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@abcsg.at
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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 (devided 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 ≥ 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 doxorubiscin)
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 doxorubiscin)
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+NPLD	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	52		
full range (min-max)	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	163.75		
full range (min-max)	155 to 173	-	
Weight Units: kg			
median	66		
full range (min-max)	51 to 110	-	

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: • symptomatic left ventricular dysfunction NYHA grade II, III, or IV or • asymptomatic left ventricular dysfunction defined as a decrease of the left ventricular ejection fraction of ≥ 15%-points as compared to base-line with a measured value still above the lower limit of normal (55%) or • asymptomatic left ventricular dysfunction defined as a decrease of the left ventricular ejection fraction (as measured by echocardiography of ≥ 10%-points as compared to baseline with a measured value below the lower limit of normal (55%) or • 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 ± 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+Bev	Doc+Trast+NPLD	Doc+Trast+Bev+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+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%)	0.36 (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+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%)	0.36 (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	Additional description: Night sweats		
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
Psychiatric disorders			
Depression	Additional description: Depression		
subjects affected / exposed	1 / 25 (4.00%)	0 / 21 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal pain	Additional description: Renal 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
Infections and infestations			
Abdominal abscess	Additional description: Abdominal abscess		
subjects affected / exposed	0 / 25 (0.00%)	1 / 21 (4.76%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection	Additional description: Device related infection		
subjects affected / exposed	0 / 25 (0.00%)	0 / 21 (0.00%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection	Additional description: Febrile infection		
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	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected epidermal cyst	Additional description: Infected epidermal cyst		
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
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+NPLD		
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	Additional description: Hyperventilation		
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oropharyngeal pain	Additional description: Oropharyngeal pain		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax	Additional description: Pneumothorax		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Acne	Additional description: Acne		
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Night sweats	Additional description: Night sweats		
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression	Additional description: Depression		
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal pain	Additional description: Renal pain		
subjects affected / exposed	0 / 24 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	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	Additional description: Chest pain		
subjects affected / exposed	0 / 25 (0.00%)	1 / 21 (4.76%)	2 / 27 (7.41%)
occurrences (all)	0	1	3
Chills	Additional description: Chills		
subjects affected / exposed	0 / 25 (0.00%)	0 / 21 (0.00%)	4 / 27 (14.81%)
occurrences (all)	0	0	4
Impaired healing	Additional description: Impaired healing		
subjects affected / exposed	0 / 25 (0.00%)	2 / 21 (9.52%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Fatigue	Additional description: Fatigue		
subjects affected / exposed	17 / 25 (68.00%)	15 / 21 (71.43%)	18 / 27 (66.67%)
occurrences (all)	32	29	30
Influenza like illness	Additional description: Influenza like illness		
subjects affected / exposed	1 / 25 (4.00%)	1 / 21 (4.76%)	2 / 27 (7.41%)
occurrences (all)	1	1	2
Mucosal dryness	Additional description: Mucosal dryness		
subjects affected / exposed	4 / 25 (16.00%)	1 / 21 (4.76%)	2 / 27 (7.41%)
occurrences (all)	5	2	4
Mucosal inflammation	Additional description: Mucosal inflammation		
subjects affected / exposed	2 / 25 (8.00%)	2 / 21 (9.52%)	2 / 27 (7.41%)
occurrences (all)	2	4	3
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	8 / 25 (32.00%)	1 / 21 (4.76%)	7 / 27 (25.93%)
occurrences (all)	14	1	8
Pain	Additional description: Pain		
subjects affected / exposed	3 / 25 (12.00%)	2 / 21 (9.52%)	4 / 27 (14.81%)
occurrences (all)	7	2	4
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	2 / 25 (8.00%)	3 / 21 (14.29%)	8 / 27 (29.63%)
occurrences (all)	3	3	8
Immune system disorders			
Hypersensitivity	Additional description: Hypersensitivity		
subjects affected / exposed	3 / 25 (12.00%)	1 / 21 (4.76%)	1 / 27 (3.70%)
occurrences (all)	6	1	1
Respiratory, thoracic and mediastinal disorders			

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

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

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

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

Toothache	Additional description: Toothache		
subjects affected / exposed	2 / 25 (8.00%)	0 / 21 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Stomatitis	Additional description: Stomatitis		
subjects affected / exposed	5 / 25 (20.00%)	9 / 21 (42.86%)	6 / 27 (22.22%)
occurrences (all)	11	16	7
Vomiting	Additional description: Vomiting		
subjects affected / exposed	2 / 25 (8.00%)	5 / 21 (23.81%)	3 / 27 (11.11%)
occurrences (all)	2	5	6
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: Alopecia		
subjects affected / exposed	8 / 25 (32.00%)	10 / 21 (47.62%)	12 / 27 (44.44%)
occurrences (all)	8	11	12
Dermatitis	Additional description: Dermatitis		
subjects affected / exposed	1 / 25 (4.00%)	2 / 21 (9.52%)	0 / 27 (0.00%)
occurrences (all)	1	4	0
Dry skin	Additional description: Dry skin		
subjects affected / exposed	2 / 25 (8.00%)	5 / 21 (23.81%)	3 / 27 (11.11%)
occurrences (all)	2	5	3
Erythema	Additional description: Erythema		
subjects affected / exposed	2 / 25 (8.00%)	2 / 21 (9.52%)	1 / 27 (3.70%)
occurrences (all)	3	2	1
Nail discolouration	Additional description: Nail discolouration		
subjects affected / exposed	2 / 25 (8.00%)	2 / 21 (9.52%)	0 / 27 (0.00%)
occurrences (all)	2	2	0
Nail disorder	Additional description: Nail disorder		
subjects affected / exposed	7 / 25 (28.00%)	1 / 21 (4.76%)	2 / 27 (7.41%)
occurrences (all)	10	1	2
Nail dystrophy	Additional description: Nail dystrophy		
subjects affected / exposed	3 / 25 (12.00%)	1 / 21 (4.76%)	1 / 27 (3.70%)
occurrences (all)	4	1	1
Nail toxicity	Additional description: Nail toxicity		
subjects affected / exposed	3 / 25 (12.00%)	4 / 21 (19.05%)	0 / 27 (0.00%)
occurrences (all)	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	3 / 25 (12.00%)	2 / 21 (9.52%)	4 / 27 (14.81%)
occurrences (all)	6	2	5
Infections and infestations			
Device related infection	Additional description: Device related infection		
subjects affected / exposed	0 / 25 (0.00%)	0 / 21 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Folliculitis	Additional description: Folliculitis		
subjects affected / exposed	2 / 25 (8.00%)	1 / 21 (4.76%)	0 / 27 (0.00%)
occurrences (all)	2	1	0
Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	3 / 25 (12.00%)	5 / 21 (23.81%)	2 / 27 (7.41%)
occurrences (all)	6	6	2
Oral candidiasis	Additional description: Oral candidiasis		
subjects affected / exposed	0 / 25 (0.00%)	2 / 21 (9.52%)	2 / 27 (7.41%)
occurrences (all)	0	5	2
Paronychia	Additional description: Paronychia		
subjects affected / exposed	1 / 25 (4.00%)	2 / 21 (9.52%)	0 / 27 (0.00%)
occurrences (all)	1	3	0
Rhinitis	Additional description: Rhinitis		
subjects affected / exposed	2 / 25 (8.00%)	4 / 21 (19.05%)	5 / 27 (18.52%)
occurrences (all)	2	4	6
Rash pustular	Additional description: Rash pustular		
subjects affected / exposed	0 / 25 (0.00%)	2 / 21 (9.52%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	5 / 25 (20.00%)	3 / 21 (14.29%)	2 / 27 (7.41%)
occurrences (all)	7	4	2
Metabolism and nutrition disorders			
Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed	3 / 25 (12.00%)	0 / 21 (0.00%)	6 / 27 (22.22%)
occurrences (all)	3	0	6
Hyperglycaemia	Additional description: Hyperglycaemia		
subjects affected / exposed	2 / 25 (8.00%)	0 / 21 (0.00%)	1 / 27 (3.70%)
occurrences (all)	2	0	2

Non-serious adverse events	Doc+Trast+Bev+NPLD		

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

Ototoxicity	Additional description: Ototoxicity		
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Vertigo	Additional description: Vertigo		
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	5		
Eye disorders			
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Dry eye	Additional description: Dry eye		
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Eye pruritus	Additional description: Eye pruritus		
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Lacrimation increased	Additional description: Lacrimation increased		
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	6		
Gastrointestinal disorders			
Abdominal pain upper	Additional description: Abdominal pain upper		
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Anal haemorrhage	Additional description: Anal haemorrhage		
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Constipation	Additional description: Constipation		
subjects affected / exposed	7 / 24 (29.17%)		
occurrences (all)	10		
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	9 / 24 (37.50%)		
occurrences (all)	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	Additional description: Dry skin		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Erythema	Additional description: Erythema		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Nail discolouration	Additional description: Nail discolouration		
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Nail disorder	Additional description: Nail disorder		
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Nail dystrophy	Additional description: Nail dystrophy		
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Nail toxicity	Additional description: Nail toxicity		
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Onychalgia	Additional description: Onychalgia		
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Palmar-plantar erythrodysaesthesia syndrome	Additional description: Palmar-plantar erythrodysaesthesia syndrome		
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Pruritus	Additional description: Pruritus		
subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Rash	Additional description: Rash		
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	5		
Skin disorder	Additional description: Skin disorder		
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			

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