



Clinical trial results:

A Randomised Trial Evaluating the VEGF Inhibitor, Bevacizumab (Avastin), as Adjuvant Therapy following Resection of AJCC Stage IIB (T3bN0M0 & T4aN0M0), IIC (T4bN0M0) and III (TxN1-3M0) Cutaneous Melanoma

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2006-005505-64 |
| Trial protocol | GB |
| Global end of trial date | 31 March 2022 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 08 April 2023 |
| First version publication date | 08 April 2023 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | AVAST-M |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN81261306 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Cambridge University Hospitals NHS Foundation Trust |
| Sponsor organisation address | Hills Road, Cambridge, United Kingdom, CB2 0QQ |
| Public contact | Mrs Carrie Bayliss, Cambridge University Hospitals NHS Foundation Trust, Cambridge Clinical Trials Unit , +44 01223 348158, cuh.cctu@nhs.net |
| Scientific contact | Dr Pippa Corrie, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital , +44 01223 216083, philippa.corrie@nhs.net |

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 | 15 March 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 31 March 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 31 March 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Primary Objective:

To determine the overall survival of patients treated with bevacizumab, compared with standard observation after resection of high risk melanoma.

Secondary Objectives:

To compare the two arms of the study in terms of the following parameters:

- Disease free interval
- Distant metastasis-free interval
- Safety and toxicity
- Quality of life (QoL)

Protection of trial subjects:

The study was approved by a Research Ethics Committee and received authorisation from the Medicine and Healthcare Product Regulatory Authority. Patients received verbal and written information prior to consenting to the trial, and had time to consider their participation and had an opportunity to ask questions. Consenting patients had a series of screening tests to ensure they were suitable for the study and it was safe to proceed. Only the participant's direct care team had access to their recruited participants personal/identifiable information during the trial. On registration to the trial the participants were allocated a unique trial identification number which was used on all data forms and samples sent to the Sponsor, alongside their date of birth and initials. Any participant related information shared by the Sponsor (e.g. for the purposes of analysing translational endpoints) was anonymised, with only reference to the participant's trial identification number being included. This allowed their personal data to remain anonymous.

Background therapy:

N/A

Evidence for comparator:

N/A

| | |
|---|--------------|
| Actual start date of recruitment | 04 July 2007 |
| 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 | United Kingdom: 1343 |
| Worldwide total number of subjects | 1343 |
| EEA total number of subjects | 0 |

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) | 1014 |
| From 65 to 84 years | 324 |
| 85 years and over | 5 |

Subject disposition

Recruitment

Recruitment details:

The AVAST-M trial planned to recruit 1320 patients (660 patients in each arm), with minimum 5 years follow up. Long term follow-up data for survival and disease recurrence would be collected up to 10 years where possible, or until death. Recruitment commenced on 04/07/2017 and closed on 31/03/2012. In total 1343 patients were randomised.

Pre-assignment

Screening details:

A total of 3394 patients were assessed for eligibility, 694 patients did not give informed consent. 1343 patients were successfully screened for eligibility and randomised. Target recruitment of 1320 patients was reached on 23/02/2012. Recruitment remained open to enable those who had already signed consent to enter the study.

Period 1

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

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Treatment |

Arm description:

The treatment period continued for up to a total of 17 bevacizumab treatments or 1 calendar year, whichever occurred sooner, or until recurrence of disease, or patient/clinician withdrawal for any other reason. After completion of the treatment period patients were followed-up every 3 months until 2 years, then 6 monthly until 5 years and then annually until up to 10 years from randomisation (where possible).

If patients were withdrawn early from bevacizumab treatment (for reasons other than first distant recurrence) they, where possible, continued to have the scheduled study visits and investigations until first distant recurrence.

In the event of first distant recurrence, follow up as per above schedule ceased and patients were monitored and managed as indicated locally. Annual follow up (survival and disease recurrence) continued until 10 years from randomisation (where possible), death, loss to follow up or withdrawal of consent.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | L01FG01 |
| Other name | Avastin |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Bevacizumab (Avastin) was administered by intravenous (i.v.) infusion in accordance with the instructions in the Summary of Product Characteristics, at a dose of 7.5mg/kg on day 1 of the study treatment period. Bevacizumab treatment did not commence within 28 days of major surgery and until all the surgical wounds had fully healed.

Bevacizumab infusions were administered every 3 weeks (+/- 7 calendar days of the scheduled treatment day). Treatment was given for 1 calendar year (max 17 infusions over 1 year) or until disease recurred.

Dose was based on actual weight at baseline visit, unless more than 10% body weight change from baseline occurred. In this case dosage was recalculated. It was also acceptable to recalculate the bevacizumab dose every cycle using patients' actual weight.

Rounding of the dose was optional and if the investigator decided to round the dose it could only be

rounded to the nearest ml. The recommended infusion duration was 30 (+/- 10) minutes.

| | |
|--|-----------------|
| Arm title | Observation |
| Arm description: Patients received no interventions on this arm. Patients were followed-up at 6 weeks, 3 months, then every 3 months until 2 years, then 6 monthly until 5 years and then annually until up to 10 years from randomisation (where possible). In the event of first distant recurrence or withdrawal from study, follow up as per above schedule ceased and patients were monitored and managed as indicated locally. Annual follow up (survival and disease recurrence) continued until 10 years from randomisation (where possible), death, loss to follow up or withdrawal of consent. | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | Treatment | Observation |
|---------------------------------------|-----------|-------------|
| Started | 671 | 672 |
| Completed | 588 | 600 |
| Not completed | 83 | 72 |
| Consent withdrawn by subject | 12 | 7 |
| Lost to follow-up | 71 | 65 |

Baseline characteristics

Reporting groups

| Reporting group title | Treatment |
|-----------------------|-----------|
|-----------------------|-----------|

Reporting group description:

The treatment period continued for up to a total of 17 bevacizumab treatments or 1 calendar year, whichever occurred sooner, or until recurrence of disease, or patient/clinician withdrawal for any other reason. After completion of the treatment period patients were followed-up every 3 months until 2 years, then 6 monthly until 5 years and then annually until up to 10 years from randomisation (where possible).

If patients were withdrawn early from bevacizumab treatment (for reasons other than first distant recurrence) they, where possible, continued to have the scheduled study visits and investigations until first distant recurrence.

In the event of first distant recurrence, follow up as per above schedule ceased and patients were monitored and managed as indicated locally. Annual follow up (survival and disease recurrence) continued until 10 years from randomisation (where possible), death, loss to follow up or withdrawal of consent.

| Reporting group title | Observation |
|-----------------------|-------------|
|-----------------------|-------------|

Reporting group description:

Patients received no interventions on this arm. Patients were followed-up at 6 weeks, 3 months, then every 3 months until 2 years, then 6 monthly until 5 years and then annually until up to 10 years from randomisation (where possible).

In the event of first distant recurrence or withdrawal from study, follow up as per above schedule ceased and patients were monitored and managed as indicated locally. Annual follow up (survival and disease recurrence) continued until 10 years from randomisation (where possible), death, loss to follow up or withdrawal of consent.

| Reporting group values | Treatment | Observation | Total |
|-------------------------------------|-----------|-------------|-------|
| Number of subjects | 671 | 672 | 1343 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 513 | 501 | 1014 |
| From 65-84 years | 157 | 167 | 324 |
| 85 years and over | 1 | 4 | 5 |
| Age continuous | | | |
| Units: years | | | |
| median | 56 | 55 | |
| full range (min-max) | 18 to 87 | 19 to 88 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 294 | 296 | 590 |
| Male | 377 | 376 | 753 |
| Breslow thickness of primary tumour | | | |
| Units: Subjects | | | |
| ≤2.0mm | 198 | 201 | 399 |
| >2.0mm - 4.0mm | 203 | 202 | 405 |
| >4.0mm | 221 | 217 | 438 |
| Unknown | 49 | 52 | 101 |
| Ulceration of primary tumour | | | |
| Units: Subjects | | | |
| Present | 262 | 256 | 518 |

| | | | |
|---|-----|-----|------|
| Absent | 310 | 323 | 633 |
| Unknown | 99 | 93 | 192 |
| N classification Units: Subjects | | | |
| N0 | 169 | 160 | 329 |
| N1a | 100 | 96 | 196 |
| N1b | 119 | 119 | 238 |
| N2a | 41 | 39 | 80 |
| N2b | 65 | 67 | 132 |
| N2c | 61 | 68 | 129 |
| N3 | 98 | 106 | 204 |
| NA | 18 | 17 | 35 |
| ECOG performance status Units: Subjects | | | |
| ECOG 0 | 602 | 593 | 1195 |
| ECOG 1 | 67 | 79 | 146 |
| Missing | 2 | 0 | 2 |
| Stage of melanoma Units: Subjects | | | |
| IIB | 103 | 106 | 209 |
| IIC | 84 | 71 | 155 |
| IIIA | 103 | 92 | 195 |
| IIIB | 240 | 255 | 495 |
| IIIC | 141 | 148 | 289 |
| Site of primary tumour Units: Subjects | | | |
| Head and Neck | 74 | 83 | 157 |
| Upper Limb | 112 | 97 | 209 |
| Lower Limb | 219 | 230 | 449 |
| Trunk | 233 | 228 | 461 |
| Unknown | 28 | 32 | 60 |
| Other | 5 | 2 | 7 |
| Regional lymph node involvement at any time Units: Subjects | | | |
| Yes - Detected by SLNB | 171 | 164 | 335 |
| Yes - Detected clinically | 249 | 264 | 513 |
| Yes - Unknown detection method | 0 | 1 | 1 |
| No | 222 | 214 | 436 |
| Not Assessed | 28 | 27 | 55 |
| Missing | 1 | 2 | 3 |
| Previous adjuvant treatment for melanoma Units: Subjects | | | |
| Yes- Radiotherapy | 9 | 14 | 23 |
| Yes - Chemotherapy | 0 | 1 | 1 |
| Yes - Hormonal therapy | 0 | 0 | 0 |
| Yes - Interferon | 3 | 2 | 5 |
| Yes - Vaccine | 1 | 3 | 4 |
| Yes - Other immunotherapy | 2 | 1 | 3 |
| No | 639 | 636 | 1275 |
| Missing | 17 | 13 | 30 |

| | | | |
|---|--------------|--------------|---|
| Yes - Radiotherapy and Chemotherapy | 0 | 1 | 1 |
| Yes - Radiotherapy and Other immunotherapy | 0 | 1 | 1 |
| BMI | | | |
| BMI at baseline was available for 662 subjects on the Treatment Arm and 641 subjects on the Observation Arm; Total n = 1303 | | | |
| Units: kilogram(s)/square metre | | | |
| median | 27.7 | 27.5 | |
| inter-quartile range (Q1-Q3) | 24.6 to 31.2 | 24.7 to 30.6 | - |

End points

End points reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Treatment |
|-----------------------|-----------|

Reporting group description:

The treatment period continued for up to a total of 17 bevacizumab treatments or 1 calendar year, whichever occurred sooner, or until recurrence of disease, or patient/clinician withdrawal for any other reason. After completion of the treatment period patients were followed-up every 3 months until 2 years, then 6 monthly until 5 years and then annually until up to 10 years from randomisation (where possible).

If patients were withdrawn early from bevacizumab treatment (for reasons other than first distant recurrence) they, where possible, continued to have the scheduled study visits and investigations until first distant recurrence.

In the event of first distant recurrence, follow up as per above schedule ceased and patients were monitored and managed as indicated locally. Annual follow up (survival and disease recurrence) continued until 10 years from randomisation (where possible), death, loss to follow up or withdrawal of consent.

| | |
|-----------------------|-------------|
| Reporting group title | Observation |
|-----------------------|-------------|

Reporting group description:

Patients received no interventions on this arm. Patients were followed-up at 6 weeks, 3 months, then every 3 months until 2 years, then 6 monthly until 5 years and then annually until up to 10 years from randomisation (where possible).

In the event of first distant recurrence or withdrawal from study, follow up as per above schedule ceased and patients were monitored and managed as indicated locally. Annual follow up (survival and disease recurrence) continued until 10 years from randomisation (where possible), death, loss to follow up or withdrawal of consent.

Primary: Overall survival

| | |
|-----------------|------------------|
| End point title | Overall survival |
|-----------------|------------------|

End point description:

Overall survival time is the time between the date of randomisation and death, whatever the cause. Patients discontinuing the study, or lost to follow-up, and still alive were censored at the last known date alive.

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

End point timeframe:

On study

| End point values | Treatment | Observation | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 671 | 672 | | |
| Units: number of deaths | 280 | 294 | | |

Statistical analyses

| | |
|----------------------------|------------------|
| Statistical analysis title | Overall Survival |
|----------------------------|------------------|

Statistical analysis description:

A Cox proportional hazard model was used to compare overall survival across trial arms and obtain hazard ratios and associated 95% CIs.

| | |
|---|-------------------------|
| Comparison groups | Treatment v Observation |
| Number of subjects included in analysis | 1343 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.55 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 1.12 |

Secondary: Disease free interval

| | |
|---|-----------------------|
| End point title | Disease free interval |
| End point description: Disease-free interval (DFI) is defined as the time between the date of randomisation and the date of tumour progression which occurs at any site of the body (inclusive of both distant and locoregional recurrence), or date of death due to melanoma, whichever occurs first. | |
| End point type | Secondary |
| End point timeframe: On study, until disease progression or death due to melanoma | |

| End point values | Treatment | Observation | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 671 | 672 | | |
| Units: Events | 346 | 386 | | |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Disease free interval |
| Statistical analysis description: A Cox proportional hazard model was used to compare disease free interval across trial arms and obtain hazard ratios and associated 95% CIs. | |
| Comparison groups | Observation v Treatment |

| | |
|---|-------------------|
| Number of subjects included in analysis | 1343 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.02 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 0.97 |

Secondary: Distant metastasis-free interval

| | |
|--|----------------------------------|
| End point title | Distant metastasis-free interval |
| End point description: | |
| Distant metastasis-free interval (DMFI) is defined as the time between the date of randomisation and the date of recurrent disease occurring at distant sites (excluding locoregional disease amenable to surgical resection), or date of death due to melanoma, whichever occurs first. | |
| End point type | Secondary |
| End point timeframe: | |
| On study until distant progression, or death due to melanoma | |

| End point values | Treatment | Observation | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 671 | 672 | | |
| Units: Events | 301 | 327 | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Distant metastatic free interval |
| Statistical analysis description: | |
| A Cox proportional hazard model was used to compare distant metastatic free interval across trial arms and obtain hazard ratios and associated 95% CIs. | |
| Comparison groups | Treatment v Observation |
| Number of subjects included in analysis | 1343 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.14 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.89 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 1.04 |

Secondary: Quality of life (QoL)

| | |
|--|-----------------------|
| End point title | Quality of life (QoL) |
| End point description: | |
| Global health scale assessed through the EORTC QLQC30 patient-completed questionnaire at time points: 3 monthly until 2 years, then at 2.5 years, 3 years, 4 years and 5 years | |
| End point type | Secondary |
| End point timeframe: | |
| On Study until 5 years from randomisation | |

| End point values | Treatment | Observation | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 600 | 626 | | |
| Units: Standardised area under a curve | | | | |
| median (inter-quartile range (Q1-Q3)) | 81.7 (69.8 to 90.7) | 81.9 (68.6 to 91.7) | | |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Global health scale |
| Statistical analysis description: | |
| The global health scale of the EORTC-QLQ-C30 QoL questionnaire data were analysed by standardised area under the curve (AUC) and compared across trial arms using Wilcoxon rank sum tests | |
| Comparison groups | Treatment v Observation |
| Number of subjects included in analysis | 1226 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.52 |
| Method | Wilcoxon (Mann-Whitney) |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment arm: All adverse events which occurred from randomisation until 28 days after the final dose of study drug

Observation arm: All adverse events which occurred from randomisation until year 1 or distant recurrence, whichever occurred first

Adverse event reporting additional description:

The national cancer institute common terminology criteria for adverse events (CTCAE) version 3.0 were used in this study. All toxic events were graded according to NCI CTCAE V3.0.

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

Dictionary used

| | |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

| | |
|--------------------|-----|
| Dictionary version | 3.0 |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Treatment |
|-----------------------|-----------|

Reporting group description: -

| | |
|-----------------------|-------------|
| Reporting group title | Observation |
|-----------------------|-------------|

Reporting group description: -

| Serious adverse events | Treatment | Observation | |
|---|--------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 140 / 671 (20.86%) | 49 / 672 (7.29%) | |
| number of deaths (all causes) | 280 | 294 | |
| number of deaths resulting from adverse events | 8 | 3 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Secondary Malignancy | | | |
| subjects affected / exposed | 2 / 671 (0.30%) | 6 / 672 (0.89%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 40 / 671 (5.96%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 44 / 49 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hematoma | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Portal flow | | | |
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis/thrombus/embolism | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Pregnancy | | | |
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy of partner | | | |
| subjects affected / exposed | 2 / 671 (0.30%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ectopic pregnancy | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 3 / 671 (0.45%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 671 (0.60%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Fever | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 7 / 671 (1.04%) | 3 / 672 (0.45%) | |
| occurrences causally related to treatment / all | 3 / 7 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rigors/chills | | | |
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seroma | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 3 / 672 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sweating | | | |
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Allergic reaction | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (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 | | | |
| Breast | | | |
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erectile dysfunction | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Hemorrhage vaginal | | | |
| subjects affected / exposed | 2 / 671 (0.30%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Irregular menses | | | |
| subjects affected / exposed | 3 / 671 (0.45%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnea | | | |
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 671 (0.45%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest tightness | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Voice changes | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusion | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Depression | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Hemoglobin | | | |
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| 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 | | | |
| Intraop Injury - Other (Specify) | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac General - Other (Specify) | | | |
| subjects affected / exposed | 4 / 671 (0.60%) | 2 / 672 (0.30%) | |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Cardiac ischemia/infarction | | | |
| subjects affected / exposed | 4 / 671 (0.60%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac pain | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asystole | | | |
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular systolic dysfunction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vasovagal episode | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| CNS hemorrhage | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CNS ischemia | | | |
| subjects affected / exposed | 3 / 671 (0.45%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 7 / 671 (1.04%) | 2 / 672 (0.30%) | |
| occurrences causally related to treatment / all | 4 / 7 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Memory impairment | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sensory neuropathy | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 671 (0.30%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Syncope (fainting) | | | |
| subjects affected / exposed | 2 / 671 (0.30%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anemia | | | |
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Ear and labyrinth disorders | | | |
| External ear pain | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoacusis | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Blurred vision | | | |
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cataract | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Optic neuritis | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 5 / 671 (0.75%) | 2 / 672 (0.30%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhea | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 3 / 672 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal - Other (Specify, ___) | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemorrhage rectum | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal hemorrhage | | | |
| subjects affected / exposed | 2 / 671 (0.30%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucositis | | | |
| subjects affected / exposed | 2 / 671 (0.30%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 671 (0.30%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ruptured appendix | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 671 (0.30%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Gallbladder pain | | | |
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage of liver | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver Cirrhosis | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatology/Skin - Other (Specify, ___) | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash | | | |
| subjects affected / exposed | 2 / 671 (0.30%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|-----------------|--|
| Ulceration | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (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 | | | |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (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 | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 671 (0.30%) | 3 / 672 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Chest wall pain | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (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 | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint pain | | | |
| subjects affected / exposed | 4 / 671 (0.60%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal/Soft Tissue - Other (Specify, __) | Additional description: Granulomatous Erosion | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Infections and infestations | | | |
| Abdominal infection | | | |
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 8 / 671 (1.19%) | 7 / 672 (1.04%) | |
| occurrences causally related to treatment / all | 1 / 9 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection - Other | | | |
| subjects affected / exposed | 6 / 671 (0.89%) | 2 / 672 (0.30%) | |
| occurrences causally related to treatment / all | 3 / 6 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic infection | | | |
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| 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 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 3 / 671 (0.45%) | 5 / 672 (0.74%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| ALT | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| AST | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GGT | | | |
| subjects affected / exposed | 3 / 671 (0.45%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypercalcemia | | | |
| subjects affected / exposed | 0 / 671 (0.00%) | 1 / 672 (0.15%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycemia | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatremia | | | |

| | | | |
|---|---------------------------------------|-----------------|--|
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophosphatemia | | | |
| subjects affected / exposed | 1 / 671 (0.15%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders Other (Specify, __) | Additional description: Increased LDH | | |
| subjects affected / exposed | 2 / 671 (0.30%) | 0 / 672 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

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

| Non-serious adverse events | Treatment | Observation | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 624 / 671 (93.00%) | 414 / 672 (61.61%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 232 / 671 (34.58%) | 52 / 672 (7.74%) | |
| occurrences (all) | 346 | 57 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 39 / 671 (5.81%) | 15 / 672 (2.23%) | |
| occurrences (all) | 45 | 15 | |
| Headache | | | |
| subjects affected / exposed | 162 / 671 (24.14%) | 30 / 672 (4.46%) | |
| occurrences (all) | 262 | 34 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 242 / 671 (36.07%) | 60 / 672 (8.93%) | |
| occurrences (all) | 352 | 61 | |
| Pain | | | |

| | | | |
|--|---------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 146 / 671 (21.76%) 208 | 67 / 672 (9.97%) 77 | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 43 / 671 (6.41%) | 18 / 672 (2.68%) | |
| occurrences (all) | 45 | 19 | |
| Diarrhea | | | |
| subjects affected / exposed | 90 / 671 (13.41%) | 27 / 672 (4.02%) | |
| occurrences (all) | 129 | 30 | |
| Nausea | | | |
| subjects affected / exposed | 100 / 671 (14.90%) | 22 / 672 (3.27%) | |
| occurrences (all) | 141 | 25 | |
| Vomiting | | | |
| subjects affected / exposed | 47 / 671 (7.00%) | 7 / 672 (1.04%) | |
| occurrences (all) | 59 | 7 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 54 / 671 (8.05%) | 28 / 672 (4.17%) | |
| occurrences (all) | 60 | 28 | |
| Epistaxis | | | |
| subjects affected / exposed | 116 / 671 (17.29%) | 1 / 672 (0.15%) | |
| occurrences (all) | 147 | 1 | |
| Voice changes | | | |
| subjects affected / exposed | 34 / 671 (5.07%) | 0 / 672 (0.00%) | |
| occurrences (all) | 39 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 63 / 671 (9.39%) | 14 / 672 (2.08%) | |
| occurrences (all) | 81 | 14 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 56 / 671 (8.35%) | 28 / 672 (4.17%) | |
| occurrences (all) | 60 | 29 | |
| Joint pain | | | |
| subjects affected / exposed | 50 / 671 (7.45%) | 16 / 672 (2.38%) | |
| occurrences (all) | 64 | 19 | |

| | | | |
|---|------------------------|------------------------|--|
| Pain in extremity subjects affected / exposed occurrences (all) | 41 / 671 (6.11%) 46 | 36 / 672 (5.36%) 41 | |
|---|------------------------|------------------------|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 02 October 2007 | <ul style="list-style-type: none">-To include an appendix in the protocol for the treatment of hypertension-To make changes to the conduct of the trial, including inclusion and exclusion criteria-To add additional research bloods-To include a patient card-To update the protocol, patient information sheet and GP letter to reflect recently published information regarding use of bevacizumab in the treatment of melanoma and other cancers.-To update the protocol, patient information sheet and GP letter to reflect recently published information regarding use of interferon as adjuvant treatment of melanoma. |
| 10 July 2008 | <ul style="list-style-type: none">- To include new patient groups (AJCC stage IIB (T3bNoMo))- Lengthen time baseline CT/MRI scans and Chest X-ray need to be done prior to randomisation.- To clarify a number of points in the protocol especially regarding what happens to patients if they have recurrence.- To change the CI, to change the PI at some sites and to add new sites. |
| 13 July 2009 | <p>Inclusion criteria:</p> <ul style="list-style-type: none">- Addition of 12 week timelimit from SLNB to CLND if these are the latest surgeries for melanoma.- Addition that BP must be ≤ 150 systolic AND ≤ 100 diastolic mmHg.- Addition of the clause 'unless pre-existing abnormality' to the adequate liver function criterion. <p>Exclusion criteria:</p> <ul style="list-style-type: none">- Deletion of 'even if previously treated' from evidence of CNS metastases criterion.- Deletion of the uncontrolled hypertension criterion, as BP values added to inclusion criteria.- Deletion of 'or participation in another clinical trial' from treatment with any other investigational agent criterion.- Changing treatment period from 51 weeks to 1 calendar year to make it easier to keep track of when the treatment period ends.- Inclusion of guidance on seromas.- Removal of dose capping for Avastin- Inclusion of a section on pregnancy reporting.- Adding into the study assessments, flowchart & schedule that contact needs to be made with patients for survival info annually from 5.5 yrs.- Other wording clarifications |
| 11 March 2011 | <p>New sections have been added to reflect new safety information and study results. A number of points have been clarified to help with the conduct of the trial and several eligibility criteria have been amended.</p> <p>The PIS and ICF have been combined to make a single document. A number of grammatical changes & re-ordering of content have been made. Information has been added to reflect new study results and safety information.</p> <p>Addition of a sentence to say guidelines on the management of hypertension are available from the coordination team if required.</p> |

| | |
|------------------|---|
| 03 November 2016 | <p>Request to close the study to the MHRA for regulatory purposes in March 2017 to correspond with 5 year follow-up analysis.</p> <p>This amendment was declined by MHRA</p> |
| 22 May 2017 | Update to reference safety information, addition of new undesirable effects |
| 28 August 2017 | <p>As the 5 year final analysis has now been performed, patient clinic visits and trial interventions will cease following 5 years post randomisation. Survival and recurrence data only will continue to be collected until 10 years post randomisation up to 2022.</p> <p>Patients on the AVAST-M trial have consented to be followed up for up to 10 years after randomisation. This includes collecting survival and recurrence information.</p> <p>Once established, survival and recurrence data will be collected centrally until 2022 on an annual basis by remote data collection from the appropriate Government Department of Health national registry (i.e. Public Health England (National Cancer Registration and Analysis Service or Office for National Statistics)).</p> <p>Long term follow-up data for survival and disease recurrence may be collected using NHS Spine by the local research team.</p> <p>Reference Safety Information identified for Investigational Medicinal Product in protocol as requested by the MHRA.</p> |
| 28 February 2018 | <p>Patients in Scotland and Wales (n=75) will not participate in remote data collection due to the financial aspects of applying to each different Government registry.</p> <p>All patients in the AVAST-M trial have already completed 5 years of follow-up after randomisation. The 5 year follow-up data has provided us with sufficient information to enable the main trial objectives for this stage in the trial to be answered.</p> <p>The 5 year analysis has now been performed and patient clinic visits and trial investigations have ceased (as per amendment 41). Survival and recurrence data only is being collected until up to 10 years post randomisation up to 2022 for patients in England only.</p> <p>Patients on the AVAST-M trial have consented to be followed up for up to 10 years after randomisation, therefore we will not be re-consenting patients to the trial as a result of this amendment</p> <p>A new Trial Participant letter for patients in Scotland and Wales which has been included as part of this substantial amendment outlining changes to follow-up arrangements for the AVAST-M trial for patients in Scotland and Wales.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24745696>

<http://www.ncbi.nlm.nih.gov/pubmed/30010756>