



## 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
<b>Arm title</b>	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/m<sup>2</sup> (in arms A and B) or 75mg/m<sup>2</sup> (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.

<b>Arm title</b>	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/m<sup>2</sup> (in arms A and B) or 75mg/m<sup>2</sup> (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.

<b>Arm title</b>	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/m<sup>2</sup> (in arms A and B) or 75mg/m<sup>2</sup> (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/m<sup>2</sup> by 60 min IV infusion on Day 1 of each treatment cycle; 6 cycles in 3-weekly treatment cycles.

<b>Arm title</b>	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/m<sup>2</sup> (in arms A and B) or 75mg/m<sup>2</sup> (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/m<sup>2</sup> by 60 min IV infusion on Day 1 of each treatment cycle; 6 cycles in 3-weekly treatment cycles.

<b>Number of subjects in period 1</b>	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	-

<b>Number of subjects in period 1</b>	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

<b>Reporting group values</b>	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 <sup>[1]</sup>
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"><li>• symptomatic left ventricular dysfunction NYHA grade II, III, or IV</li></ul> or <ul style="list-style-type: none"><li>• asymptomatic left ventricular dysfunction defined as a decrease of the left ventricular ejection fraction of <math>\geq 15\%</math>-points as compared to base-line with a measured value still above the lower limit of normal (55%)</li></ul> or <ul style="list-style-type: none"><li>• asymptomatic left ventricular dysfunction defined as a decrease of the left ventricular ejection fraction (as measured by echocardiography of <math>\geq 10\%</math>-points as compared to baseline with a measured value below the lower limit of normal (55%)</li></ul> or <ul style="list-style-type: none"><li>• significant arrhythmias requiring medical treatment or invasive diagnostic measures</li></ul>	
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 <sup>[2]</sup>	25 <sup>[3]</sup>	26 <sup>[4]</sup>	24 <sup>[5]</sup>
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 <sup>[6]</sup>			
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

<b>Statistical analysis title</b>	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

<b>Statistical analysis title</b>	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

<b>End point values</b>	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

<b>Statistical analysis title</b>	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

<b>Statistical analysis title</b>	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

<b>Statistical analysis title</b>	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

<b>Serious adverse events</b>	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
<b>Non-serious adverse events</b>	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