



Clinical trial results:

Multicentre randomized phase II study of neoadjuvant trastuzumab plus docetaxel with and without bevacizumab and trastuzumab plus docetaxel plus non-pegylated liposome-encapsulated doxorubicin (NPLD) with and without bevacizumab in HER2-positive early breast cancer

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2010-023324-25 |
| Trial protocol | AT |
| Global end of trial date | 16 April 2014 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 11 September 2021 |
| First version publication date | 11 September 2021 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | ABCSG32 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01367028 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | ABCSG (Austrian Breast & Colorectal Cancer Study Group) |
| Sponsor organisation address | Nußdorfer Platz 8/12, Vienna, Austria, 1190 |
| Public contact | Hannes Fohler (Trial Office Director), ABCSG (Austrian Breast & Colorectal Cancer Study Group), +43 1408 92 30, info@abcsbg.at |
| Scientific contact | Prof. Guenther Steger, ABCSG (Austrian Breast & Colorectal Cancer Study Group), +43 1408 92 30, info@abcsbg.at |

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 | 16 April 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 April 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 April 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the cardiac toxicity of the combination trastuzumab and docetaxel with bevacizumab and trastuzumab, docetaxel, and NPLD plus/minus bevacizumab in comparison to the standard therapy, i.e. trastuzumab and docetaxel.

Protection of trial subjects:

An independent Data Monitoring Committee (IDMC) was established to assess Patient Safety. The responsibility of the IDMC was to evaluate deviations of medical relevance and safety issues. The DMC decided whether or not the patient should continue the study treatment due to safety issues. Furthermore, a dedicated meeting took place after 25 patients have finished therapy. In addition, the study specific ICF included guidance for patients where to reach the study doctor as well as patient advocacy in case of any questions and patients were encouraged to consult the study doctor in case of any questions (e.g. concerning cardiac insufficiency).

Background therapy:

Docetaxel + Trastuzumab were considered as standard therapy (Trastuzumab was provided for this study whereas Docetaxel was considered SoC and used as per local standard).

Evidence for comparator:

In most of Europe, trastuzumab is licensed in combination with docetaxel as first-line therapy of HER2 positive metastatic breast cancer, where a significant survival benefit has been demonstrated for the combination compared with chemotherapy.

| | |
|---|--------------|
| Actual start date of recruitment | 07 June 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Austria: 100 |
| Worldwide total number of subjects | 100 |
| EEA total number of subjects | 100 |

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) | 78 |
| From 65 to 84 years | 22 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 100 patients was recruited (divided into the 4 arms). Recruitment was completed within 27 months.

Pre-assignment

Screening details:

Once a potential patient signed the ICF, their screening period started and screening assessments were performed within 28 days prior to randomization. Among other criteria, patients were required to have an LVEF \geq 55% at screening.

Pre-assignment period milestones

| | |
|------------------------------|-----|
| Number of subjects started | 100 |
| Number of subjects completed | 100 |

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 | Doc+Trast |

Arm description:

Docetaxel + Trastuzumab

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Docetaxel is an approved treatment and therefore was no study treatment (NIMP). 100mg/m² (in arms A and B) or 75mg/m² (in arms C and D); 6 cycles in 3-weekly treatment cycles.

| | |
|--|--|
| Investigational medicinal product name | Herceptin |
| Investigational medicinal product code | |
| Other name | Trastuzumab |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

8mg/kg loading dose on Day 1 of the first study treatment cycle; followed by 6mg/kg maintenance dose on Day 1 of subsequent cycles.

| | |
|------------------|---------------|
| Arm title | Doc+Trast+Bev |
|------------------|---------------|

Arm description:

Docetaxel + Trastuzumab + Bevacizumab

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Docetaxel is an approved treatment and therefore was no study treatment (NIMP). 100mg/m² (in arms A and B) or 75mg/m² (in arms C and D); 6 cycles in 3-weekly treatment cycles.

| | |
|--|--|
| Investigational medicinal product name | Herceptin |
| Investigational medicinal product code | |
| Other name | Trastuzumab |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

8mg/kg loading dose on Day 1 of the first study treatment cycle; followed by 6mg/kg maintenance dose on Day 1 of subsequent cycles.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Avastin |
| Investigational medicinal product code | |
| Other name | Bevacizumab |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

15 mg/kg on Day 1 of each treatment cycle; 6 cycles in 3-weekly treatment cycles.

| | |
|------------------|----------------|
| Arm title | Doc+Trast+NPLD |
|------------------|----------------|

Arm description:

Docetaxel + Trastuzumab + NPLD

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Docetaxel is an approved treatment and therefore was no study treatment (NIMP). 100mg/m² (in arms A and B) or 75mg/m² (in arms C and D); 6 cycles in 3-weekly treatment cycles.

| | |
|--|--|
| Investigational medicinal product name | Herceptin |
| Investigational medicinal product code | |
| Other name | Trastuzumab |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

8mg/kg loading dose on Day 1 of the first study treatment cycle; followed by 6mg/kg maintenance dose on Day 1 of subsequent cycles.

| | |
|--|--|
| Investigational medicinal product name | Myocet |
| Investigational medicinal product code | |
| Other name | NLPD (non-pegylated liposomal doxorubicin) |
| Pharmaceutical forms | Powder and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

50mg/m² by 60 min IV infusion on Day 1 of each treatment cycle; 6 cycles in 3-weekly treatment cycles.

| | |
|------------------|--------------------|
| Arm title | Doc+Trast+Bev+NPLD |
|------------------|--------------------|

Arm description:

Docetaxel +Trastuzumab + Bevacizumab + NPLD

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Docetaxel is an approved treatment and therefore was no study treatment (NIMP). 100mg/m² (in arms A and B) or 75mg/m² (in arms C and D); 6 cycles in 3-weekly treatment cycles.

| | |
|--|--|
| Investigational medicinal product name | Herceptin |
| Investigational medicinal product code | |
| Other name | Trastuzumab |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

8mg/kg loading dose on Day 1 of the first study treatment cycle; followed by 6mg/kg maintenance dose on Day 1 of subsequent cycles.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Avastin |
| Investigational medicinal product code | |
| Other name | Bevacizumab |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

15 mg/kg on Day 1 of each treatment cycle; 6 cycles in 3-weekly treatment cycles.

| | |
|--|--|
| Investigational medicinal product name | Myocet |
| Investigational medicinal product code | |
| Other name | NLPD (non-pegylated liposomal doxorubicin) |
| Pharmaceutical forms | Powder and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

50mg/m² by 60 min IV infusion on Day 1 of each treatment cycle; 6 cycles in 3-weekly treatment cycles.

| Number of subjects in period 1 | Doc+Trast | Doc+Trast+Bev | Doc+Trast+NPLD |
|---------------------------------------|-----------|---------------|----------------|
| Started | 25 | 25 | 26 |
| Completed | 24 | 20 | 24 |
| Not completed | 1 | 5 | 2 |
| Consent withdrawn by subject | - | 3 | 2 |
| wrong regime | - | 1 | - |
| Adverse event, non-fatal | 1 | 1 | - |

| Number of subjects in period 1 | Doc+Trast+Bev+NPLD |
|---------------------------------------|--------------------|
| Started | 24 |
| Completed | 21 |
| Not completed | 3 |
| Consent withdrawn by subject | 3 |
| wrong regime | - |
| Adverse event, non-fatal | - |

Baseline characteristics

Reporting groups

| | |
|---|--------------------|
| Reporting group title | Doc+Trast |
| Reporting group description: Docetaxel + Trastuzumab | |
| Reporting group title | Doc+Trast+Bev |
| Reporting group description: Docetaxel + Trastuzumab + Bevacizumab | |
| Reporting group title | Doc+Trast+NPLD |
| Reporting group description: Docetaxel + Trastuzumab + NPLD | |
| Reporting group title | Doc+Trast+Bev+NPLD |
| Reporting group description: Docetaxel +Trastuzumab + Bevacizumab + NPLD | |

| Reporting group values | Doc+Trast | Doc+Trast+Bev | Doc+Trast+NPLD |
|---|-----------|---------------|----------------|
| Number of subjects | 25 | 25 | 26 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 20 | 20 | 21 |
| From 65-84 years | 5 | 5 | 5 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| median | 49 | 51 | 51.5 |
| full range (min-max) | 23 to 75 | 28 to 79 | 30 to 75 |
| Gender categorical Units: Subjects | | | |
| Female | 25 | 25 | 26 |
| Male | 0 | 0 | 0 |
| Menopausal status Units: Subjects | | | |
| perimenopausal | 0 | 2 | 0 |
| postmenopausal | 12 | 12 | 13 |
| premenopausal | 13 | 11 | 13 |
| ECOG Units: Subjects | | | |
| 0 (zero) | 25 | 25 | 26 |

| | | | |
|-------------------------|------------|------------|------------|
| 1 (one) | 0 | 0 | 0 |
| T-stage | | | |
| Units: Subjects | | | |
| T1 | 7 | 5 | 10 |
| T2 | 15 | 18 | 12 |
| T3 | 1 | 1 | 3 |
| T4 | 1 | 1 | 1 |
| Missing | 1 | 0 | 0 |
| N-stage | | | |
| Units: Subjects | | | |
| N0 | 15 | 15 | 19 |
| N1 | 9 | 8 | 7 |
| N2 | 1 | 1 | 0 |
| N3 | 0 | 1 | 0 |
| Grading | | | |
| Units: Subjects | | | |
| G1 | 0 | 0 | 1 |
| G2 | 8 | 9 | 7 |
| G3 | 16 | 15 | 16 |
| GX | 1 | 1 | 1 |
| Missing | 0 | 0 | 1 |
| Hormone receptor status | | | |
| Units: Subjects | | | |
| negative | 13 | 12 | 12 |
| positive | 12 | 13 | 14 |
| Height | | | |
| Units: cm | | | |
| median | 166 | 166 | 164.5 |
| full range (min-max) | 150 to 176 | 151 to 176 | 155 to 179 |
| Weight | | | |
| Units: kg | | | |
| median | 64 | 67.9 | 68.8 |
| full range (min-max) | 51.6 to 92 | 46 to 113 | 47 to 94 |

| Reporting group values | Doc+Trast+Bev+NP LD | Total | |
|---|------------------------|-------|--|
| Number of subjects | 24 | 100 | |
| 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) | 17 | 78 | |
| From 65-84 years | 7 | 22 | |
| 85 years and over | 0 | 0 | |

| | | | |
|--|----------------------|-----|--|
| Age continuous Units: years median full range (min-max) | 52 29 to 77 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 24 | 100 | |
| Male | 0 | 0 | |
| Menopausal status Units: Subjects | | | |
| perimenopausal | 0 | 2 | |
| postmenopausal | 14 | 51 | |
| premenopausal | 10 | 47 | |
| ECOG Units: Subjects | | | |
| 0 (zero) | 23 | 99 | |
| 1 (one) | 1 | 1 | |
| T-stage Units: Subjects | | | |
| T1 | 7 | 29 | |
| T2 | 14 | 59 | |
| T3 | 3 | 8 | |
| T4 | 0 | 3 | |
| Missing | 0 | 1 | |
| N-stage Units: Subjects | | | |
| N0 | 14 | 63 | |
| N1 | 10 | 34 | |
| N2 | 0 | 2 | |
| N3 | 0 | 1 | |
| Grading Units: Subjects | | | |
| G1 | 1 | 2 | |
| G2 | 6 | 30 | |
| G3 | 16 | 63 | |
| GX | 1 | 4 | |
| Missing | 0 | 1 | |
| Hormone receptor status Units: Subjects | | | |
| negative | 10 | 47 | |
| positive | 14 | 53 | |
| Height Units: cm median full range (min-max) | 163.75 155 to 173 | - | |
| Weight Units: kg median full range (min-max) | 66 51 to 110 | - | |

End points

End points reporting groups

| | |
|--|--------------------|
| Reporting group title | Doc+Trast |
| Reporting group description: Docetaxel + Trastuzumab | |
| Reporting group title | Doc+Trast+Bev |
| Reporting group description: Docetaxel + Trastuzumab + Bevacizumab | |
| Reporting group title | Doc+Trast+NPLD |
| Reporting group description: Docetaxel + Trastuzumab + NPLD | |
| Reporting group title | Doc+Trast+Bev+NPLD |
| Reporting group description: Docetaxel +Trastuzumab + Bevacizumab + NPLD | |
| Subject analysis set title | ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The ITT population consists of all randomized patients with signed informed consent. Every subject is analysed according to the randomized treatment independent of the treatment administered. Efficacy endpoints as well as demographic and baseline characteristics are based on the ITT population. | |
| Subject analysis set title | Safety |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The safety population comprises all randomized patients with informed consent who received at least one dose of any study medication. Every patient is analysed according to the actual treatment received. Safety endpoints (including all adverse events) are based on the safety population. Since the primary endpoint represents a safety issue, it is analysed based on the SAF population as well. | |

Primary: Cardiac toxicity

| | |
|--|---------------------------------|
| End point title | Cardiac toxicity ^[1] |
| End point description: The primary study endpoint is cardiac toxicity of the combination trastuzumab and docetaxel with bevacizumab and trastuzumab, docetaxel, and NPLD plus/minus bevacizumab using a composite endpoint. The composite endpoint of cardiac toxicity is defined by the appearance of either of the following variables: <ul style="list-style-type: none">• symptomatic left ventricular dysfunction NYHA grade II, III, or IV or <ul style="list-style-type: none">• asymptomatic left ventricular dysfunction defined as a decrease of the left ventricular ejection fraction of $\geq 15\%$-points as compared to base-line with a measured value still above the lower limit of normal (55%) or <ul style="list-style-type: none">• asymptomatic left ventricular dysfunction defined as a decrease of the left ventricular ejection fraction (as measured by echocardiography of $\geq 10\%$-points as compared to baseline with a measured value below the lower limit of normal (55%) or <ul style="list-style-type: none">• significant arrhythmias requiring medical treatment or invasive diagnostic measures | |
| End point type | Primary |
| End point timeframe: Between day 1 of cycle 1 and day 28 \pm 3 days after the day of final surgery | |

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: Analysis is descriptive only.

| End point values | Doc+Trast | Doc+Trast+Be v | Doc+Trast+NP LD | Doc+Trast+Be v+NPLD |
|-----------------------------|-------------------|-------------------|--------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 ^[2] | 25 ^[3] | 26 ^[4] | 24 ^[5] |
| Units: Subjects | 0 | 0 | 2 | 1 |

Notes:

[2] - Number in safety analysis set:25

[3] - Number in safety analysis set:21

[4] - Number in safety analysis set:27

[5] - Number in safety analysis set:24

| End point values | Safety | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 100 ^[6] | | | |
| Units: Subjects | 3 | | | |

Notes:

[6] - Number in safety analysis set:97

Statistical analyses

No statistical analyses for this end point

Secondary: Pathological Complete Response (ypCR)

| | |
|-----------------|---------------------------------------|
| End point title | Pathological Complete Response (ypCR) |
|-----------------|---------------------------------------|

End point description:

Pathological complete response (ypCR), defined as absence of invasive tumor (ypT0 or ypTis).
Secondary efficacy endpoints are described using frequency tables and associated 95% confidence intervals.

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

End point timeframe:

At final surgery

| End point values | Doc+Trast | Doc+Trast+Be v | Doc+Trast+NP LD | Doc+Trast+Be v+NPLD |
|----------------------------------|---------------------|--------------------|---------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 22 | 24 | 21 |
| Units: percent | | | | |
| number (confidence interval 95%) | 0.36 (0.17 to 0.55) | 0.5 (0.29 to 0.71) | 0.63 (0.43 to 0.82) | 0.62 (0.41 to 0.83) |

Statistical analyses

| | |
|----------------------------|---------------|
| Statistical analysis title | D+T+B vs. D+T |
|----------------------------|---------------|

Statistical analysis description:

The group receiving treatment combination docetaxel + trastuzumab + bevacizumab is compared to the control group receiving standard therapy (docetaxel + trastuzumab) using Fisher's Exact test.

| | |
|-------------------|---------------------------|
| Comparison groups | Doc+Trast v Doc+Trast+Bev |
|-------------------|---------------------------|

| | |
|---|---------------|
| Number of subjects included in analysis | 47 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.386 |
| Method | Fisher exact |

| | |
|-----------------------------------|---------------|
| Statistical analysis title | D+T+N vs. D+T |
|-----------------------------------|---------------|

Statistical analysis description:

The group receiving treatment combination docetaxel + trastuzumab + NPLD is compared to the control group receiving standard therapy (docetaxel + trastuzumab) using Fisher's Exact test.

| | |
|---|----------------------------|
| Comparison groups | Doc+Trast v Doc+Trast+NPLD |
| Number of subjects included in analysis | 49 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0887 |
| Method | Fisher exact |

| | |
|-----------------------------------|-----------------|
| Statistical analysis title | D+T+B+N vs. D+T |
|-----------------------------------|-----------------|

Statistical analysis description:

The group receiving treatment combination docetaxel + trastuzumab + bevacizumab + NPLD is compared to the control group receiving standard therapy (docetaxel + trastuzumab) using Fisher's Exact test.

| | |
|---|--------------------------------|
| Comparison groups | Doc+Trast+Bev+NPLD v Doc+Trast |
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1378 |
| Method | Fisher exact |

Secondary: Total pathological complete response (ytpCR)

| | |
|-----------------|--|
| End point title | Total pathological complete response (ytpCR) |
|-----------------|--|

End point description:

Total pathological complete response (ytpCR), defined as absence of invasive tumor and tumor cells in the breast (ypT0 or ypTis) and the axillar lymphnodes (ypN=0). Secondary efficacy endpoints are described using frequency tables and associated 95% confidence intervals.

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

End point timeframe:

At final surgery

| End point values | Doc+Trast | Doc+Trast+Be v | Doc+Trast+NPLD | Doc+Trast+Be v+NPLD |
|----------------------------------|---------------------|--------------------|---------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 22 | 24 | 21 |
| Units: percent | | | | |
| number (confidence interval 95%) | 0.36 (0.17 to 0.55) | 0.41 (0.2 to 0.61) | 0.58 (0.39 to 0.78) | 0.57 (0.36 to 0.78) |

Statistical analyses

| Statistical analysis title | D+T+B vs. D+T |
|---|---------------------------|
| Statistical analysis description: The group receiving treatment combination docetaxel + trastuzumab + bevacizumab is compared to the control group receiving standard therapy (docetaxel + trastuzumab) using Fisher's Exact test. | |
| Comparison groups | Doc+Trast v Doc+Trast+Bev |
| Number of subjects included in analysis | 47 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.7712 |
| Method | Fisher exact |

| Statistical analysis title | D+T+N vs. D+T |
|--|----------------------------|
| Statistical analysis description: The group receiving treatment combination docetaxel + trastuzumab + NPLD is compared to the control group receiving standard therapy (docetaxel + trastuzumab) using Fisher's Exact test. | |
| Comparison groups | Doc+Trast v Doc+Trast+NPLD |
| Number of subjects included in analysis | 49 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1564 |
| Method | Fisher exact |

| Statistical analysis title | D+T+B+N vs. D+T |
|--|--------------------------------|
| Statistical analysis description: The group receiving treatment combination docetaxel + trastuzumab + bevacizumab + NPLD is compared to the control group receiving standard therapy (docetaxel + trastuzumab) using Fisher's Exact test. | |
| Comparison groups | Doc+Trast v Doc+Trast+Bev+NPLD |
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.235 |
| Method | Fisher exact |

Secondary: Overall clinical response rate (cORR)

| | |
|---|---------------------------------------|
| End point title | Overall clinical response rate (cORR) |
| End point description: Overall clinical response rate (cORR) defined as the percentage of patients with either a complete clinical response (cCR) or a partial clinical response (cPR). Secondary efficacy endpoints are described using frequency tables and associated 95% confidence intervals. | |
| End point type | Secondary |
| End point timeframe: At final surgery | |

| End point values | Doc+Trast | Doc+Trast+Bev | Doc+Trast+NPLD | Doc+Trast+Bev+NPLD |
|----------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 25 | 22 | 24 | 21 |
| Units: percent | | | | |
| number (confidence interval 95%) | 0.56 (0.37 to 0.75) | 0.36 (0.16 to 0.56) | 0.25 (0.08 to 0.42) | 0.24 (0.06 to 0.42) |

Statistical analyses

| | |
|---|---------------------------|
| Statistical analysis title | D+T+B vs. D+T |
| Statistical analysis description: The group receiving treatment combination docetaxel + trastuzumab + bevacizumab is compared to the control group receiving standard therapy (docetaxel + trastuzumab) using Fisher's Exact test. | |
| Comparison groups | Doc+Trast v Doc+Trast+Bev |
| Number of subjects included in analysis | 47 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.2445 |
| Method | Fisher exact |

| | |
|--|----------------------------|
| Statistical analysis title | D+T+N vs. D+T |
| Statistical analysis description: The group receiving treatment combination docetaxel + trastuzumab + NPLD is compared to the control group receiving standard therapy (docetaxel + trastuzumab) using Fisher's Exact test. | |
| Comparison groups | Doc+Trast v Doc+Trast+NPLD |
| Number of subjects included in analysis | 49 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0421 |
| Method | Fisher exact |

| | |
|----------------------------|-----------------|
| Statistical analysis title | D+T+B+N vs. D+T |
|----------------------------|-----------------|

Statistical analysis description:

The group receiving treatment combination docetaxel + trastuzumab + bevacizumab + NPLD is compared to the control group receiving standard therapy (docetaxel + trastuzumab) using Fisher's Exact test.

| | |
|---|--------------------------------|
| Comparison groups | Doc+Trast v Doc+Trast+Bev+NPLD |
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0376 |
| Method | Fisher exact |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

from Informed Consent Form signature until the Follow up visit (scheduled 28 days +/- 3days after surgery)

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 14.0 |

Reporting groups

| | |
|--------------------------------|--------------------|
| Reporting group title | Doc+Trast |
| Reporting group description: - | |
| Reporting group title | Doc+Trast+Bev |
| Reporting group description: - | |
| Reporting group title | Doc+Trast+NPLD |
| Reporting group description: - | |
| Reporting group title | Doc+Trast+Bev+NPLD |
| Reporting group description: - | |

| Serious adverse events | Doc+Trast | Doc+Trast+Bev | Doc+Trast+NPLD |
|---|---|-----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 25 (16.00%) | 6 / 21 (28.57%) | 9 / 27 (33.33%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Vascular disorders | | | |
| Hypertension | Additional description: Hypertension | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | Additional description: Hypertensive crisis | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | Additional description: Febrile neutropenia | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 21 (4.76%) | 2 / 27 (7.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | Additional description: Leukopenia | | |

| | | | |
|--|---|----------------|----------------|
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | Additional description: Asthenia | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | Additional description: Chest pain | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | Additional description: Fatigue | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | Additional description: General physical health deterioration | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | Additional description: Pain | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal rigidity | Additional description: Abdominal rigidity | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ulcerative | Additional description: Colitis ulcerative | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|----------------|----------------|
| Diarrhoea | Additional description: Diarrhoea | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 21 (0.00%) | 2 / 27 (7.41%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | Additional description: Large intestine perforation | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | Additional description: Nausea | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 21 (4.76%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | Additional description: Dyspnoea | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperventilation | Additional description: Hyperventilation | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oropharyngeal pain | Additional description: Oropharyngeal pain | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | Additional description: Pneumothorax | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Acne | Additional description: Acne | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|--|----------------|----------------|
| Night sweats subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: Night sweats | | |
| | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| | 0 / 0 | 0 / 0 | 1 / 1 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders Depression subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: Depression | | |
| | 1 / 25 (4.00%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| | 0 / 3 | 0 / 0 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders Renal pain subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: Renal pain | | |
| | 0 / 25 (0.00%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| | 0 / 0 | 1 / 1 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations Abdominal abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: Abdominal abscess | | |
| | 0 / 25 (0.00%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| | 0 / 0 | 0 / 2 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: Device related infection | | |
| | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 2 / 27 (7.41%) |
| | 0 / 0 | 0 / 0 | 1 / 2 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: Febrile infection | | |
| | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| | 0 / 0 | 0 / 0 | 0 / 1 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Infected epidermal cyst subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: Infected epidermal cyst | | |
| | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | Additional description: Infection | | |
| | | | |

| | | | |
|---|---|----------------|----------------|
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | Additional description: Pneumonia | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | Additional description: Postoperative wound infection | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | Additional description: Sepsis | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superinfection | Additional description: Superinfection | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | Additional description: Wound infection | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hypercalcaemia | Additional description: Hypercalcaemia | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|------------------------|--|--|
| Serious adverse events | Doc+Trast+Bev+NP LD | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 24 (37.50%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

| | | | |
|--------------------|--|---|--|
| Vascular disorders | | | |
| | Hypertension | Additional description: Hypertension | |
| | subjects affected / exposed | 0 / 24 (0.00%) | |
| | occurrences causally related to treatment / all | 0 / 0 | |
| | deaths causally related to treatment / all | 0 / 0 | |
| | Hypertensive crisis | Additional description: Hypertensive crisis | |
| | subjects affected / exposed | 0 / 24 (0.00%) | |
| | occurrences causally related to treatment / all | 0 / 0 | |
| | deaths causally related to treatment / all | 0 / 0 | |
| | Blood and lymphatic system disorders | | |
| | Febrile neutropenia | Additional description: Febrile neutropenia | |
| | subjects affected / exposed | 4 / 24 (16.67%) | |
| | occurrences causally related to treatment / all | 5 / 5 | |
| | deaths causally related to treatment / all | 0 / 0 | |
| | Leukopenia | Additional description: Leukopenia | |
| | subjects affected / exposed | 0 / 24 (0.00%) | |
| | occurrences causally related to treatment / all | 0 / 0 | |
| | deaths causally related to treatment / all | 0 / 0 | |
| | General disorders and administration site conditions | | |
| | Asthenia | Additional description: Asthenia | |
| | subjects affected / exposed | 0 / 24 (0.00%) | |
| | occurrences causally related to treatment / all | 0 / 0 | |
| | deaths causally related to treatment / all | 0 / 0 | |
| | Chest pain | Additional description: Chest pain | |
| | subjects affected / exposed | 0 / 24 (0.00%) | |
| | occurrences causally related to treatment / all | 0 / 0 | |
| | deaths causally related to treatment / all | 0 / 0 | |
| | Fatigue | Additional description: Fatigue | |
| | subjects affected / exposed | 1 / 24 (4.17%) | |
| | occurrences causally related to treatment / all | 1 / 1 | |
| | deaths causally related to treatment / all | 0 / 0 | |
| | General physical health deterioration | Additional description: General physical health deterioration | |

| | | | |
|---|---|--|--|
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain | Additional description: Pain | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal rigidity | Additional description: Abdominal rigidity | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis ulcerative | Additional description: Colitis ulcerative | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | Additional description: Diarrhoea | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestine perforation | Additional description: Large intestine perforation | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | Additional description: Nausea | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | Additional description: Dyspnoea | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|--|--|--|
| Hyperventilation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: Hyperventilation | | |
| | 0 / 24 (0.00%) | | |
| | 0 / 0 | | |
| | 0 / 0 | | |
| Oropharyngeal pain subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: Oropharyngeal pain | | |
| | 1 / 24 (4.17%) | | |
| | 1 / 1 | | |
| | 0 / 0 | | |
| Pneumothorax subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: Pneumothorax | | |
| | 1 / 24 (4.17%) | | |
| | 0 / 1 | | |
| | 0 / 0 | | |
| Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: Acne | | |
| | 0 / 24 (0.00%) | | |
| | 0 / 0 | | |
| | 0 / 0 | | |
| Night sweats subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: Night sweats | | |
| | 0 / 24 (0.00%) | | |
| | 0 / 0 | | |
| | 0 / 0 | | |
| Psychiatric disorders Depression subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: Depression | | |
| | 0 / 24 (0.00%) | | |
| | 0 / 0 | | |
| | 0 / 0 | | |
| Renal and urinary disorders Renal pain subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | Additional description: Renal pain | | |
| | 0 / 24 (0.00%) | | |
| | 0 / 0 | | |
| | 0 / 0 | | |
| Infections and infestations Abdominal abscess | Additional description: Abdominal abscess | | |
| | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device related infection | Additional description: Device related infection | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile infection | Additional description: Febrile infection | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infected epidermal cyst | Additional description: Infected epidermal cyst | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infection | Additional description: Infection | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | Additional description: Pneumonia | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Postoperative wound infection | Additional description: Postoperative wound infection | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | Additional description: Sepsis | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Superinfection | Additional description: Superinfection | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound infection | Additional description: Wound infection | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hypercalcaemia | Additional description: Hypercalcaemia | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Doc+Trast | Doc+Trast+Bev | Doc+Trast+NPLD |
|---|--------------------------------------|-------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 25 / 25 (100.00%) | 21 / 21 (100.00%) | 26 / 27 (96.30%) |
| Vascular disorders | | | |
| Flushing | Additional description: Flushing | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hot flush | Additional description: Hot flush | | |
| subjects affected / exposed | 4 / 25 (16.00%) | 2 / 21 (9.52%) | 3 / 27 (11.11%) |
| occurrences (all) | 5 | 2 | 3 |
| Hypertension | Additional description: Hypertension | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 2 / 21 (9.52%) | 2 / 27 (7.41%) |
| occurrences (all) | 0 | 2 | 3 |
| Hypotension | Additional description: Hypotension | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 0 | 0 | 2 |
| General disorders and administration site conditions | | | |
| Asthenia | Additional description: Asthenia | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 2 / 21 (9.52%) | 2 / 27 (7.41%) |
| occurrences (all) | 1 | 2 | 2 |

| | | | |
|---|--|------------------------|------------------------|
| Chest pain subjects affected / exposed occurrences (all) | Additional description: Chest pain | | |
| | 0 / 25 (0.00%) 0 | 1 / 21 (4.76%) 1 | 2 / 27 (7.41%) 3 |
| Chills subjects affected / exposed occurrences (all) | Additional description: Chills | | |
| | 0 / 25 (0.00%) 0 | 0 / 21 (0.00%) 0 | 4 / 27 (14.81%) 4 |
| Impaired healing subjects affected / exposed occurrences (all) | Additional description: Impaired healing | | |
| | 0 / 25 (0.00%) 0 | 2 / 21 (9.52%) 2 | 0 / 27 (0.00%) 0 |
| Fatigue subjects affected / exposed occurrences (all) | Additional description: Fatigue | | |
| | 17 / 25 (68.00%) 32 | 15 / 21 (71.43%) 29 | 18 / 27 (66.67%) 30 |
| Influenza like illness subjects affected / exposed occurrences (all) | Additional description: Influenza like illness | | |
| | 1 / 25 (4.00%) 1 | 1 / 21 (4.76%) 1 | 2 / 27 (7.41%) 2 |
| Mucosal dryness subjects affected / exposed occurrences (all) | Additional description: Mucosal dryness | | |
| | 4 / 25 (16.00%) 5 | 1 / 21 (4.76%) 2 | 2 / 27 (7.41%) 4 |
| Mucosal inflammation subjects affected / exposed occurrences (all) | Additional description: Mucosal inflammation | | |
| | 2 / 25 (8.00%) 2 | 2 / 21 (9.52%) 4 | 2 / 27 (7.41%) 3 |
| Oedema peripheral subjects affected / exposed occurrences (all) | Additional description: Oedema peripheral | | |
| | 8 / 25 (32.00%) 14 | 1 / 21 (4.76%) 1 | 7 / 27 (25.93%) 8 |
| Pain subjects affected / exposed occurrences (all) | Additional description: Pain | | |
| | 3 / 25 (12.00%) 7 | 2 / 21 (9.52%) 2 | 4 / 27 (14.81%) 4 |
| Pyrexia subjects affected / exposed occurrences (all) | Additional description: Pyrexia | | |
| | 2 / 25 (8.00%) 3 | 3 / 21 (14.29%) 3 | 8 / 27 (29.63%) 8 |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | Additional description: Hypersensitivity | | |
| | 3 / 25 (12.00%) 6 | 1 / 21 (4.76%) 1 | 1 / 27 (3.70%) 1 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|------------------------|-----------------------|
| Cough subjects affected / exposed occurrences (all) | Additional description: Cough | | |
| | 4 / 25 (16.00%) 4 | 1 / 21 (4.76%) 1 | 2 / 27 (7.41%) 2 |
| Dysphonia subjects affected / exposed occurrences (all) | Additional description: Dysphonia | | |
| | 0 / 25 (0.00%) 0 | 2 / 21 (9.52%) 2 | 0 / 27 (0.00%) 0 |
| Dyspnoea subjects affected / exposed occurrences (all) | Additional description: Dyspnoea | | |
| | 5 / 25 (20.00%) 8 | 0 / 21 (0.00%) 0 | 1 / 27 (3.70%) 1 |
| Dyspnoea exertional subjects affected / exposed occurrences (all) | Additional description: Dyspnoea exertional | | |
| | 3 / 25 (12.00%) 3 | 1 / 21 (4.76%) 1 | 0 / 27 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | Additional description: Epistaxis | | |
| | 5 / 25 (20.00%) 7 | 10 / 21 (47.62%) 13 | 8 / 27 (29.63%) 11 |
| Nasal dryness subjects affected / exposed occurrences (all) | Additional description: Nasal dryness | | |
| | 1 / 25 (4.00%) 1 | 2 / 21 (9.52%) 2 | 2 / 27 (7.41%) 2 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | Additional description: Oropharyngeal pain | | |
| | 1 / 25 (4.00%) 2 | 5 / 21 (23.81%) 7 | 0 / 27 (0.00%) 0 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | Additional description: Rhinorrhoea | | |
| | 1 / 25 (4.00%) 2 | 0 / 21 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Psychiatric disorders | | | |
| | Additional description: Anxiety | | |
| | 2 / 25 (8.00%) 2 | 0 / 21 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| | Additional description: Insomnia | | |
| | 3 / 25 (12.00%) 7 | 1 / 21 (4.76%) 1 | 1 / 27 (3.70%) 1 |
| | Additional description: Sleep disorder | | |
| | 4 / 25 (16.00%) 4 | 3 / 21 (14.29%) 3 | 4 / 27 (14.81%) 5 |
| Investigations | | | |

| | | | |
|---|--|----------------------|-----------------------|
| Body temperature increased subjects affected / exposed occurrences (all) | Additional description: Body temperature increased | | |
| | 1 / 25 (4.00%) 2 | 2 / 21 (9.52%) 2 | 1 / 27 (3.70%) 1 |
| Injury, poisoning and procedural complications Seroma subjects affected / exposed occurrences (all) | Additional description: Seroma | | |
| | 1 / 25 (4.00%) 1 | 2 / 21 (9.52%) 2 | 0 / 27 (0.00%) 0 |
| Cardiac disorders Pericardial effusion subjects affected / exposed occurrences (all) Cardiovascular disorder subjects affected / exposed occurrences (all) Sinus bradycardia subjects affected / exposed occurrences (all) Sinus tachycardia subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all) | Additional description: Pericardial effusion | | |
| | 0 / 25 (0.00%) 0 | 2 / 21 (9.52%) 2 | 0 / 27 (0.00%) 0 |
| | Additional description: Cardiovascular disorder | | |
| | 0 / 25 (0.00%) 0 | 0 / 21 (0.00%) 0 | 2 / 27 (7.41%) 2 |
| | Additional description: Sinus bradycardia | | |
| | 0 / 25 (0.00%) 0 | 0 / 21 (0.00%) 0 | 2 / 27 (7.41%) 2 |
| | Additional description: Sinus tachycardia | | |
| | 2 / 25 (8.00%) 2 | 0 / 21 (0.00%) 0 | 1 / 27 (3.70%) 1 |
| | Additional description: Tachycardia | | |
| | 0 / 25 (0.00%) 0 | 1 / 21 (4.76%) 1 | 2 / 27 (7.41%) 2 |
| Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Neuropathy peripheral subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) | Additional description: Dysgeusia | | |
| | 8 / 25 (32.00%) 9 | 6 / 21 (28.57%) 8 | 9 / 27 (33.33%) 12 |
| | Additional description: Headache | | |
| | 3 / 25 (12.00%) 3 | 2 / 21 (9.52%) 3 | 2 / 27 (7.41%) 2 |
| | Additional description: Neuropathy peripheral | | |
| | 2 / 25 (8.00%) 5 | 3 / 21 (14.29%) 6 | 0 / 27 (0.00%) 0 |
| | Additional description: Paraesthesia | | |
| | 5 / 25 (20.00%) 8 | 1 / 21 (4.76%) 1 | 7 / 27 (25.93%) 7 |

| | | | |
|---|---|-----------------|-----------------|
| Parosmia subjects affected / exposed occurrences (all) | Additional description: Parosmia | | |
| | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 2 / 27 (7.41%) |
| | 0 | 0 | 2 |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | Additional description: Peripheral sensory neuropathy | | |
| | 1 / 25 (4.00%) | 1 / 21 (4.76%) | 2 / 27 (7.41%) |
| | 3 | 1 | 2 |
| Polyneuropathy subjects affected / exposed occurrences (all) | Additional description: Polyneuropathy | | |
| | 8 / 25 (32.00%) | 7 / 21 (33.33%) | 6 / 27 (22.22%) |
| | 14 | 11 | 7 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | Additional description: Anaemia | | |
| | 1 / 25 (4.00%) | 1 / 21 (4.76%) | 2 / 27 (7.41%) |
| | 2 | 1 | 3 |
| Neutropenia subjects affected / exposed occurrences (all) | Additional description: Neutropenia | | |
| | 0 / 25 (0.00%) | 3 / 21 (14.29%) | 0 / 27 (0.00%) |
| | 0 | 3 | 0 |
| Ear and labyrinth disorders | | | |
| Ototoxicity subjects affected / exposed occurrences (all) | Additional description: Ototoxicity | | |
| | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 2 / 27 (7.41%) |
| | 0 | 0 | 2 |
| Vertigo subjects affected / exposed occurrences (all) | Additional description: Vertigo | | |
| | 4 / 25 (16.00%) | 2 / 21 (9.52%) | 3 / 27 (11.11%) |
| | 4 | 2 | 5 |
| Eye disorders | | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | Additional description: Conjunctivitis | | |
| | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 3 / 27 (11.11%) |
| | 0 | 0 | 4 |
| Dry eye subjects affected / exposed occurrences (all) | Additional description: Dry eye | | |
| | 2 / 25 (8.00%) | 0 / 21 (0.00%) | 2 / 27 (7.41%) |
| | 2 | 0 | 2 |
| Eye pruritus subjects affected / exposed occurrences (all) | Additional description: Eye pruritus | | |
| | 0 / 25 (0.00%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| | 0 | 0 | 0 |
| Lacrimation increased subjects affected / exposed occurrences (all) | Additional description: Lacrimation increased | | |
| | 6 / 25 (24.00%) | 7 / 21 (33.33%) | 3 / 27 (11.11%) |
| | 6 | 10 | 3 |
| Gastrointestinal disorders | | | |

| | | | |
|--|--|------------------------|------------------------|
| Abdominal pain upper subjects affected / exposed occurrences (all) | Additional description: Abdominal pain upper | | |
| | 2 / 25 (8.00%) 2 | 2 / 21 (9.52%) 3 | 1 / 27 (3.70%) 1 |
| Abdominal pain subjects affected / exposed occurrences (all) | Additional description: Abdominal pain | | |
| | 2 / 25 (8.00%) 2 | 1 / 21 (4.76%) 1 | 1 / 27 (3.70%) 1 |
| Anal haemorrhage subjects affected / exposed occurrences (all) | Additional description: Anal haemorrhage | | |
| | 0 / 25 (0.00%) 0 | 2 / 21 (9.52%) 2 | 0 / 27 (0.00%) 0 |
| Constipation subjects affected / exposed occurrences (all) | Additional description: Constipation | | |
| | 10 / 25 (40.00%) 17 | 4 / 21 (19.05%) 9 | 10 / 27 (37.04%) 17 |
| Diarrhoea subjects affected / exposed occurrences (all) | Additional description: Diarrhoea | | |
| | 13 / 25 (52.00%) 30 | 10 / 21 (47.62%) 20 | 8 / 27 (29.63%) 10 |
| Dry mouth subjects affected / exposed occurrences (all) | Additional description: Dry mouth | | |
| | 2 / 25 (8.00%) 2 | 2 / 21 (9.52%) 2 | 0 / 27 (0.00%) 0 |
| Dyspepsia subjects affected / exposed occurrences (all) | Additional description: Dyspepsia | | |
| | 4 / 25 (16.00%) 5 | 1 / 21 (4.76%) 1 | 3 / 27 (11.11%) 3 |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | Additional description: Gastrooesophageal reflux disease | | |
| | 1 / 25 (4.00%) 1 | 1 / 21 (4.76%) 1 | 0 / 27 (0.00%) 0 |
| Dysphagia subjects affected / exposed occurrences (all) | Additional description: Dysphagia | | |
| | 1 / 25 (4.00%) 1 | 2 / 21 (9.52%) 2 | 0 / 27 (0.00%) 0 |
| Gingivitis subjects affected / exposed occurrences (all) | Additional description: Gingivitis | | |
| | 0 / 25 (0.00%) 0 | 2 / 21 (9.52%) 3 | 0 / 27 (0.00%) 0 |
| Haemorrhoids subjects affected / exposed occurrences (all) | Additional description: Haemorrhoids | | |
| | 2 / 25 (8.00%) 2 | 1 / 21 (4.76%) 1 | 0 / 27 (0.00%) 0 |
| Nausea subjects affected / exposed occurrences (all) | Additional description: Nausea | | |
| | 7 / 25 (28.00%) 15 | 9 / 21 (42.86%) 11 | 14 / 27 (51.85%) 26 |

| | | | |
|---|---|------------------|------------------|
| Toothache subjects affected / exposed occurrences (all) | Additional description: Toothache | | |
| | 2 / 25 (8.00%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| | 2 | 0 | 0 |
| Stomatitis subjects affected / exposed occurrences (all) | Additional description: Stomatitis | | |
| | 5 / 25 (20.00%) | 9 / 21 (42.86%) | 6 / 27 (22.22%) |
| | 11 | 16 | 7 |
| Vomiting subjects affected / exposed occurrences (all) | Additional description: Vomiting | | |
| | 2 / 25 (8.00%) | 5 / 21 (23.81%) | 3 / 27 (11.11%) |
| | 2 | 5 | 6 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | Additional description: Alopecia | | |
| | 8 / 25 (32.00%) | 10 / 21 (47.62%) | 12 / 27 (44.44%) |
| | 8 | 11 | 12 |
| Dermatitis subjects affected / exposed occurrences (all) | Additional description: Dermatitis | | |
| | 1 / 25 (4.00%) | 2 / 21 (9.52%) | 0 / 27 (0.00%) |
| | 1 | 4 | 0 |
| Dry skin subjects affected / exposed occurrences (all) | Additional description: Dry skin | | |
| | 2 / 25 (8.00%) | 5 / 21 (23.81%) | 3 / 27 (11.11%) |
| | 2 | 5 | 3 |
| Erythema subjects affected / exposed occurrences (all) | Additional description: Erythema | | |
| | 2 / 25 (8.00%) | 2 / 21 (9.52%) | 1 / 27 (3.70%) |
| | 3 | 2 | 1 |
| Nail discolouration subjects affected / exposed occurrences (all) | Additional description: Nail discolouration | | |
| | 2 / 25 (8.00%) | 2 / 21 (9.52%) | 0 / 27 (0.00%) |
| | 2 | 2 | 0 |
| Nail disorder subjects affected / exposed occurrences (all) | Additional description: Nail disorder | | |
| | 7 / 25 (28.00%) | 1 / 21 (4.76%) | 2 / 27 (7.41%) |
| | 10 | 1 | 2 |
| Nail dystrophy subjects affected / exposed occurrences (all) | Additional description: Nail dystrophy | | |
| | 3 / 25 (12.00%) | 1 / 21 (4.76%) | 1 / 27 (3.70%) |
| | 4 | 1 | 1 |
| Nail toxicity subjects affected / exposed occurrences (all) | Additional description: Nail toxicity | | |
| | 3 / 25 (12.00%) | 4 / 21 (19.05%) | 0 / 27 (0.00%) |
| | 3 | 8 | 0 |
| Onychalgia | Additional description: Onychalgia | | |
| | | | |

| | | | |
|---|---|-----------------|-----------------|
| subjects affected / exposed | 0 / 25 (0.00%) | 2 / 21 (9.52%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | Additional description: Palmar-plantar erythrodysaesthesia syndrome | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 6 / 21 (28.57%) | 3 / 27 (11.11%) |
| occurrences (all) | 2 | 8 | 3 |
| Pruritus | Additional description: Pruritus | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Rash | Additional description: Rash | | |
| subjects affected / exposed | 9 / 25 (36.00%) | 7 / 21 (33.33%) | 2 / 27 (7.41%) |
| occurrences (all) | 11 | 10 | 3 |
| Skin disorder | Additional description: Skin disorder | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 21 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | Additional description: Arthralgia | | |
| subjects affected / exposed | 11 / 25 (44.00%) | 6 / 21 (28.57%) | 4 / 27 (14.81%) |
| occurrences (all) | 12 | 11 | 5 |
| Back pain | Additional description: Back pain | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 21 (4.76%) | 6 / 27 (22.22%) |
| occurrences (all) | 0 | 1 | 10 |
| Bone pain | Additional description: Bone pain | | |
| subjects affected / exposed | 5 / 25 (20.00%) | 6 / 21 (28.57%) | 8 / 27 (29.63%) |
| occurrences (all) | 6 | 8 | 14 |
| Muscular weakness | Additional description: Muscular weakness | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences (all) | 3 | 4 | 0 |
| Musculoskeletal pain | Additional description: Musculoskeletal pain | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 21 (4.76%) | 0 / 27 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Myalgia | Additional description: Myalgia | | |
| subjects affected / exposed | 7 / 25 (28.00%) | 5 / 21 (23.81%) | 4 / 27 (14.81%) |
| occurrences (all) | 12 | 5 | 9 |
| Pain in extremity | Additional description: Pain in extremity | | |

| | | | |
|--|--|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 3 / 25 (12.00%) 6 | 2 / 21 (9.52%) 2 | 4 / 27 (14.81%) 5 |
| Infections and infestations | | | |
| Device related infection | Additional description: Device related infection | | |
| subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 21 (0.00%) 0 | 2 / 27 (7.41%) 2 |
| Folliculitis | Additional description: Folliculitis | | |
| subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 1 / 21 (4.76%) 1 | 0 / 27 (0.00%) 0 |
| Nasopharyngitis | Additional description: Nasopharyngitis | | |
| subjects affected / exposed occurrences (all) | 3 / 25 (12.00%) 6 | 5 / 21 (23.81%) 6 | 2 / 27 (7.41%) 2 |
| Oral candidiasis | Additional description: Oral candidiasis | | |
| subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 2 / 21 (9.52%) 5 | 2 / 27 (7.41%) 2 |
| Paronychia | Additional description: Paronychia | | |
| subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 2 / 21 (9.52%) 3 | 0 / 27 (0.00%) 0 |
| Rhinitis | Additional description: Rhinitis | | |
| subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 4 / 21 (19.05%) 4 | 5 / 27 (18.52%) 6 |
| Rash pustular | Additional description: Rash pustular | | |
| subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 2 / 21 (9.52%) 2 | 0 / 27 (0.00%) 0 |
| Urinary tract infection | Additional description: Urinary tract infection | | |
| subjects affected / exposed occurrences (all) | 5 / 25 (20.00%) 7 | 3 / 21 (14.29%) 4 | 2 / 27 (7.41%) 2 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | Additional description: Decreased appetite | | |
| subjects affected / exposed occurrences (all) | 3 / 25 (12.00%) 3 | 0 / 21 (0.00%) 0 | 6 / 27 (22.22%) 6 |
| Hyperglycaemia | Additional description: Hyperglycaemia | | |
| subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | 0 / 21 (0.00%) 0 | 1 / 27 (3.70%) 2 |
| Non-serious adverse events | Doc+Trast+Bev+NP LD | | |

| | | | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 23 / 24 (95.83%) | | |
| Vascular disorders | | | |
| Flushing | Additional description: Flushing | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 3 | | |
| Hot flush | Additional description: Hot flush | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypertension | Additional description: Hypertension | | |
| subjects affected / exposed | 4 / 24 (16.67%) | | |
| occurrences (all) | 11 | | |
| Hypotension | Additional description: Hypotension | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 2 | | |
| General disorders and administration site conditions | | | |
| Asthenia | Additional description: Asthenia | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Chest pain | Additional description: Chest pain | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Chills | Additional description: Chills | | |
| subjects affected / exposed | 3 / 24 (12.50%) | | |
| occurrences (all) | 3 | | |
| Impaired healing | Additional description: Impaired healing | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Fatigue | Additional description: Fatigue | | |
| subjects affected / exposed | 18 / 24 (75.00%) | | |
| occurrences (all) | 54 | | |
| Influenza like illness | Additional description: Influenza like illness | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 4 | | |
| Mucosal dryness | Additional description: Mucosal dryness | | |

| | | | |
|---|--|--|--|
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Mucosal inflammation | Additional description: Mucosal inflammation | | |
| subjects affected / exposed | 3 / 24 (12.50%) | | |
| occurrences (all) | 4 | | |
| Oedema peripheral | Additional description: Oedema peripheral | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 2 | | |
| Pain | Additional description: Pain | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Pyrexia | Additional description: Pyrexia | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Immune system disorders | | | |
| Hypersensitivity | Additional description: Hypersensitivity | | |
| subjects affected / exposed | 3 / 24 (12.50%) | | |
| occurrences (all) | 5 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | Additional description: Cough | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 3 | | |
| Dysphonia | Additional description: Dysphonia | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 3 | | |
| Dyspnoea | Additional description: Dyspnoea | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dyspnoea exertional | Additional description: Dyspnoea exertional | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Epistaxis | Additional description: Epistaxis | | |
| subjects affected / exposed | 10 / 24 (41.67%) | | |
| occurrences (all) | 20 | | |
| Nasal dryness | Additional description: Nasal dryness | | |

| | | | |
|--|--|--|--|
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oropharyngeal pain | Additional description: Oropharyngeal pain | | |
| subjects affected / exposed | 3 / 24 (12.50%) | | |
| occurrences (all) | 4 | | |
| Rhinorrhoea | Additional description: Rhinorrhoea | | |
| subjects affected / exposed | 3 / 24 (12.50%) | | |
| occurrences (all) | 3 | | |
| Psychiatric disorders | | | |
| Anxiety | Additional description: Anxiety | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Insomnia | Additional description: Insomnia | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sleep disorder | Additional description: Sleep disorder | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Investigations | | | |
| Body temperature increased | Additional description: Body temperature increased | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Seroma | Additional description: Seroma | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |
| Pericardial effusion | Additional description: Pericardial effusion | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cardiovascular disorder | Additional description: Cardiovascular disorder | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sinus bradycardia | Additional description: Sinus bradycardia | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|---|--|--|
| Sinus tachycardia subjects affected / exposed occurrences (all) | Additional description: Sinus tachycardia | | |
| | 0 / 24 (0.00%) | | |
| | 0 | | |
| Tachycardia subjects affected / exposed occurrences (all) | Additional description: Tachycardia | | |
| | 1 / 24 (4.17%) | | |
| | 1 | | |
| Nervous system disorders | | | |
| Dysgeusia subjects affected / exposed occurrences (all) | Additional description: Dysgeusia | | |
| | 5 / 24 (20.83%) | | |
| | 6 | | |
| Headache subjects affected / exposed occurrences (all) | Additional description: Headache | | |
| | 4 / 24 (16.67%) | | |
| | 7 | | |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | Additional description: Neuropathy peripheral | | |
| | 1 / 24 (4.17%) | | |
| | 1 | | |
| Paraesthesia subjects affected / exposed occurrences (all) | Additional description: Paraesthesia | | |
| | 2 / 24 (8.33%) | | |
| | 2 | | |
| Parosmia subjects affected / exposed occurrences (all) | Additional description: Parosmia | | |
| | 0 / 24 (0.00%) | | |
| | 0 | | |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | Additional description: Peripheral sensory neuropathy | | |
| | 1 / 24 (4.17%) | | |
| | 1 | | |
| Polyneuropathy subjects affected / exposed occurrences (all) | Additional description: Polyneuropathy | | |
| | 4 / 24 (16.67%) | | |
| | 4 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | Additional description: Anaemia | | |
| | 2 / 24 (8.33%) | | |
| | 2 | | |
| Neutropenia subjects affected / exposed occurrences (all) | Additional description: Neutropenia | | |
| | 4 / 24 (16.67%) | | |
| | 4 | | |
| Ear and labyrinth disorders | | | |

| | | | |
|---|---|--|--|
| Otototoxicity subjects affected / exposed occurrences (all) | Additional description: Otototoxicity | | |
| | 0 / 24 (0.00%) | | |
| | 0 | | |
| Vertigo subjects affected / exposed occurrences (all) | Additional description: Vertigo | | |
| | 4 / 24 (16.67%) | | |
| | 5 | | |
| Eye disorders | | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | Additional description: Conjunctivitis | | |
| | 0 / 24 (0.00%) | | |
| | 0 | | |
| Dry eye subjects affected / exposed occurrences (all) | Additional description: Dry eye | | |
| | 0 / 24 (0.00%) | | |
| | 0 | | |
| Eye pruritus subjects affected / exposed occurrences (all) | Additional description: Eye pruritus | | |
| | 2 / 24 (8.33%) | | |
| | 2 | | |
| Lacrimation increased subjects affected / exposed occurrences (all) | Additional description: Lacrimation increased | | |
| | 6 / 24 (25.00%) | | |
| | 6 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | Additional description: Abdominal pain upper | | |
| | 2 / 24 (8.33%) | | |
| | 2 | | |
| Abdominal pain subjects affected / exposed occurrences (all) | Additional description: Abdominal pain | | |
| | 2 / 24 (8.33%) | | |
| | 2 | | |
| Anal haemorrhage subjects affected / exposed occurrences (all) | Additional description: Anal haemorrhage | | |
| | 0 / 24 (0.00%) | | |
| | 0 | | |
| Constipation subjects affected / exposed occurrences (all) | Additional description: Constipation | | |
| | 7 / 24 (29.17%) | | |
| | 10 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | Additional description: Diarrhoea | | |
| | 9 / 24 (37.50%) | | |
| | 17 | | |
| Dry mouth | Additional description: Dry mouth | | |
| | | | |

| | | | |
|--|--|--|--|
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dyspepsia | Additional description: Dyspepsia | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Gastrooesophageal reflux disease | Additional description: Gastrooesophageal reflux disease | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Dysphagia | Additional description: Dysphagia | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Gingivitis | Additional description: Gingivitis | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Haemorrhoids | Additional description: Haemorrhoids | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Nausea | Additional description: Nausea | | |
| subjects affected / exposed | 5 / 24 (20.83%) | | |
| occurrences (all) | 7 | | |
| Toothache | Additional description: Toothache | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Stomatitis | Additional description: Stomatitis | | |
| subjects affected / exposed | 5 / 24 (20.83%) | | |
| occurrences (all) | 12 | | |
| Vomiting | Additional description: Vomiting | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | Additional description: Alopecia | | |
| subjects affected / exposed | 13 / 24 (54.17%) | | |
| occurrences (all) | 15 | | |
| Dermatitis | Additional description: Dermatitis | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|--|---|--|--|
| Dry skin subjects affected / exposed occurrences (all) | Additional description: Dry skin | | |
| | 1 / 24 (4.17%) 1 | | |
| Erythema subjects affected / exposed occurrences (all) | Additional description: Erythema | | |
| | 1 / 24 (4.17%) 1 | | |
| Nail discolouration subjects affected / exposed occurrences (all) | Additional description: Nail discolouration | | |
| | 0 / 24 (0.00%) 0 | | |
| Nail disorder subjects affected / exposed occurrences (all) | Additional description: Nail disorder | | |
| | 0 / 24 (0.00%) 0 | | |
| Nail dystrophy subjects affected / exposed occurrences (all) | Additional description: Nail dystrophy | | |
| | 2 / 24 (8.33%) 2 | | |
| Nail toxicity subjects affected / exposed occurrences (all) | Additional description: Nail toxicity | | |
| | 3 / 24 (12.50%) 4 | | |
| Onychalgia subjects affected / exposed occurrences (all) | Additional description: Onychalgia | | |
| | 0 / 24 (0.00%) 0 | | |
| Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) | Additional description: Palmar-plantar erythrodysaesthesia syndrome | | |
| | 0 / 24 (0.00%) 0 | | |
| Pruritus subjects affected / exposed occurrences (all) | Additional description: Pruritus | | |
| | 0 / 24 (0.00%) 0 | | |
| Rash subjects affected / exposed occurrences (all) | Additional description: Rash | | |
| | 4 / 24 (16.67%) 5 | | |
| Skin disorder subjects affected / exposed occurrences (all) | Additional description: Skin disorder | | |
| | 2 / 24 (8.33%) 2 | | |
| Musculoskeletal and connective tissue disorders | | | |

| | | |
|---|--|--|
| Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all) Muscular weakness subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) | Additional description: Arthralgia | |
| | 4 / 24 (16.67%) | |
| | 4 | |
| | Additional description: Back pain | |
| | 3 / 24 (12.50%) | |
| | 6 | |
| | Additional description: Bone pain | |
| | 3 / 24 (12.50%) | |
| | 3 | |
| | Additional description: Muscular weakness | |
| | 1 / 24 (4.17%) | |
| | 3 | |
| | Additional description: Musculoskeletal pain | |
| | 2 / 24 (8.33%) | |
| | 3 | |
| | Additional description: Myalgia | |
| | 1 / 24 (4.17%) | |
| | 1 | |
| | Additional description: Pain in extremity | |
| | 3 / 24 (12.50%) | |
| | 3 | |
| Infections and infestations Device related infection subjects affected / exposed occurrences (all) Folliculitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Oral candidiasis subjects affected / exposed occurrences (all) Paronychia | | |
| | Additional description: Device related infection | |
| | 0 / 24 (0.00%) | |
| | 0 | |
| | Additional description: Folliculitis | |
| | 0 / 24 (0.00%) | |
| | 0 | |
| | Additional description: Nasopharyngitis | |
| | 2 / 24 (8.33%) | |
| | 2 | |
| | Additional description: Oral candidiasis | |
| | 3 / 24 (12.50%) | |
| | 7 | |
| | Additional description: Paronychia | |

| | | | |
|------------------------------------|---|--|--|
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinitis | Additional description: Rhinitis | | |
| subjects affected / exposed | 5 / 24 (20.83%) | | |
| occurrences (all) | 6 | | |
| Rash pustular | Additional description: Rash pustular | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urinary tract infection | Additional description: Urinary tract infection | | |
| subjects affected / exposed | 5 / 24 (20.83%) | | |
| occurrences (all) | 5 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | Additional description: Decreased appetite | | |
| subjects affected / exposed | 3 / 24 (12.50%) | | |
| occurrences (all) | 6 | | |
| Hyperglycaemia | Additional description: Hyperglycaemia | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported