--|
| LYM - SCR G0; DLP G0  | 999 | 518 |  |  |
| LYM - SCR G0; DLP G1  | 160 | 89  |  |  |
| LYM - SCR G0; DLP G2  | 40  | 16  |  |  |
| LYM - SCR G0; DLP G3  | 5   | 0   |  |  |
| LYM - SCR G0; DLP G4  | 0   | 0   |  |  |
| LYM - SCR G0; DLP UNK | 96  | 35  |  |  |
| LYM - SCR G1; DLP G0  | 47  | 27  |  |  |
| LYM - SCR G1; DLP G1  | 86  | 42  |  |  |
| LYM - SCR G1; DLP G2  | 15  | 4   |  |  |
| LYM - SCR G1; DLP G3  | 1   | 4   |  |  |
| LYM - SCR G1; DLP G4  | 2   | 0   |  |  |
| LYM - SCR G1; DLP UNK | 20  | 5   |  |  |
| LYM - SCR G2; DLP G0  | 3   | 1   |  |  |
| LYM - SCR G2; DLP G1  | 7   | 2   |  |  |
| LYM - SCR G2; DLP G2  | 4   | 3   |  |  |
| LYM - SCR G2; DLP G3  | 2   | 1   |  |  |
| LYM - SCR G2; DLP G4  | 0   | 0   |  |  |
| LYM - SCR G2; DLP UNK | 0   | 1   |  |  |
| LYM - SCR G3; DLP G0  | 4   | 1   |  |  |
| LYM - SCR G3; DLP G1  | 1   | 2   |  |  |
| LYM - SCR G3; DLP G2  | 3   | 0   |  |  |
| LYM - SCR G3; DLP G3  | 1   | 0   |  |  |
| LYM - SCR G3; DLP G4  | 0   | 0   |  |  |
| LYM - SCR G3; DLP UNK | 0   | 0   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of patients with abnormal neutrophils (NEU) values by maximum grade

|                 |  |
|-----------------|--|
| End point title | Number of patients with abnormal neutrophils (NEU) values by maximum grade |
|-----------------|--|

End point description:

The status of each patient as regards NEU laboratory values at baseline (SCR) up to DLP was collected and graded according to the Common Terminology Criteria (CTC) Adverse event terminology, version 3.0. The post-treatment values were presented by worst grade versus baseline grade. SCR CTC grade statuses reported were unknown (UNK), Grade 0 (G0), G1, G2, G3 and G4. CTC grade statuses reported at DLP were G0, G1, G2, G3, G4, and UNK.

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

End point timeframe:

Period of follow-up was from screening (SCR) to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)



| End point values            | MAGE-A3 Total Group | Placebo Total Group |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 1515                | 757                 |  |  |
| Units: Subjects             |                     |                     |  |  |
| NEU - SCR UNK; DLP G0       | 12                  | 3                   |  |  |
| NEU - SCR UNK; DLP G1       | 0                   | 0                   |  |  |
| NEU - SCR UNK; DLP G2       | 0                   | 0                   |  |  |
| NEU - SCR UNK; DLP G3       | 0                   | 0                   |  |  |
| NEU - SCR UNK; DLP G4       | 0                   | 0                   |  |  |
| NEU - SCR UNK; DLP UNK      | 1                   | 2                   |  |  |
| NEU - SCR G0; DLP G0        | 1200                | 625                 |  |  |
| NEU - SCR G0; DLP G1        | 47                  | 28                  |  |  |
| NEU - SCR G0; DLP G2        | 1                   | 3                   |  |  |
| NEU - SCR G0; DLP G3        | 2                   | 1                   |  |  |
| NEU - SCR G0; DLP G4        | 3                   | 1                   |  |  |
| NEU - SCR G0; DLP UNK       | 111                 | 37                  |  |  |
| NEU - SCR G1; DLP G0        | 56                  | 23                  |  |  |
| NEU - SCR G1; DLP G1        | 31                  | 10                  |  |  |
| NEU - SCR G1; DLP G2        | 3                   | 1                   |  |  |
| NEU - SCR G1; DLP G3        | 0                   | 0                   |  |  |
| NEU - SCR G1; DLP G4        | 0                   | 0                   |  |  |
| NEU - SCR G1; DLP UNK       | 3                   | 2                   |  |  |
| NEU - SCR G2; DLP G0        | 32                  | 16                  |  |  |
| NEU - SCR G2; DLP G1        | 5                   | 1                   |  |  |
| NEU - SCR G2; DLP G2        | 2                   | 2                   |  |  |
| NEU - SCR G2; DLP G3        | 0                   | 0                   |  |  |
| NEU - SCR G2; DLP G4        | 0                   | 0                   |  |  |
| NEU - SCR G2; DLP UNK       | 1                   | 1                   |  |  |
| NEU - SCR G3; DLP G0        | 3                   | 1                   |  |  |
| NEU - SCR G3; DLP G1        | 0                   | 0                   |  |  |
| NEU - SCR G3; DLP G2        | 0                   | 0                   |  |  |
| NEU - SCR G3; DLP G3        | 0                   | 0                   |  |  |
| NEU - SCR G3; DLP G4        | 0                   | 0                   |  |  |
| NEU - SCR G3; DLP UNK       | 0                   | 0                   |  |  |
| NEU - SCR G4; DLP G0        | 1                   | 0                   |  |  |
| NEU - SCR G4; DLP G1        | 0                   | 0                   |  |  |
| NEU - SCR G4; DLP G2        | 1                   | 0                   |  |  |
| NEU - SCR G4; DLP G3        | 0                   | 0                   |  |  |
| NEU - SCR G4; DLP G4        | 0                   | 0                   |  |  |
| NEU - SCR G4; DLP UNK       | 0                   | 0                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of patients with abnormal platelets (PLA) values by maximum grade

|                 |  |
|-----------------|--|
| End point title | Number of patients with abnormal platelets (PLA) values by maximum grade |
|-----------------|--|

**End point description:**

The status of each patient as regards PLA laboratory values at baseline (SCR) up to DLP was collected and graded according to the Common Terminology Criteria (CTC) Adverse event terminology, version 3.0. The post-treatment values were presented by worst grade versus baseline grade. SCR CTC grade statuses reported were unknown (UNK), Grade 0 (G0), G1 and G3. CTC grade statuses reported at DLP were G0, G1, G2, G3, G4, and UNK.

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

**End point timeframe:**

Period of follow-up was from screening (SCR) to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

| <b>End point values</b>     | MAGE-A3 Total Group | Placebo Total Group |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 1515                | 757                 |  |  |
| Units: Subjects             |                     |                     |  |  |
| PLA - SCR UNK; DLP G0       | 1                   | 1                   |  |  |
| PLA - SCR UNK; DLP G1       | 0                   | 0                   |  |  |
| PLA - SCR UNK; DLP G2       | 0                   | 0                   |  |  |
| PLA - SCR UNK; DLP G3       | 0                   | 0                   |  |  |
| PLA - SCR UNK; DLP G4       | 0                   | 0                   |  |  |
| PLA - SCR UNK; DLP UNK      | 1                   | 0                   |  |  |
| PLA - SCR G0; DLP G0        | 1275                | 648                 |  |  |
| PLA - SCR G0; DLP G1        | 78                  | 38                  |  |  |
| PLA - SCR G0; DLP G2        | 6                   | 2                   |  |  |
| PLA - SCR G0; DLP G3        | 1                   | 0                   |  |  |
| PLA - SCR G0; DLP G4        | 7                   | 2                   |  |  |
| PLA - SCR G0; DLP UNK       | 98                  | 35                  |  |  |
| PLA - SCR G1; DLP G0        | 22                  | 16                  |  |  |
| PLA - SCR G1; DLP G1        | 17                  | 10                  |  |  |
| PLA - SCR G1; DLP G2        | 2                   | 4                   |  |  |
| PLA - SCR G1; DLP G3        | 1                   | 0                   |  |  |
| PLA - SCR G1; DLP G4        | 0                   | 0                   |  |  |
| PLA - SCR G1; DLP UNK       | 5                   | 0                   |  |  |
| PLA - SCR G3; DLP G0        | 1                   | 1                   |  |  |
| PLA - SCR G3; DLP G1        | 0                   | 0                   |  |  |
| PLA - SCR G3; DLP G2        | 0                   | 0                   |  |  |
| PLA - SCR G3; DLP G3        | 0                   | 0                   |  |  |
| PLA - SCR G3; DLP G4        | 0                   | 0                   |  |  |
| PLA - SCR G3; DLP UNK       | 0                   | 0                   |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Number of patients with any adverse events (AEs) and with AEs by maximum grade reported – Up to data lock point (DLP)**

|                 |   |
|-----------------|---|
| End point title | Number of patients with any adverse events (AEs) and with AEs by maximum grade reported – Up to data lock point (DLP) |
|-----------------|---|

**End point description:**

An AE was any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs reported are here below tabulated irrespective of grade, as well as graded by maximum grade reported according to the Common Terminology Criteria (CTC) Adverse event terminology, version 3.0. Maximum grade reported and tabulated were Grade 1 (G1), G2, G3, G4 and G5. Any here below is defined as irrespective of CTC grade reported.

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

**End point timeframe:**

Within the 31-day follow-up period post treatment administration, up to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

| <b>End point values</b>     | <b>MAGE-A3 Total Group</b> | <b>Placebo Total Group</b> |  |  |
|-----------------------------|----------------------------|----------------------------|--|--|
| Subject group type          | Reporting group            | Reporting group            |  |  |
| Number of subjects analysed | 1515                       | 757                        |  |  |
| Units: Subjects             |                            |                            |  |  |
| Patients with any AEs       | 1369                       | 556                        |  |  |
| Patients with G1 AEs        | 563                        | 225                        |  |  |
| Patients with G2 AEs        | 560                        | 209                        |  |  |
| Patients with G3 AEs        | 184                        | 88                         |  |  |
| Patients with G4 AEs        | 49                         | 26                         |  |  |
| Patients with G5 AEs        | 13                         | 8                          |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Number of patients with serious adverse events (SAEs) – Up to data lock point (DLP)**

|                 |   |
|-----------------|---|
| End point title | Number of patients with serious adverse events (SAEs) – Up to data lock point (DLP) |
|-----------------|---|

**End point description:**

A SAE is any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity, was a congenital anomaly/birth defect in the offspring of a study subject, or was a Grade 4 AE according to CTC for Adverse Events, Version 3.0. Events part of natural course of lung cancer (i.e., disease progression, recurrence) were captured towards clinical efficacy assessment (CEA) and were not reported as SAEs. Death due to a progressive disease was similarly recorded towards CEA, but not as an SAE. However, if progression of lung cancer disease was greater than normally be expected, or if investigators considered that there was a causal relationship between treatment or protocol design/procedures and disease progression/ recurrence, then it was reported as SAE. Any new cancer (non-related to lung cancer) was reported as SAE.

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

**End point timeframe:**

From screening (SCR) up to data lock point (DLP) on 23 January 2014 (up to 5 years per patient)

| <b>End point values</b>     | MAGE-A3 Total Group | Placebo Total Group |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 1515                | 757                 |  |  |
| Units: Subjects             |                     |                     |  |  |
| Patient(s) with SAE(s)      | 330                 | 164                 |  |  |

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From screening (Day 0) up to data lock point (DLP) on 23 January 2014, for up to 5 years per patient.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | MAGE-A3 Total Group |
|-----------------------|---------------------|

Reporting group description:

Patients received up to 13 doses (D) of MAGE-A3 ASCI, 5 Ds every 3 weeks followed by 8 Ds every 12 weeks.

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Placebo Total Group |
|-----------------------|---------------------|

Reporting group description:

Patients received up to 13 doses (D) of placebo, 5 Ds every 3 weeks followed by 8 Ds every 12 weeks.

| Serious adverse events  | MAGE-A3 Total Group | Placebo Total Group |  |
|---|---------------------|---------------------|--|
| Total subjects affected by serious adverse events                   |                     |                     |  |
| subjects affected / exposed   | 330 / 1515 (21.78%) | 164 / 757 (21.66%)  |  |
| number of deaths (all causes)                                       | 30                  | 17                  |  |
| number of deaths resulting from adverse events                      |                     |                     |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                     |                     |  |
| Adenocarcinoma gastric  |                     |                     |  |
| subjects affected / exposed   | 4 / 1515 (0.26%)    | 0 / 757 (0.00%)     |  |
| occurrences causally related to treatment / all                     | 0 / 4               | 0 / 0               |  |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 0               |  |
| Adenocarcinoma of colon   |                     |                     |  |
| subjects affected / exposed   | 1 / 1515 (0.07%)    | 1 / 757 (0.13%)     |  |
| occurrences causally related to treatment / all                     | 0 / 1               | 0 / 1               |  |
| deaths causally related to treatment / all                          | 0 / 0               | 0 / 0               |  |
| Adenocarcinoma pancreas   |                     |                     |  |
| subjects affected / exposed   | 1 / 1515 (0.07%)    | 0 / 757 (0.00%)     |  |
| occurrences causally related to treatment / all                     | 0 / 1               | 0 / 0               |  |
| deaths causally related to treatment / all                          | 0 / 1               | 0 / 0               |  |
| Basal cell carcinoma  |                     |                     |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 8 / 1515 (0.53%) | 4 / 757 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Benign oesophageal neoplasm                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Bladder cancer                                  |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Bladder transitional cell carcinoma             |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Bladder transitional cell carcinoma stage II    |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Bowen's disease                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Breast cancer                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Brenner tumour                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Carcinoma in situ of skin                       |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cerebral haemangioma                            |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cholangiocarcinoma                              |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Clear cell renal cell carcinoma                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Colon cancer                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Dermatofibrosarcoma protuberans                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diffuse large b-cell lymphoma                   |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| 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                     | 2 / 1515 (0.13%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastrointestinal stromal tumour                 |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hepatic cancer                                  |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hepatocellular carcinoma                        |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Intraductal proliferative breast lesion         |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Invasive ductal breast carcinoma                |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Laryngeal cancer                                |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Laryngeal squamous cell carcinoma               |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Lentigo maligna                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Leukaemia                                       |                  |                 |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Malignant melanoma                              |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Malignant peritoneal neoplasm                   |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Metastases to central nervous system            |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Myelodysplastic syndrome                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Oesophageal adenocarcinoma                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Oropharyngeal cancer                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Ovarian cancer metastatic                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Ovarian fibroma                                 |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pancreatic carcinoma                            |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Pancreatic carcinoma metastatic                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Papillary thyroid cancer                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Prostate cancer                                 |                  |                 |  |
| subjects affected / exposed                     | 8 / 1515 (0.53%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Prostate cancer recurrent                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Rectal adenocarcinoma                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Renal cancer                                    |                  |                 |  |
| subjects affected / exposed                     | 3 / 1515 (0.20%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Seborrhoeic keratosis                           |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Small cell lung cancer                          |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Squamous cell carcinoma                         |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Squamous cell carcinoma of pharynx              |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Tracheal cancer                                 |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Transitional cell carcinoma                     |                  |                 |  |
| subjects affected / exposed                     | 5 / 1515 (0.33%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Squamous cell carcinoma of skin                 |                  |                 |  |
| subjects affected / exposed                     | 4 / 1515 (0.26%) | 4 / 757 (0.53%) |  |
| occurrences causally related to treatment / all | 1 / 4            | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Vascular disorders                              |                  |                 |  |
| Aortic aneurysm                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Aortic aneurysm rupture                         |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Bleeding varicose vein                          |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (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 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| 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                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Haematoma                                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypertension                                    |                  |                 |  |
| subjects affected / exposed                     | 3 / 1515 (0.20%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypotension                                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Neurogenic shock                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Pelvic venous thrombosis                        |                  |                 |  |

|  |                  |                 |  |
|--|------------------|-----------------|--|
| subjects affected / exposed                          | 1 / 1515 (0.07%) | 0 / 757 (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                          | 2 / 1515 (0.13%) | 5 / 757 (0.66%) |  |
| occurrences causally related to treatment / all      | 0 / 2            | 0 / 5           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Peripheral artery thrombosis                         |                  |                 |  |
| subjects affected / exposed                          | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all      | 2 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Peripheral embolism                                  |                  |                 |  |
| subjects affected / exposed                          | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Peripheral ischaemia                                 |                  |                 |  |
| subjects affected / exposed                          | 0 / 1515 (0.00%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Peripheral vascular disorder                         |                  |                 |  |
| subjects affected / exposed                          | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Superior vena cava syndrome                          |                  |                 |  |
| subjects affected / exposed                          | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0           |  |
| Thrombophlebitis                                     |                  |                 |  |
| subjects affected / exposed                          | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| 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                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Chest discomfort                                |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Chest pain                                      |                  |                 |  |
| subjects affected / exposed                     | 3 / 1515 (0.20%) | 3 / 757 (0.40%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Death   |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 3 / 757 (0.40%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 3           |  |
| Euthanasia                                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Fatigue   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| General physical health deterioration           |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Impaired healing                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Influenza like illness                          |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Mass  |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Multi-organ failure                             |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1           |  |
| Non-cardiac chest pain                          |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Oedema peripheral                               |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pyrexia   |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Sudden death                                    |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Immune system disorders                         |                  |                 |  |
| Hypersensitivity                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Immune system disorder                          |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Reproductive system and breast disorders        |                  |                 |  |
| Acquired hydrocele                              |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Benign prostatic hyperplasia                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cervical dysplasia                              |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Ovarian cyst                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                  |                 |  |
| Acute respiratory distress syndrome             |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Acute respiratory failure                       |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Alveolitis                                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| Apnoea  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Aspiration                                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Asthma  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Bronchopleural fistula                          |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Bronchostenosis                                 |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Dyspnoea  |                  |                 |  |
| subjects affected / exposed                     | 6 / 1515 (0.40%) | 3 / 757 (0.40%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Epistaxis                                       |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Haemoptysis                                     |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hiccups   |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypoxia   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Idiopathic pulmonary fibrosis                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Interstitial lung disease                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Laryngeal oedema                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Lung infiltration                               |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pleural effusion                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pleurisy  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pneumonia aspiration                            |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 3 / 1515 (0.20%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pneumothorax                                    |                  |                 |  |
| subjects affected / exposed                     | 4 / 1515 (0.26%) | 3 / 757 (0.40%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pneumothorax spontaneous                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pulmonary artery thrombosis                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Pulmonary embolism                              |                  |                 |  |
| subjects affected / exposed                     | 7 / 1515 (0.46%) | 4 / 757 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Pulmonary granuloma                             |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pulmonary haemorrhage                           |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pulmonary mass                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Respiratory distress                            |                  |                 |  |

|   |                   |                 |  |
|---|-------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 1515 (0.00%)  | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Respiratory failure                             |                   |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%)  | 3 / 757 (0.40%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 3           |  |
| Sleep apnoea syndrome                           |                   |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%)  | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Chronic obstructive pulmonary disease           |                   |                 |  |
| subjects affected / exposed                     | 17 / 1515 (1.12%) | 4 / 757 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 18            | 1 / 7           |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0           |  |
| Psychiatric disorders                           |                   |                 |  |
| Alcohol withdrawal syndrome                     |                   |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%)  | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Completed suicide                               |                   |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%)  | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0           |  |
| Confusional state                               |                   |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%)  | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Delirium  |                   |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%)  | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0           |  |
| Depression                                      |                   |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Mental status changes                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Investigations                                  |                  |                 |  |
| Alanine aminotransferase increased              |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Aspartate aminotransferase increased            |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Blood uric acid increased                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gamma-glutamyltransferase increased             |                  |                 |  |
| subjects affected / exposed                     | 3 / 1515 (0.20%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hepatic enzyme increased                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Liver function test abnormal                    |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| 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                                   |                  |                 |  |
| Accidental overdose                             |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Alcohol poisoning                               |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Clavicle fracture                               |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Fall  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Femoral neck fracture                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Femur fracture                                  |                  |                 |  |
| subjects affected / exposed                     | 6 / 1515 (0.40%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Fibula fracture                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Fracture  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hip fracture                                    |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Humerus fracture                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Incision site pain                              |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Incisional hernia                               |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Joint dislocation                               |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Multiple fractures                              |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Multiple injuries                               |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Post procedural haematoma                       |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| 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                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Postoperative thoracic procedure complication   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Procedural complication                         |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Procedural haemorrhage                          |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| 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                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Rib fracture                                    |                  |                 |  |
| subjects affected / exposed                     | 3 / 1515 (0.20%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Road traffic accident                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Skull fracture                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Spinal compression fracture                     |                  |                 |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Spinal fracture                                 |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Splenic rupture                                 |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| 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                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Tendon rupture                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Thoracic vertebral fracture                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Tibia fracture                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Toxicity to various agents                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Traumatic intracranial haemorrhage              |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Upper limb fracture                             |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Vascular graft occlusion                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Vascular pseudoaneurysm                         |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Wound   |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Wrist fracture                                  |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cardiac disorders                               |                  |                 |  |
| Acute coronary syndrome                         |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Acute myocardial infarction                     |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Adams-stokes syndrome                           |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Angina pectoris                                 |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Angina unstable                                 |                  |                 |  |
| subjects affected / exposed                     | 3 / 1515 (0.20%) | 3 / 757 (0.40%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Atrial fibrillation                             |                  |                 |  |
| subjects affected / exposed                     | 4 / 1515 (0.26%) | 3 / 757 (0.40%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2           |  |
| Atrial flutter                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Atrial tachycardia                              |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Atrioventricular block                          |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Atrioventricular block complete                 |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Atrioventricular block second degree            |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Bradyarrhythmia                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cardiac arrest                                  |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 1           |  |
| Cardiac failure                                 |                  |                 |  |
| subjects affected / exposed                     | 5 / 1515 (0.33%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cardiac failure congestive                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 3 / 757 (0.40%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Cardiac fibrillation                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cardiac flutter                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cardio-respiratory arrest                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Cardiomyopathy                                  |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Congestive cardiomyopathy                       |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Coronary artery disease                         |                  |                 |  |
| subjects affected / exposed                     | 3 / 1515 (0.20%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Coronary artery occlusion                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Coronary artery stenosis                        |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypertensive heart disease                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Left ventricular dysfunction                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Left ventricular failure                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Mitral valve incompetence                       |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Myocardial infarction                           |                  |                 |  |
| subjects affected / exposed                     | 4 / 1515 (0.26%) | 3 / 757 (0.40%) |  |
| occurrences causally related to treatment / all | 3 / 6            | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Myocardial ischaemia                            |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Palpitations                                    |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pericardial effusion                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Prinzmetal angina                               |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Silent myocardial infarction                    |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Sinus bradycardia                               |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Stress cardiomyopathy                           |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Ventricular tachycardia                         |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Nervous system disorders                        |                  |                 |  |
| Brain injury                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Carotid artery stenosis                         |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Cerebral haemorrhage                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cerebral infarction                             |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cerebral ischaemia                              |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Cerebrovascular accident                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Convulsion                                      |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Dementia alzheimer's type                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Dizziness                                       |                  |                 |  |
| subjects affected / exposed                     | 3 / 1515 (0.20%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Epilepsy  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Headache  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hemiparesis                                     |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Intracranial aneurysm                           |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| 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 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Loss of consciousness                           |                  |                 |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Presyncope                                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Sciatica  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Subarachnoid haemorrhage                        |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Syncope   |                  |                 |  |
| subjects affected / exposed                     | 4 / 1515 (0.26%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Transient global amnesia                        |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Transient ischaemic attack                      |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Unresponsive to stimuli                         |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Blood and lymphatic system disorders            |                  |                 |  |
| Anaemia   |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 7 / 1515 (0.46%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 8            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Anaemia macrocytic                              |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypersplenism                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypochromic anaemia                             |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Idiopathic thrombocytopenic purpura             |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Lymphadenitis                                   |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Lymphocytosis                                   |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Neutropenia                                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Thrombocytopenia                                |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Ear and labyrinth disorders                     |                  |                 |  |
| Vertigo positional                              |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Eye disorders                                   |                  |                 |  |
| Age-related macular degeneration                |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Macular fibrosis                                |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| 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 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Retinal detachment                              |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastrointestinal disorders                      |                  |                 |  |
| Abdominal hernia                                |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Abdominal pain                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| Abdominal pain lower                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Abdominal pain upper                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Ascites   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Colitis ischaemic                               |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Colitis microscopic                             |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Colitis ulcerative                              |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Constipation                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diaphragmatic hernia                            |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diarrhoea                                       |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diverticular perforation                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diverticulitis intestinal haemorrhagic          |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diverticulum intestinal                         |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Duodenal obstruction                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Duodenal stenosis                               |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Duodenal ulcer                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (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                     | 2 / 1515 (0.13%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Dyspepsia                                       |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastric haemorrhage                             |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastric polyps                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastric ulcer                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastritis                                       |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastrooesophageal reflux disease                |                  |                 |  |
| subjects affected / exposed                     | 5 / 1515 (0.33%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Haematemesis                                    |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hiatus hernia                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Ileus   |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| 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                     | 7 / 1515 (0.46%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Inguinal hernia, obstructive                    |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Intestinal obstruction                          |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Intestinal polyp                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Large intestine polyp                           |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Melaena   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Nausea  |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Oesophagitis                                    |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Oesophagitis ulcerative                         |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pancreatic necrosis                             |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pancreatitis acute                              |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Pancreatitis chronic                            |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Peritoneal adhesions                            |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Umbilical hernia                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Vomiting  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hepatobiliary disorders                         |                  |                 |  |
| Autoimmune hepatitis                            |                  |                 |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Bile duct stone                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cholangitis                                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cholangitis acute                               |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cholangitis chronic                             |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cholecystitis                                   |                  |                 |  |
| subjects affected / exposed                     | 3 / 1515 (0.20%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cholecystitis acute                             |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cholelithiasis                                  |                  |                 |  |
| subjects affected / exposed                     | 4 / 1515 (0.26%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hepatic failure                                 |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Jaundice  |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Portal vein thrombosis                          |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                  |                 |  |
| Angioedema                                      |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Eczema  |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Leukocytoclastic vasculitis                     |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Rash pruritic                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Renal and urinary disorders                     |                  |                 |  |
| Glomerulonephritis rapidly progressive          |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| Haematuria                                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hydronephrosis                                  |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Nephrolithiasis                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Renal cyst                                      |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Renal failure acute                             |                  |                 |  |
| subjects affected / exposed                     | 5 / 1515 (0.33%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Ureteric dilatation                             |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Urethral stenosis                               |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Urinary bladder polyp                           |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Endocrine disorders                             |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| Autoimmune thyroiditis                          |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypothyroidism                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                  |                 |  |
| Arthralgia                                      |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Arthritis                                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Back pain                                       |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Fibromyalgia                                    |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Intervertebral disc protrusion                  |                  |                 |  |
| subjects affected / exposed                     | 3 / 1515 (0.20%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Lumbar spinal stenosis                          |                  |                 |  |
| subjects affected / exposed                     | 4 / 1515 (0.26%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| Musculoskeletal chest pain                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Musculoskeletal discomfort                      |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Musculoskeletal pain                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Osteoarthritis                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Osteonecrosis                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pain in extremity                               |                  |                 |  |
| subjects affected / exposed                     | 3 / 1515 (0.20%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Rheumatoid arthritis                            |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Spinal column stenosis                          |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Spinal osteoarthritis                           |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Systemic sclerosis                              |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Infections and infestations                     |                  |                 |  |
| Abscess   |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Acute hepatitis b                               |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Anal abscess                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Appendicitis                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Appendicitis perforated                         |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Bronchiolitis                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Bronchitis                                      |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 3 / 1515 (0.20%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Bronchopneumonia                                |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Bronchopulmonary aspergillosis                  |                  |                 |  |
| subjects affected / exposed                     | 3 / 1515 (0.20%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Carbuncle                                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cellulitis                                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cellulitis streptococcal                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Chest wall abscess                              |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Citrobacter infection                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Device related infection                        |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diarrhoea infectious                            |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Diverticulitis                                  |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Enterocolitis infectious                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Erysipelas                                      |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastroenteritis                                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastroenteritis clostridial                     |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 2 / 757 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastroenteritis salmonella                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hepatitis b                                     |                  |                 |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                                   | 1 / 1515 (0.07%) | 0 / 757 (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                                   | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all               | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0           |  |
| Infectious pleural effusion                                   |                  |                 |  |
| subjects affected / exposed                                   | 3 / 1515 (0.20%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all               | 0 / 3            | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 1            | 0 / 0           |  |
| Infective exacerbation of chronic obstructive airways disease |                  |                 |  |
| subjects affected / exposed                                   | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0           |  |
| Lobar pneumonia   |                  |                 |  |
| subjects affected / exposed                                   | 5 / 1515 (0.33%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 5            | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0           |  |
| Lower respiratory tract infection                             |                  |                 |  |
| subjects affected / exposed                                   | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0           |  |
| Lower respiratory tract infection viral                       |                  |                 |  |
| subjects affected / exposed                                   | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0           |  |
| Lung infection  |                  |                 |  |
| subjects affected / exposed                                   | 4 / 1515 (0.26%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all               | 0 / 4            | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0            | 0 / 0           |  |
| Peritonitis   |                  |                 |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 1515 (0.07%)  | 0 / 757 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pneumonia                                       |                   |                  |  |
| subjects affected / exposed                     | 26 / 1515 (1.72%) | 15 / 757 (1.98%) |  |
| occurrences causally related to treatment / all | 0 / 27            | 1 / 16           |  |
| deaths causally related to treatment / all      | 0 / 5             | 1 / 4            |  |
| Pneumonia bacterial                             |                   |                  |  |
| subjects affected / exposed                     | 4 / 1515 (0.26%)  | 4 / 757 (0.53%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0            |  |
| Pneumonia haemophilus                           |                   |                  |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%)  | 1 / 757 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pneumonia pseudomonas aeruginosa                |                   |                  |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%)  | 0 / 757 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pneumonia staphylococcal                        |                   |                  |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%)  | 1 / 757 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Post procedural infection                       |                   |                  |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%)  | 0 / 757 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Postoperative wound infection                   |                   |                  |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%)  | 1 / 757 (0.13%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pulmonary tuberculosis                          |                   |                  |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Q fever   |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Renal abscess                                   |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Respiratory tract infection                     |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Rhinitis  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Rickettsiosis                                   |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Sepsis  |                  |                 |  |
| subjects affected / exposed                     | 5 / 1515 (0.33%) | 3 / 757 (0.40%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 2           |  |
| Staphylococcal bacteraemia                      |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Staphylococcal infection                        |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Streptococcal bacteraemia                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Upper respiratory tract infection               |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Urinary tract infection                         |                  |                 |  |
| subjects affected / exposed                     | 4 / 1515 (0.26%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Urinary tract infection bacterial               |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Vestibular neuronitis                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Viral pericarditis                              |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Viral upper respiratory tract infection         |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Metabolism and nutrition disorders              |                  |                 |  |
| Dehydration                                     |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diabetes mellitus                               |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diabetes mellitus inadequate control            |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diabetic ketoacidosis                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Failure to thrive                               |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hyperglycaemia                                  |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hyperkalaemia                                   |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hypoglycaemia                                   |                  |                 |  |
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hyponatraemia                                   |                  |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 2 / 1515 (0.13%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Insulin-requiring type 2 diabetes mellitus      |                  |                 |  |
| subjects affected / exposed                     | 0 / 1515 (0.00%) | 1 / 757 (0.13%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Metabolic alkalosis                             |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Metabolic disorder                              |                  |                 |  |
| subjects affected / exposed                     | 1 / 1515 (0.07%) | 0 / 757 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| 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>                     | MAGE-A3 Total Group  | Placebo Total Group |  |
|---|----------------------|---------------------|--|
| Total subjects affected by non-serious adverse events |                      |                     |  |
| subjects affected / exposed                           | 1225 / 1515 (80.86%) | 300 / 757 (39.63%)  |  |
| Nervous system disorders                              |                      |                     |  |
| Headache  |                      |                     |  |
| subjects affected / exposed                           | 129 / 1515 (8.51%)   | 40 / 757 (5.28%)    |  |
| occurrences (all)                                     | 241                  | 50                  |  |
| General disorders and administration site conditions  |                      |                     |  |
| Asthenia  |                      |                     |  |
| subjects affected / exposed                           | 92 / 1515 (6.07%)    | 26 / 757 (3.43%)    |  |
| occurrences (all)                                     | 199                  | 55                  |  |
| Chills  |                      |                     |  |
| subjects affected / exposed                           | 118 / 1515 (7.79%)   | 7 / 757 (0.92%)     |  |
| occurrences (all)                                     | 249                  | 16                  |  |
| Fatigue   |                      |                     |  |
| alternative assessment type:                          |                      |                     |  |

|   |                        |                  |  |
|---|------------------------|------------------|--|
| Systematic                                      |                        |                  |  |
| subjects affected / exposed                     | 243 / 1515<br>(16.04%) | 50 / 757 (6.61%) |  |
| occurrences (all)                               | 579                    | 85               |  |
| Influenza like illness                          |                        |                  |  |
| subjects affected / exposed                     | 198 / 1515<br>(13.07%) | 23 / 757 (3.04%) |  |
| occurrences (all)                               | 682                    | 39               |  |
| Injection site erythema                         |                        |                  |  |
| subjects affected / exposed                     | 104 / 1515 (6.86%)     | 3 / 757 (0.40%)  |  |
| occurrences (all)                               | 344                    | 3                |  |
| Injection site pain                             |                        |                  |  |
| subjects affected / exposed                     | 476 / 1515<br>(31.42%) | 35 / 757 (4.62%) |  |
| occurrences (all)                               | 1880                   | 73               |  |
| Injection site reaction                         |                        |                  |  |
| subjects affected / exposed                     | 273 / 1515<br>(18.02%) | 14 / 757 (1.85%) |  |
| occurrences (all)                               | 1368                   | 17               |  |
| Pain  |                        |                  |  |
| alternative assessment type:<br>Systematic      |                        |                  |  |
| subjects affected / exposed                     | 237 / 1515<br>(15.64%) | 14 / 757 (1.85%) |  |
| occurrences (all)                               | 578                    | 26               |  |
| Pyrexia   |                        |                  |  |
| subjects affected / exposed                     | 529 / 1515<br>(34.92%) | 38 / 757 (5.02%) |  |
| occurrences (all)                               | 1732                   | 49               |  |
| Gastrointestinal disorders                      |                        |                  |  |
| Diarrhoea                                       |                        |                  |  |
| subjects affected / exposed                     | 76 / 1515 (5.02%)      | 31 / 757 (4.10%) |  |
| occurrences (all)                               | 110                    | 42               |  |
| Nausea  |                        |                  |  |
| subjects affected / exposed                     | 108 / 1515 (7.13%)     | 36 / 757 (4.76%) |  |
| occurrences (all)                               | 177                    | 45               |  |
| Respiratory, thoracic and mediastinal disorders |                        |                  |  |
| Cough   |                        |                  |  |
| subjects affected / exposed                     | 131 / 1515 (8.65%)     | 71 / 757 (9.38%) |  |
| occurrences (all)                               | 155                    | 80               |  |
| Dyspnoea  |                        |                  |  |

|  |   |  |  |
|--|---|--|--|
| subjects affected / exposed<br>occurrences (all)   | 83 / 1515 (5.48%)<br>91                                     | 47 / 757 (6.21%)<br>52                               |  |
| Skin and subcutaneous tissue disorders<br>Erythema<br>subjects affected / exposed<br>occurrences (all)   | 120 / 1515 (7.92%)<br>258                                   | 6 / 757 (0.79%)<br>6                                 |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Myalgia<br>subjects affected / exposed<br>occurrences (all) | 105 / 1515 (6.93%)<br>161<br><br>183 / 1515 (12.08%)<br>588 | 31 / 757 (4.10%)<br>35<br><br>20 / 757 (2.64%)<br>23 |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)  | 125 / 1515 (8.25%)<br>251                                   | 24 / 757 (3.17%)<br>29                               |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all)   | 79 / 1515 (5.21%)<br>112                                    | 28 / 757 (3.70%)<br>30                               |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 23 November 2010 | Amendment 1 included the following changes: 1) Evaluation of efficacy of study treatment in GS+ vs GS- population was upgraded to secondary objective of the trial; 2) Analysis of impact of study treatment on patients' health-related Quality of Life or utility was added as new secondary objective along with corresponding endpoints; 3) New, optional translational research was added including pharmacogenetic testing, DNA demethylation analysis & antigen spreading; 4) Recording of autoimmune diseases as AEs of specific interest was included in protocol & a list of types of diseases/disorders with potential autoimmune causality to be considered established; 5) Hematology & biochemistry safety laboratory tests were added for Week 12 visit; 6) Allowed concomitant medication was changed: a) systemic corticosteroids was prohibited only when prescribed for chronic treatment (more than 7 consecutive days [D]), b) immunoglobulins &/or any blood products administration was allowed provided a minimum of 7D between immunoglobulins &/or blood products & study treatment administration; 7) Study treatment postponement was allowed to permit influenza vaccination in framework of imposed influenza vaccination programs to allow a minimum of 7D between influenza vaccine & study treatment administration; 8) Clarifications were added to protocol (e.g. allowed time intervals for scans, randomization & surgery, clarifications on acceptance of scans, etc.) without changing study procedures; 9) Country specific appendices were included for countries also participating in PRAME-AS15-NSC-001 (ADJ) (GSK ID: 113174) study to allow simultaneous screening for both studies, i.e. both MAGE-A3 & PRAME expression could be tested on the tumor samples. 10) Japan was added as participating country & an appendix with Japan specific requirements was added. 11) Certain information was updated, e.g. contact numbers for emergency code breaking & SAE reporting, description of the ECOG performance status. |
| 18 October 2011  | Amendment 2 included the following changes: 1) After trial initiation, a GS at the tumor site associated with a clinical response to MAGE-A3 ASCI was identified in 2 trials in melanoma and lung cancer. This opens the possibility to identify patients likely to benefit from MAGE-A3 ASCI. To clinically validate these GS biomarkers, DFS analysis in patients presenting the GS was added as co-primary (1ry) objective; 2) At the time of the initially planned 1st interim analysis (IA) there would not have been enough events reported in GS+ population to conclude on relevance of GS selection approach. Clinical validation of GS could only be performed on data set available at time of 2nd IA or final analysis (FA). It was decided to remove 1st efficacy IA; 3) In addition, secondary (2ry) endpoints to evaluate OS & lung-cancer-related survival in GS+ and GS- patients were added; 4) Other 2ry objectives were clarified in accordance with addition of above co-1ry objective; 5) Alpha levels assigned to objectives A and B were adapted to take into account correlation between test statistics for no-CT and overall; 6) A weighted Bonferroni-Holm strategy using the closure principle was put in place in case of efficacy claims at the FA; 7) The Wald test was replaced by Likelihood Ratio test as primary test in Cox models, due to that a slight increase in 1-sided type I error is expected when using an unbalanced design together with Wald test; 8) It was clarified that at time of the analyses, 2-sided p-values will be reported & design considerations adapted using 2-sided significance levels; 9) To validate predictive value of GS, an interaction test between MAGE-A3 ASCI vs placebo & GS status was planned; 10) A new criterion for study treatment postponement to allow recovery of possibly related CTC grade $\geq 2$ AEs was added; 11) IDMC responsibilities were modified to accommodate that an independent statistician (vs the sponsor) was to provide the FA for review by the IDMC.      |

|              |  |
|--------------|--|
| 06 June 2012 | Protocol Amendment 3 included the following changes: 1) At the European Medicines Agency's (EMA) request, GSK Biologicals updated its procedure for emergency unblinding during the conduct of a clinical study; 2) According to the revised procedure, the responsibility and the decision to break the treatment code in emergency situations resided solely with the investigator and consequently, the investigator would have full authority to break the treatment code. Wording in the protocol was adapted accordingly; 3) To ensure the availability of images that could be valuable to the accurate assessment of a patient's disease status, instructions that GSK could collect for review any imaging performed within the scope of this trial and not only images that are related to the identification of recurrences were included; 4) Clarification that at the concluding examination following a recurrence, any tumor assessment performed at the visit showing recurrence did not have to be repeated; 5) Some corrections were made, i.e. footnote cross references, clinical cut off for anti-MAGE-A3 antibodies enzyme-linked immunosorbent assay (ELISA), the power to detect a differential effect in the GS+ population for validation of the gene profile. |
|--------------|--|

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date          | Interruption  | Restart date |
|---------------|---|--------------|
| 01 April 2014 | The study was terminated early on 1 April 2014 following assessment of the lack of efficacy of the MAGE-A3 ASCI study product by the IDMC for the study, as the first two co-primary objectives (DFS in the overall population and DFS in the No-CT population) were not reached. The third co-primary objective, i.e. DFS in the test set of the GS+ population, could not be assessed as no GS classifier could be identified in the training set. The final analysis presented in this summary was performed on all the data collected up to the data lock point (DLP) of 23 January 2014. No follow-up analysis was performed including additional data collected until the end of the study as these were very limited data. Safety data were recorded after the data lock point of the Final Analysis. These safety data are not reported in the safety section of this summary and are as follows for the period spreading from DLP to study end (23 September 2014): 1) For this entire period of assessment, SAEs were additionally reported by 7 and 3 patients in the MAGE-A3 and Placebo groups, respectively, none of these SAEs having a fatal outcome and one of them reported in the MAGE-A3 Group (MedDRA preferred term: mediastinitis) being assessed by the investigators as related to MAGE-A3 ASCI study product; and 2) during the 31-day periods following each treatment administration, at least one AE was reported by 38 and 15 patients in MAGE-A3 and Placebo groups, respectively. Overall these additional safety data did not alter the rates of AEs as displayed in this summary. | -            |

Notes:

## Limitations and caveats

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

Objective C to demonstrate clinical efficacy in terms of DFS of the MAGE-A3 product versus placebo in NSCLC after complete surgical resection in the GS+ population could not be evaluated as no GS classifier could be identified in the training set.

Notes:

