



Clinical trial results:

An open-label, multi-center, expanded access study for postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer who have progressed following prior endocrine therapy, investigating the treatment of everolimus (RAD001) in combination with exemestane

Summary

| | |
|--------------------------|---|
| EudraCT number | 2012-000073-23 |
| Trial protocol | AT NL SE NO ES DK FI BE CZ IT HU IE SK BG |
| Global end of trial date | 01 September 2014 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 27 November 2019 |
| First version publication date | 27 November 2019 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CRAD001YIC04 |
|-----------------------|--------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharmaceuticals AG, +41 613241111, |
| Scientific contact | Clinical Disclosure Office, Novartis Pharmaceuticals AG, +41 613241111, |

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 | 01 September 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 September 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate safety of everolimus in postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer after recurrence or progression following Non-steroidal aromatase inhibitors (NSAIs) treatment.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------|
| Actual start date of recruitment | 16 May 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Netherlands: 71 |
| Country: Number of subjects enrolled | Norway: 20 |
| Country: Number of subjects enrolled | Poland: 47 |
| Country: Number of subjects enrolled | Slovakia: 20 |
| Country: Number of subjects enrolled | Spain: 429 |
| Country: Number of subjects enrolled | Sweden: 6 |
| Country: Number of subjects enrolled | Austria: 4 |
| Country: Number of subjects enrolled | Belgium: 237 |
| Country: Number of subjects enrolled | Bulgaria: 35 |
| Country: Number of subjects enrolled | Denmark: 8 |
| Country: Number of subjects enrolled | Finland: 10 |
| Country: Number of subjects enrolled | Hungary: 67 |
| Country: Number of subjects enrolled | Italy: 1153 |
| Country: Number of subjects enrolled | Romania: 26 |
| Worldwide total number of subjects | 2133 |
| EEA total number of subjects | 2133 |

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) | 1171 |
| From 65 to 84 years | 950 |
| 85 years and over | 12 |

Subject disposition

Recruitment

Recruitment details:

This was a multi-center, open-label, single arm, Phase III b, expanded access study. In this study up to 2500 patients from up to 500 centers were to be recruited.

Pre-assignment

Screening details:

A total of 2133 postmenopausal female subjects with advanced or metastatic breast cancer were enrolled in the study, out of which, 2131 were included in the safety population.

Period 1

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

Arms

| | |
|------------------|-------------------------|
| Arm title | Everolimus + Exemestane |
|------------------|-------------------------|

Arm description:

Subjects received everolimus 10 mg (2x5mg) in combination with exemestane 25 mg, orally, once daily.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Everolimus |
| Investigational medicinal product code | RAD001 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Two everolimus tablets 5 mg or one everolimus tablet 10 mg, orally, once daily.

| | |
|--|------------|
| Investigational medicinal product name | Exemestane |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Exemestane 25 mg tablet, orally, once daily.

| Number of subjects in period 1 | Everolimus + Exemestane |
|---------------------------------------|-------------------------|
| Started | 2133 |
| Completed | 82 |
| Not completed | 2051 |
| Abnormal laboratory value(s) | 11 |
| Disease progression | 786 |
| Unsatisfactory therapeutic effect | 6 |
| Administrative problems | 2 |
| Adverse event(s) | 338 |

| | |
|---|-----|
| Abnormal test procedure result(s) | 1 |
| Subject withdrew consent | 72 |
| Everolimus locally reimbursed | 713 |
| Protocol violation | 35 |
| Death | 32 |
| Other | 28 |
| Subject's condition no longer requires study drug | 14 |
| Lost to follow-up | 13 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Everolimus + Exemestane |
|-----------------------|-------------------------|

Reporting group description:

Subjects received everolimus 10 mg (2x5mg) in combination with exemestane 25 mg, orally, once daily.

| Reporting group values | Everolimus + Exemestane | Total | |
|--|-------------------------|-------|--|
| Number of subjects | 2133 | 2133 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 1171 | 1171 | |
| From 65-84 years | 950 | 950 | |
| 85 years and over | 12 | 12 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 62.7 | | |
| standard deviation | ± 9.86 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 2133 | 2133 | |
| Male | 0 | 0 | |

End points

End points reporting groups

| | |
|--|-------------------------|
| Reporting group title | Everolimus + Exemestane |
| Reporting group description: | |
| Subjects received everolimus 10 mg (2x5mg) in combination with exemestane 25 mg, orally, once daily. | |

Primary: Number of Subjects with Adverse Events (AEs)

| | |
|--|---|
| End point title | Number of Subjects with Adverse Events (AEs) ^[1] |
| End point description: | |
| An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE includes any noxious, pathological, or unintended change in anatomical, physiological, or metabolic functions as indicated by physical signs or symptoms occurring in any phase of the clinical study whether or not considered related to the study medication. Safety population included all subjects who received at least one dose of everolimus or exemestane and had at least one post-baseline safety assessment. | |
| End point type | Primary |
| End point timeframe: | |
| From first dose of study treatment through 28 days after last dose of study treatment (Up to approximately 24 months) | |

Notes:

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

Justification: No statistical hypothesis was planned for this endpoint.

| End point values | Everolimus + Exemestane | | | |
|-----------------------------|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2131 | | | |
| Units: Subjects | | | | |
| number (not applicable) | 2018 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Grade 3/4 AEs

| | |
|--|---------------------------------------|
| End point title | Number of Subjects with Grade 3/4 AEs |
| End point description: | |
| Subjects with grade 3 and 4 severity AE were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, unless otherwise specified. If CTCAE grading did not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to grade 1 to grade 4, was used. Safety population included all subjects who received at least one dose of everolimus or exemestane and had at least one post-baseline safety assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| From first dose of study treatment through 28 days after last dose of study treatment (Up to approximately 24 months) | |

| | | | | |
|-----------------------------|----------------------------|--|--|--|
| End point values | Everolimus + Exemestane | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2131 | | | |
| Units: Subjects | | | | |
| number (not applicable) | 214 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Without Chemo in Metastatic Setting |
|-----------------------|-------------------------------------|

Reporting group description:

Without Chemo in Metastatic Setting

| | |
|-----------------------|----------------------------------|
| Reporting group title | With Chemo in Metastatic Setting |
|-----------------------|----------------------------------|

Reporting group description:

With Chemo in Metastatic Setting

| Serious adverse events | Without Chemo in Metastatic Setting | With Chemo in Metastatic Setting | |
|---|-------------------------------------|----------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 163 / 847 (19.24%) | 288 / 1284 (22.43%) | |
| number of deaths (all causes) | 24 | 97 | |
| number of deaths resulting from adverse events | 1 | 1 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Invasive lobular breast carcinoma | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphangiosis carcinomatosa | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant ascites | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to meninges | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic pain | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour of ampulla of Vater | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Blood pressure fluctuation | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| 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 / 847 (0.12%) | 5 / 1284 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemic shock | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant hypertension | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic venous thrombosis | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (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 | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (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 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 2 / 847 (0.24%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |

| | | | |
|--|-----------------|-------------------|--|
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| 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 / 847 (0.12%) | 9 / 1284 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 1 | 4 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 3 / 1284 (0.23%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 3 | |
| Disease progression | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Face oedema | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 847 (0.47%) | 7 / 1284 (0.55%) | |
| occurrences causally related to treatment / all | 4 / 4 | 3 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 4 / 847 (0.47%) | 12 / 1284 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 4 | 2 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | |
| Hyperpyrexia | | | |

| | | | |
|---|-----------------|-------------------|--|
| subjects affected / exposed | 0 / 847 (0.00%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperthermia malignant | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 3 / 1284 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 847 (0.35%) | 6 / 1284 (0.47%) | |
| occurrences causally related to treatment / all | 1 / 3 | 7 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Performance status decreased | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 847 (0.94%) | 26 / 1284 (2.02%) | |
| occurrences causally related to treatment / all | 3 / 8 | 9 / 26 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sense of oppression | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Reproductive system and breast disorders | | | |
| Breast ulceration | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vaginal inflammation | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 3 / 1284 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chylothorax | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cough | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 6 / 1284 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|-------------------|--|
| Dyspnoea | | | |
| subjects affected / exposed | 17 / 847 (2.01%) | 35 / 1284 (2.73%) | |
| occurrences causally related to treatment / all | 7 / 18 | 13 / 35 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea at rest | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (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 | 5 / 847 (0.59%) | 5 / 1284 (0.39%) | |
| occurrences causally related to treatment / all | 5 / 5 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthopnoea | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |

| | | | |
|---|------------------|-------------------|--|
| subjects affected / exposed | 12 / 847 (1.42%) | 14 / 1284 (1.09%) | |
| occurrences causally related to treatment / all | 3 / 12 | 0 / 17 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 14 / 847 (1.65%) | 33 / 1284 (2.57%) | |
| occurrences causally related to treatment / all | 14 / 14 | 29 / 33 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 4 / 847 (0.47%) | 4 / 1284 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 2 / 847 (0.24%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 847 (0.24%) | 6 / 1284 (0.47%) | |
| occurrences causally related to treatment / all | 0 / 2 | 3 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 3 / 1284 (0.23%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disorientation | | | |

| | | | |
|--|-----------------|------------------|--|
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Social avoidant behaviour | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 4 / 1284 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 4 / 1284 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 3 / 847 (0.35%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood electrolytes decreased | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eastern cooperative oncology group performance status worsened | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 4 / 1284 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sputum abnormal | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Acetabulum fracture | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ankle fracture | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| 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 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 4 / 1284 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint injury | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis chemical | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post-traumatic pain | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiation pneumonitis | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| 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 | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Traumatic intracranial haemorrhage | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| 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 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 3 / 847 (0.35%) | 5 / 1284 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 3 | 2 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 847 (0.00%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 2 / 847 (0.24%) | 8 / 1284 (0.62%) | |
| occurrences causally related to treatment / all | 1 / 2 | 5 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiovascular insufficiency | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palpitations | | | |
| subjects affected / exposed | 2 / 847 (0.24%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia paroxysmal | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Ataxia | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haematoma | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 3 / 1284 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coma hepatic | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 847 (0.00%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial paresis | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Headache | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 3 / 1284 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic encephalopathy | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myelopathy | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorder | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |

| | | | |
|---|-----------------|-------------------|--|
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 8 / 847 (0.94%) | 19 / 1284 (1.48%) | |
| occurrences causally related to treatment / all | 6 / 8 | 11 / 21 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 5 / 1284 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytosis | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |

| | | | |
|---|-----------------|-------------------|--|
| Diplopia | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eyelid ptosis | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periorbital oedema | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| 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 | 3 / 847 (0.35%) | 11 / 1284 (0.86%) | |
| occurrences causally related to treatment / all | 0 / 3 | 3 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal inflammation | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |

| | | | |
|---|------------------|-------------------|--|
| subjects affected / exposed | 3 / 847 (0.35%) | 10 / 1284 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Crohn's disease | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 14 / 847 (1.65%) | 6 / 1284 (0.47%) | |
| occurrences causally related to treatment / all | 10 / 14 | 5 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric disorder | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric perforation | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis haemorrhagic | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| 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 | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| 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 | 0 / 847 (0.00%) | 3 / 1284 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 4 / 847 (0.47%) | 3 / 1284 (0.23%) | |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstruction gastric | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema mouth | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 6 / 847 (0.71%) | 4 / 1284 (0.31%) | |
| occurrences causally related to treatment / all | 6 / 6 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 847 (0.00%) | 3 / 1284 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 6 / 847 (0.71%) | 7 / 1284 (0.55%) | |
| occurrences causally related to treatment / all | 3 / 6 | 2 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Biliary colic | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (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 | 0 / 847 (0.00%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 2 / 847 (0.24%) | 3 / 1284 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatic function abnormal | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver disorder | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Acute febrile neutrophilic dermatosis | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erythema | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Crush syndrome | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyuria | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prerenal failure | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 4 / 847 (0.47%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 1 / 4 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure acute | | | |
| subjects affected / exposed | 4 / 847 (0.47%) | 7 / 1284 (0.55%) | |
| occurrences causally related to treatment / all | 4 / 4 | 4 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure chronic | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 2 / 847 (0.24%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal tubular necrosis | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Hypercalcaemia of malignancy | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 3 / 1284 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 2 / 847 (0.24%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone lesion | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|------------------|--|
| Bone pain | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 5 / 1284 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (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 | 0 / 847 (0.00%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 3 / 1284 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 847 (0.00%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 847 (0.24%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridial infection | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus mononucleosis | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 2 / 847 (0.24%) | 4 / 1284 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 3 / 1284 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster disseminated | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parotitis | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 847 (0.47%) | 7 / 1284 (0.55%) | |
| occurrences causally related to treatment / all | 2 / 4 | 4 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia viral | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyopneumothorax | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| 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 / 847 (0.12%) | 3 / 1284 (0.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Salmonellosis | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 847 (0.12%) | 4 / 1284 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 4 / 1284 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vulval abscess | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 2 / 847 (0.24%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Decreased appetite | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 3 / 847 (0.35%) | 7 / 1284 (0.55%) | |
| occurrences causally related to treatment / all | 2 / 3 | 2 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 847 (0.24%) | 3 / 1284 (0.23%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 2 / 1284 (0.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fluid retention | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Food intolerance | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 8 / 847 (0.94%) | 7 / 1284 (0.55%) | |
| occurrences causally related to treatment / all | 8 / 8 | 4 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperlipidaemia | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 847 (0.00%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 2 / 847 (0.24%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 4 / 847 (0.47%) | 5 / 1284 (0.39%) | |
| occurrences causally related to treatment / all | 2 / 4 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 5 / 847 (0.59%) | 1 / 1284 (0.08%) | |
| occurrences causally related to treatment / all | 2 / 5 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polydipsia | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 847 (0.12%) | 0 / 1284 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | Without Chemo in Metastatic Setting | With Chemo in Metastatic Setting | |
|---|--|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 770 / 847 (90.91%) | 1153 / 1284 (89.80%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 38 / 847 (4.49%) | 28 / 1284 (2.18%) | |
| occurrences (all) | 43 | 29 | |
| Lymphoedema | | | |
| subjects affected / exposed | 23 / 847 (2.72%) | 22 / 1284 (1.71%) | |
| occurrences (all) | 24 | 22 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 193 / 847 (22.79%) | 284 / 1284 (22.12%) | |
| occurrences (all) | 215 | 323 | |
| Fatigue | | | |
| subjects affected / exposed | 126 / 847 (14.88%) | 163 / 1284 (12.69%) | |
| occurrences (all) | 140 | 169 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 115 / 847 (13.58%) | 138 / 1284 (10.75%) | |
| occurrences (all) | 129 | 169 | |
| Pyrexia | | | |
| subjects affected / exposed | 96 / 847 (11.33%) | 176 / 1284 (13.71%) | |
| occurrences (all) | 117 | 213 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 108 / 847 (12.75%) | 142 / 1284 (11.06%) | |
| occurrences (all) | 117 | 158 | |
| Dyspnoea | | | |
| subjects affected / exposed | 71 / 847 (8.38%) | 111 / 1284 (8.64%) | |
| occurrences (all) | 75 | 118 | |
| Epistaxis | | | |
| subjects affected / exposed | 58 / 847 (6.85%) | 88 / 1284 (6.85%) | |
| occurrences (all) | 59 | 97 | |
| Pneumonitis | | | |

| | | | |
|---|--|--|--|
| subjects affected / exposed occurrences (all) | 63 / 847 (7.44%) 69 | 104 / 1284 (8.10%) 108 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 25 / 847 (2.95%) 25 | 40 / 1284 (3.12%) 41 | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Blood cholesterol increased subjects affected / exposed occurrences (all) Blood creatinine increased subjects affected / exposed occurrences (all) Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all) Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all) | 47 / 847 (5.55%) 49 41 / 847 (4.84%) 43 16 / 847 (1.89%) 18 28 / 847 (3.31%) 28 17 / 847 (2.01%) 17 41 / 847 (4.84%) 42 80 / 847 (9.45%) 83 | 66 / 1284 (5.14%) 75 69 / 1284 (5.37%) 76 43 / 1284 (3.35%) 43 26 / 1284 (2.02%) 32 31 / 1284 (2.41%) 31 84 / 1284 (6.54%) 87 135 / 1284 (10.51%) 140 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) | 23 / 847 (2.72%) 24 84 / 847 (9.92%) 89 | 19 / 1284 (1.48%) 19 92 / 1284 (7.17%) 93 | |

| | | | |
|--|---------------------------|-------------------------------|--|
| Headache subjects affected / exposed occurrences (all) | 54 / 847 (6.38%) 55 | 84 / 1284 (6.54%) 97 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 107 / 847 (12.63%) 130 | 179 / 1284 (13.94%) 204 | |
| Leukopenia subjects affected / exposed occurrences (all) | 19 / 847 (2.24%) 23 | 22 / 1284 (1.71%) 25 | |
| Neutropenia subjects affected / exposed occurrences (all) | 24 / 847 (2.83%) 27 | 51 / 1284 (3.97%) 68 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 35 / 847 (4.13%) 42 | 88 / 1284 (6.85%) 123 | |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 27 / 847 (3.19%) 29 | 30 / 1284 (2.34%) 31 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 28 / 847 (3.31%) 29 | 37 / 1284 (2.88%) 39 | |
| Aphthous stomatitis subjects affected / exposed occurrences (all) | 17 / 847 (2.01%) 17 | 25 / 1284 (1.95%) 27 | |
| Constipation subjects affected / exposed occurrences (all) | 37 / 847 (4.37%) 39 | 70 / 1284 (5.45%) 76 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 158 / 847 (18.65%) 183 | 187 / 1284 (14.56%) 225 | |
| Dry mouth subjects affected / exposed occurrences (all) | 25 / 847 (2.95%) 25 | 34 / 1284 (2.65%) 35 | |
| Nausea | | | |

| | | | |
|---|--------------------|---------------------|--|
| subjects affected / exposed | 94 / 847 (11.10%) | 156 / 1284 (12.15%) | |
| occurrences (all) | 103 | 167 | |
| Stomatitis | | | |
| subjects affected / exposed | 474 / 847 (55.96%) | 649 / 1284 (50.55%) | |
| occurrences (all) | 608 | 850 | |
| Vomiting | | | |
| subjects affected / exposed | 73 / 847 (8.62%) | 94 / 1284 (7.32%) | |
| occurrences (all) | 79 | 106 | |
| Hepatobiliary disorders | | | |
| Hypertransaminasaemia | | | |
| subjects affected / exposed | 6 / 847 (0.71%) | 28 / 1284 (2.18%) | |
| occurrences (all) | 6 | 31 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 27 / 847 (3.19%) | 19 / 1284 (1.48%) | |
| occurrences (all) | 27 | 19 | |
| Dry skin | | | |
| subjects affected / exposed | 36 / 847 (4.25%) | 39 / 1284 (3.04%) | |
| occurrences (all) | 38 | 41 | |
| Erythema | | | |
| subjects affected / exposed | 30 / 847 (3.54%) | 33 / 1284 (2.57%) | |
| occurrences (all) | 35 | 36 | |
| Pruritus | | | |
| subjects affected / exposed | 76 / 847 (8.97%) | 90 / 1284 (7.01%) | |
| occurrences (all) | 82 | 96 | |
| Rash | | | |
| subjects affected / exposed | 161 / 847 (19.01%) | 190 / 1284 (14.80%) | |
| occurrences (all) | 177 | 213 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 63 / 847 (7.44%) | 96 / 1284 (7.48%) | |
| occurrences (all) | 71 | 101 | |
| Back pain | | | |
| subjects affected / exposed | 47 / 847 (5.55%) | 50 / 1284 (3.89%) | |
| occurrences (all) | 48 | 52 | |

| | | | |
|---|---------------------------|-------------------------------|--|
| Bone pain subjects affected / exposed occurrences (all) | 52 / 847 (6.14%) 53 | 71 / 1284 (5.53%) 81 | |
| Myalgia subjects affected / exposed occurrences (all) | 27 / 847 (3.19%) 30 | 36 / 1284 (2.80%) 37 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 37 / 847 (4.37%) 39 | 52 / 1284 (4.05%) 54 | |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 17 / 847 (2.01%) 17 | 12 / 1284 (0.93%) 13 | |
| Cystitis subjects affected / exposed occurrences (all) | 23 / 847 (2.72%) 24 | 33 / 1284 (2.57%) 36 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 18 / 847 (2.13%) 18 | 21 / 1284 (1.64%) 24 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 37 / 847 (4.37%) 39 | 23 / 1284 (1.79%) 29 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 134 / 847 (15.82%) 136 | 200 / 1284 (15.58%) 220 | |
| Hypercholesterolaemia subjects affected / exposed occurrences (all) | 71 / 847 (8.38%) 76 | 144 / 1284 (11.21%) 151 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 118 / 847 (13.93%) 128 | 142 / 1284 (11.06%) 167 | |
| Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 49 / 847 (5.79%) 53 | 74 / 1284 (5.76%) 79 | |
| Hypocalcaemia | | | |

| | | | |
|-----------------------------|------------------|-------------------|--|
| subjects affected / exposed | 22 / 847 (2.60%) | 21 / 1284 (1.64%) | |
| occurrences (all) | 25 | 22 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 27 / 847 (3.19%) | 33 / 1284 (2.57%) | |
| occurrences (all) | 32 | 39 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 10 October 2012 | The protocol was amended to reflect the indication granted by European Commission in Jul 2012, i.e. "Afinitor is indicated for the treatment of hormone receptor-positive, human epidermal growth factor receptor 2 (HER2/neu) negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor" • Inclusion criteria 1 updated to "Adult women (≥ 18 years of age) with metastatic or locally advanced breast cancer not amenable to curative treatment by surgery or radiotherapy, whose disease recurred or progressed following a Non-steroidal aromatase inhibitor (NSAI) treatment • The wording "refractory to NSAIs" has been changed to "after recurrence or progression following NSAIs treatment" • Addition of only PgR-positive breast cancer and the deletion of disease refractory to NSAIs • Exclusion criteria was updated to for Delete criteria regarding previous treatment with exemestane or mammalian target of rapamycin (mTOR) inhibitors, bilateral diffuse lymphangitic carcinomatosis, and subjects who test positive for hepatitis B or C • Added criteria regarding pre-menopausal, pregnant or lactating women, the known hypersensitivity to exemestane or any excipients, the rare hereditary problems of galactose intolerance and subject with positive baseline hepatitis B or C results the Screening period was extended to 28 days to allow time for prophylactic treatment • Management guidelines for specific toxicities were updated. |
| 20 December 2012 | The protocol was updated to better clarify the subject population. "Radiological or clinical evidence of recurrence or progression on last therapy prior to enrollment" has been added to inclusion criteria in order to make sure that subjects have relapsed on the last therapy prior to enrollment • A local sub-study was planned in two countries (Italy and Belgium) in 110 subjects newly enrolled in the core study with the aim of evaluating if Caphosol® is more effective than "standard care" (good mouth hygiene and mouth washes with normal saline) in reduction of incidence and severity of oral mucositis (OM) due to everolimus combination with exemestane. |
| 10 September 2013 | The protocol was updated to extend the study duration from 31 Jan 2014 till 30 June 2014 and to increase the number of subjects from 2200 to 2500 • The local sub-study that was planned to be performed in two countries (Italy and Belgium) in 110 subjects newly enrolled in the core study was dropped with this amendment. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported