Clinical trial results:
Investigating Denosumab as an add-on to neoadjuvant chemotherapy in RANK/L-positive or RANK/L-negative primary breast cancer and two different nab-Paclitaxel schedules in a 2x2 factorial design (GeparX)

Summary

EudraCT number	2015-001755-72
Trial protocol	DE
Global end of trial date	28 February 2020

Results information

Result version number	v1 (current)
This version publication date	16 September 2021
First version publication date	16 September 2021
Summary attachment (see zip file)	GeparX CSR synopsis (CSR_GeparX_version SYNOPSE_2.0_final_plus Annex.pdf)

Trial information

Trial identification

Sponsor protocol code	GBG88

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02682693
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GBG Forschungs GmbH
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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	13 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 January 2020
Global end of trial reached?	Yes
Global end of trial date	28 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Co-Primary Objectives
- To compare the pathological complete response (pCR, ypT0 ypN0) rates of neoadjuvant treatment with or without denosumab in addition to backbone treatment consisting of nab-Paclitaxel 125mg/m² weekly (plus carboplatin in triple-negative disease) followed by epirubicin/cyclophosphamide or of nab-Paclitaxel 125mg/m² day 1,8 q22 (plus carboplatin in triple-negative disease) followed by epirubicin/cyclophosphamide plus anti-HER2 treatment (i. e. trastuzumab/pertuzumab in case of positive HER2-status) in patients with early breast cancer.
- To compare the pCR (ypT0 ypN0) rates of nab-Paclitaxel 125mg/m² weekly (plus carboplatin in triple-negative disease) followed by epirubicin/cyclophosphamide or nab-Paclitaxel 125mg/m² day 1,8 q22 (plus carboplatin in triple-negative disease) followed by epirubicin/cyclophosphamide plus anti-HER2 treatment (i. e. trastuzumab/pertuzumab in case of positive HER2-status) in patients with early breast cancer.

Protection of trial subjects:

The trial protocol including amendments, the patient information and the informed consent were reviewed and approved from a properly constituted IRB/IEC for each site prior to the study start. The trial was in compliance with the International Conference on Harmonization (ICH) - Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (E6), and the Commission Directives in the European Community as well as with the applicable German national laws and regulations, and with Declaration of Helsinki and its revisions in all aspects of preparation, monitoring, reporting, auditing, and archiving. IDMC was to ensure the ethical conduct of the trial and to protect patients' safety interests in this study.

Background therapy:

For all patients Epirubicin 90 mg/m² i.v. on day 1 every 2 or 3 weeks for 4 cycles in combination with Cyclophosphamide 600 mg/m² i.v. on day 1 every 2 or 3 weeks for 4 cycles..
For patients with TNBC only Carboplatin AUC 2.0 i.v. on day 1, 8, 15 every 3 weeks for 4 cycles For patients with HER2-positive disease Pertuzumab at 840mg (loading dose) and 420mg (maintenance dose) i.v. on the day before the first nab-Paclitaxel cycle and denosumab administration (loading dose) and on day 1 q day 22 (maintenance dose) for a minimum of 4 cycles (according to label)

Evidence for comparator: -	
Actual start date of recruitment	13 February 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 780
Worldwide total number of subjects	780
EEA total number of subjects	780

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)	710
From 65 to 84 years	70
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Approximately 25 months (Q-I 2017 –Q-I 2019). 780 patients were randomized (390 in denosumab arm and 390 in no denosumab arm, thereafter 390 to nab-paclitaxel weekly and 390 to nab-paclitaxel d1, 8 q3w), and started therapy. 756/780 (96.9%) patients underwent surgery

Pre-assignment

Screening details:

Patients with unilateral or bilateral primary breast cancer with stages cT2 - cT4a-d or cT1c with either clinically node positive or pathologically nodal positive or estrogen receptor (ER)-negative/ progesterone receptor (PR)-negative or Ki-67 >20% or HER2+ breast cancer.

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	Denosumab

Arm description:

A total of 390 patients were randomized to receive denosumab plus nab-paclitaxel (randomized secondarily to two schedules) followed by epirubicin and cyclophosphamide and started treatment; 371 patients received surgery.

Arm type	Experimental
Investigational medicinal product name	Denosumab (XGEVA®)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Denosumab was administered s.c. into the thigh, abdomen or upper arm. The schedule of administration was 120 mg given on day 1 (+/- 3 days) every 4 weeks for 6 cycles. The first injection was to be given on day 2 after the administration of anti-HER2 treatments.

Investigational medicinal product name	Trastuzumab (ABP 980)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab (ABP 980) was administered i.v. (for all patients with HER2 positive tumors and concomitantly with pertuzumab) over 90 min with 4.5 h monitoring of the patient (loading dose) or over 30-90 min with 30 min monitoring of the patient (maintenance dose). The schedule of administration was 8 mg/kg body weight (loading dose), thereafter 6 mg/kg body weight (maintenance dose), with the first injection given the day before the application of nab-Paclitaxel and denosumab. The following injections on day 1 q day 22 for 8 cycles (8 infusions) together with nab-Paclitaxel-EC.

Arm title	No denosumab

Arm description:

A total of 390 patients were randomized to receive no denosumab plus nab-paclitaxel (randomized secondarily to two schedules) followed by epirubicin and cyclophosphamide and started treatment; 385 patients received surgery.

Arm type	no Denosumab

Investigational medicinal product name	Trastuzumab (ABP 980)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab (ABP 980) was administered i.v. (for all patients with HER2 positive tumors and concomitantly with pertuzumab) over 90 min with 4.5 h monitoring of the patient (loading dose) or over 30-90 min with 30 min monitoring of the patient (maintenance dose). The schedule of administration was 8 mg/kg body weight (loading dose), thereafter 6 mg/kg body weight (maintenance dose), with the first injection given the day before the application of nab-Paclitaxel and denosumab. The following injections on day 1 q day 22 for 8 cycles (8 infusions) together with nab-Paclitaxel-EC.

Number of subjects in period 1	Denosumab	No denosumab
Started	390	390
Completed	390	390

Baseline characteristics

Reporting groups	
Reporting group title	Denosumab
Reporting group description:	
A total of 390 patients were randomized to receive denosumab plus nab-paclitaxel (randomized secondarily to two schedules) followed by epirubicin and cyclophosphamide and started treatment; 371 patients received surgery.	
Reporting group title	No denosumab
Reporting group description:	
A total of 390 patients were randomized to receive no denosumab plus nab-paclitaxel (randomized secondarily to two schedules) followed by epirubicin and cyclophosphamide and started treatment; 385 patients received surgery.	

Reporting group values	Denosumab	No denosumab	Total
Number of subjects	390	390	780
Age categorical Units: Subjects			
<30	8	11	19
30-<40	66	68	134
40-<50	122	132	254
50-<60	123	108	231
60-<70	59	61	120
>=70	12	10	22
Age continuous Units: years			
median	49	48.5	
full range (min-max)	23 to 78	22 to 80	-
Gender categorical Units: Subjects			
Female	389	390	779
Male	1	0	1
Tumor stage, sonography Units: Subjects			
cT1	135	156	291
cT2	222	213	435
cT3	18	11	29
cT4	11	6	17
missing	4	4	8
Nodal stage, sonography Units: Subjects			
cN0	232	233	465
cN1	134	136	270
cN2	18	12	30
cN3	3	6	9
missing	3	3	6
Tumor grading Units: Subjects			
G1	7	7	14
G2	128	119	247

G3	255	264	519
Nodal stage, sonography Units: Subjects			
Invasive carcinoma NST	374	375	749
Invasive lobular carcinoma or mixed lobular carcin	6	9	15
other	10	6	16
ER/PgR, central Units: Subjects			
both ER and PgR negative	185	180	365
ER and/or PgR positive	205	210	415
HER2, central Units: Subjects			
negative	313	314	627
positive	77	76	153
Subtype (stratification) Units: Subjects			
HER2-/HR+	153	157	310
TNBC	160	157	317
HER2+	77	76	153
Ki-67, central (stratification) Units: Subjects			
≤20%	73	59	132
>20%	317	331	648
LPBC, central (stratification) Units: Subjects			
no LPBC (≤50% sTILs)	359	359	718
LPBC (>50% sTILs)	31	31	62
Planned EC schedule (stratification) Units: Subjects			
2-weekly	206	208	414
3-weekly	184	182	366

Subject analysis sets

Subject analysis set title	nab-Paclitaxel weekly
Subject analysis set type	Intention-to-treat
Subject analysis set description: nab-Paclitaxel weekly	
Subject analysis set title	nab-Paclitaxel d1,8 q3w
Subject analysis set type	Intention-to-treat
Subject analysis set description: nab-Paclitaxel d1,8 q3w	

Reporting group values	nab-Paclitaxel weekly	nab-Paclitaxel d1,8 q3w	
Number of subjects	390	390	
Age categorical Units: Subjects			
<30	7	12	
30-<40	71	63	
40-<50	127	127	

50-<60	112	119	
60-<70	63	57	
>=70	10	12	
Age continuous Units: years			
median	49	49.5	
full range (min-max)	23 to 78	22 to 80	
Gender categorical Units: Subjects			
Female	389	390	
Male	1	0	
Tumor stage, sonography Units: Subjects			
cT1	132	159	
cT2	230	205	
cT3	13	16	
cT4	9	8	
missing	6	2	
Nodal stage, sonography Units: Subjects			
cN0	238	227	
cN1	131	139	
cN2	16	14	
cN3	5	4	
missing	0	6	
Tumor grading Units: Subjects			
G1	7	7	
G2	126	121	
G3	257	262	
Nodal stage, sonography Units: Subjects			
Invasive carcinoma NST	380	369	
Invasive lobular carcinoma or mixed lobular carcin	5	10	
other	5	11	
ER/PgR, central Units: Subjects			
both ER and PgR negative	177	188	
ER and/or PgR positive	213	202	
HER2, central Units: Subjects			
negative	314	313	
positive	76	77	
Subtype (stratification) Units: Subjects			
HER2-/HR+	155	155	
TNBC	159	158	
HER2+	76	77	
Ki-67, central (stratification) Units: Subjects			

≤20%	63	69	
>20%	327	321	
LPBC, central (stratification) Units: Subjects			
no LPBC (≤50% sTILs)	359	359	
LPBC (>50% sTILs)	31	31	
Planned EC schedule (stratification) Units: Subjects			
2-weekly	207	207	
3-weekly	183	183	

End points

End points reporting groups

Reporting group title	Denosumab
Reporting group description:	
A total of 390 patients were randomized to receive denosumab plus nab-paclitaxel (randomized secondarily to two schedules) followed by epirubicin and cyclophosphamide and started treatment; 371 patients received surgery.	
Reporting group title	No denosumab
Reporting group description:	
A total of 390 patients were randomized to receive no denosumab plus nab-paclitaxel (randomized secondarily to two schedules) followed by epirubicin and cyclophosphamide and started treatment; 385 patients received surgery.	
Subject analysis set title	nab-Paclitaxel weekly
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
nab-Paclitaxel weekly	
Subject analysis set title	nab-Paclitaxel d1,8 q3w
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
nab-Paclitaxel d1,8 q3w	

Primary: pCR (ypT0 ypN0)

End point title	pCR (ypT0 ypN0)
End point description:	
End point type	Primary
End point timeframe:	
from start of treatment to surgery, 24 weeks	

End point values	Denosumab	No denosumab	nab-Paclitaxel weekly	nab-Paclitaxel d1,8 q3w
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	390	390	390	390
Units: percent				
number (confidence interval 90%)	41.0 (36.9 to 45.1)	42.8 (38.7 to 46.9)	44.9 (40.7 to 49.0)	39.0 (34.9 to 43.0)

Statistical analyses

Statistical analysis title	continuity corrected χ2-test denosumab

Statistical analysis description:

Co-primary objectives were tested (stratified) according to the improved Bonferroni procedure: the smaller of the two p-values was compared with α = 0.1 and the larger p-value was compared with α = 0.2 to keep the overall significance level of the study of α = 0.2.
The primary endpoint was summarized as pathological complete response rate for each treatment group for both randomizations. Two-sided 90% confidence intervals were calculated according to Pearson and Clopper.

Comparison groups	No denosumab v Denosumab
Number of subjects included in analysis	780
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.582
Method	Chi-squared corrected

Notes:

[1] - The null hypothesis was that there was no difference in pCR rates between treatment arms; the alternative hypothesis was that there was a difference for both randomizations.

Statistical analysis title	continuity corrected χ2-test nab-Paclitaxel

Statistical analysis description:

Co-primary objectives were tested (stratified) according to the improved Bonferroni procedure (stratified test) : the smaller of the two p-values was compared with α = 0.1 and the larger p-value was compared with α = 0.2 to keep the overall significance level of the study of α = 0.2.
The primary endpoint was summarized as pathological complete response rate for each treatment group for both randomizations.

Comparison groups	nab-Paclitaxel weekly v nab-Paclitaxel d1,8 q3w
Number of subjects included in analysis	780
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.062
Method	Chi-squared corrected

Notes:

[2] - The null hypothesis was that there was no difference in pCR rates between treatment arms; the alternative hypothesis was that there was a difference for both randomizations.

Secondary: pCR (ypT0/is, ypN0)

End point title	pCR (ypT0/is, ypN0)

End point description:

End point type	Secondary

End point timeframe:

from start of treatment to surgery, 12 weeks

End point values	Denosumab	No denosumab	nab-Paclitaxel weekly	nab-Paclitaxel d1,8 q3w
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	390	390	390	390
Units: percent				
number (confidence interval 90%)	45.9 (41.7 to 50.0)	48.5 (44.3 to 52.6)	50.5 (46.3 to 54.7)	43.8 (39.7 to 48.0)

Statistical analyses

Statistical analysis title	pCR (ypT0/is ypN0)
Comparison groups	No denosumab v Denosumab

Number of subjects included in analysis	780
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.436
Method	Chi-squared corrected

Statistical analysis title	pCR (ypT0/is, ypN0)
Comparison groups	nab-Paclitaxel weekly v nab-Paclitaxel d1,8 q3w
Number of subjects included in analysis	780
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043
Method	Chi-squared corrected

Secondary: pCR (ypT0 ypN0/+)

End point title	pCR (ypT0 ypN0/+)

End point description:

End point type	Secondary

End point timeframe:

from start of treatment to surgery, 24 weeks

End point values	Denosumab	No denosumab	nab-Paclitaxel weekly	nab-Paclitaxel d1,8 q3w
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	390	390	390	390
Units: percent				
number (confidence interval 90%)	42.6 (38.4 to 46.7)	46.4 (42.3 to 50.6)	47.4 (43.3 to 51.6)	41.5 (37.4 to 45.6)

Statistical analyses

Statistical analysis title	continuity corrected χ2-test denosumab
Comparison groups	Denosumab v No denosumab
Number of subjects included in analysis	780
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	Chi-squared corrected

Statistical analysis title	continuity corrected χ2-test nab-Paclitaxel
Comparison groups	nab-Paclitaxel weekly v nab-Paclitaxel d1,8 q3w
Number of subjects included in analysis	780
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.055
Method	Chi-squared corrected

Secondary: pCR (ypT0/is, ypN0/+)	
End point title	pCR (ypT0/is, ypN0/+)
End point description:	
End point type	Secondary
End point timeframe:	
from start of treatment to surgery, 24 weeks	

End point values	Denosumab	No denosumab	nab-Paclitaxel weekly	nab-Paclitaxel d1,8 q3w
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	390	390	390	390
Units: percent				
number (confidence interval 90%)	48.7 (44.6 to 52.9)	53.3 (49.2 to 57.5)	54.9 (50.7 to 59.0)	47.2 (43.0 to 51.3)

Statistical analyses

Statistical analysis title	continuity corrected χ2-test denosumab
Comparison groups	Denosumab v No denosumab
Number of subjects included in analysis	780
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15
Method	Chi-squared corrected

Statistical analysis title	continuity corrected χ2-test nab-Paclitaxel
Comparison groups	nab-Paclitaxel d1,8 q3w v nab-Paclitaxel weekly

Number of subjects included in analysis	780
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	Chi-squared corrected

Secondary: pCR (ypT(any), ypN0)	
End point title	pCR (ypT(any), ypN0)
End point description:	

End point type	Secondary
End point timeframe:	
from start of treatment to surgery, 24 weeks	

End point values	Denosumab	No denosumab	nab-Paclitaxel weekly	nab-Paclitaxel d1,8 q3w
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	390	390	390	390
Units: percent				
number (confidence interval 90%)	74.6 (71.0 to 78.2)	76.2 (72.6 to 79.7)	77.4 (74.0 to 80.9)	73.3 (69.7 to 77.0)

Statistical analyses

Statistical analysis title	continuity corrected χ2-test denosumab
Comparison groups	Denosumab v No denosumab
Number of subjects included in analysis	780
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.588
Method	Chi-squared corrected

Statistical analysis title	continuity corrected χ2-test nab-Paclitaxel
Comparison groups	nab-Paclitaxel weekly v nab-Paclitaxel d1,8 q3w
Number of subjects included in analysis	780
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.261
Method	Chi-squared corrected

Secondary: pCR (ypT0 ypN0) in predefined subgroups

End point title	pCR (ypT0 ypN0) in predefined subgroups

End point description:

End point type	Secondary

End point timeframe:

from start of treatment to surgery, 24 weeks

End point values	Denosumab	No denosumab	nab-Paclitaxel weekly	nab-Paclitaxel d1,8 q3w
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	390	390	390	390
Units: percent				
number (confidence interval 90%)				
HER2-/HR+	21.6 (16.1 to 27.0)	22.3 (16.8 to 27.8)	22.6 (17.1 to 28.1)	21.3 (15.9 to 26.7)
TNBC	52.5 (46.0 to 59.0)	58.0 (51.5 to 64.4)	60.4 (54.0 to 66.8)	50.0 (43.5 to 56.5)
HER2+	55.8 (46.5 to 65.2)	53.9 (44.5 to 63.4)	57.9 (48.6 to 67.2)	51.9 (42.6 to 61.3)
no LPBC	38.4 (34.2 to 42.7)	41.2 (37.0 to 45.5)	42.6 (38.3 to 46.9)	37.0 (32.9 to 41.2)
LPBC	71.0 (57.6 to 84.4)	61.3 (46.9 to 75.7)	71.0 (57.6 to 84.4)	61.3 (46.9 to 75.7)
EC 2-weekly	40.3 (34.7 to 45.9)	43.3 (37.6 to 48.9)	46.9 (41.2 to 52.6)	36.7 (31.2 to 42.2)
EC 3-weekly	41.8 (35.9 to 47.8)	42.3 (36.3 to 48.3)	42.6 (36.6 to 48.6)	41.5 (35.5 to 47.5)
with Dmab	0 (0 to 0)	0 (0 to 0)	48.2 (42.3 to 54.1)	33.8 (28.3 to 39.4)
without Dmab	0 (0 to 0)	0 (0 to 0)	41.5 (35.7 to 47.3)	44.1 (38.3 to 50.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Breast conserving surgery

End point title	Breast conserving surgery

End point description:

End point type	Secondary

End point timeframe:

from start of treatment to surgery, 24 weeks

End point values	Denosumab	No denosumab	nab-Paclitaxel weekly	nab-Paclitaxel d1,8 q3w
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	390	390	390	390
Units: percent				
number (not applicable)	70.4	76.1	74.5	72.1

Statistical analyses

Statistical analysis title	continuity corrected χ2-test denosumab
Comparison groups	Denosumab v No denosumab
Number of subjects included in analysis	780
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.078
Method	Chi-squared corrected

Statistical analysis title	continuity corrected χ2-test nab-Paclitaxel
Comparison groups	nab-Paclitaxel weekly v nab-Paclitaxel d1,8 q3w
Number of subjects included in analysis	780
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.444
Method	Chi-squared corrected

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events occurring during the study treatment period were reported.

Adverse event reporting additional description:

Non-serious AEs are reported per patient; any grade (1-4) during the complete treatment duration for the overall safety population. AEs per patient occurring more frequently (> 20%) in all arms are shown. Note, overall number of single AE occurrences per term was not assessed, only per Patient.
AEs reported as free text are not shown

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Denosumab

Reporting group description:

A total of 390 patients were randomized to receive denosumab plus nab-paclitaxel (randomized secondarily to two schedules) followed by epirubicin and cyclophosphamide and started treatment; 371 patients received surgery.

Reporting group title	no Denosumab
Reporting group description: -	
Reporting group title	nab-Paclitaxel weekly
Reporting group description: -	
Reporting group title	nab-Paclitaxel d1,8 q22

Reporting group description: -

Serious adverse events	Denosumab	no Denosumab	nab-Paclitaxel weekly
Total subjects affected by serious adverse events			
subjects affected / exposed	108 / 377 (28.65%)	110 / 391 (28.13%)	126 / 395 (31.90%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arterial occlusive disease			

subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	0 / 395 (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
Circulatory collapse			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	0 / 395 (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
Hypertension			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	0 / 395 (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
Hypertensive crisis			
subjects affected / exposed	1 / 377 (0.27%)	1 / 391 (0.26%)	2 / 395 (0.51%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	3 / 377 (0.80%)	3 / 391 (0.77%)	4 / 395 (1.01%)
occurrences causally related to treatment / all	1 / 3	1 / 3	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian vein thrombosis			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis superficial			

subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	0 / 395 (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
Vena cava thrombosis			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	0 / 395 (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
Venous thrombosis			
subjects affected / exposed	0 / 377 (0.00%)	2 / 391 (0.51%)	0 / 395 (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
General disorders and administration site conditions			
Administration site extravasation			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	0 / 377 (0.00%)	2 / 391 (0.51%)	2 / 395 (0.51%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 377 (0.27%)	3 / 391 (0.77%)	3 / 395 (0.76%)
occurrences causally related to treatment / all	1 / 1	1 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	0 / 395 (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
Fatigue			
subjects affected / exposed	6 / 377 (1.59%)	2 / 391 (0.51%)	5 / 395 (1.27%)
occurrences causally related to treatment / all	6 / 6	2 / 2	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			

subjects affected / exposed	16 / 377 (4.24%)	15 / 391 (3.84%)	19 / 395 (4.81%)
occurrences causally related to treatment / all	13 / 16	15 / 15	17 / 19
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	23 / 377 (6.10%)	14 / 391 (3.58%)	26 / 395 (6.58%)
occurrences causally related to treatment / all	15 / 23	13 / 14	20 / 26
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactoid reaction			
subjects affected / exposed	3 / 377 (0.80%)	0 / 391 (0.00%)	2 / 395 (0.51%)
occurrences causally related to treatment / all	3 / 3	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 377 (0.00%)	2 / 391 (0.51%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Abortion missed			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	0 / 395 (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
Respiratory, thoracic and mediastinal disorders			
Alveolitis			
subjects affected / exposed	1 / 377 (0.27%)	2 / 391 (0.51%)	2 / 395 (0.51%)
occurrences causally related to treatment / all	1 / 1	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	6 / 377 (1.59%)	0 / 391 (0.00%)	3 / 395 (0.76%)
occurrences causally related to treatment / all	4 / 6	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	0 / 395 (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
Pulmonary embolism			
subjects affected / exposed	2 / 377 (0.53%)	0 / 391 (0.00%)	2 / 395 (0.51%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	1 / 377 (0.27%)	1 / 391 (0.26%)	0 / 395 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device occlusion			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
C-reactive protein increased			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	0 / 395 (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

Ejection fraction decreased			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anastomotic stenosis			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	19 / 395 (4.81%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	2 / 377 (0.53%)	1 / 391 (0.26%)	3 / 395 (0.76%)
occurrences causally related to treatment / all	2 / 2	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	19 / 395 (4.81%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 377 (0.27%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiovascular disorder			
subjects affected / exposed	0 / 377 (0.00%)	4 / 391 (1.02%)	0 / 395 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	0 / 395 (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
Nervous system disorders			
Acoustic neuritis			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	0 / 395 (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
Facial paresis			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intercostal neuralgia			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	0 / 395 (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
Peripheral motor neuropathy			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy			

subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 377 (2.65%)	7 / 391 (1.79%)	12 / 395 (3.04%)
occurrences causally related to treatment / all	10 / 10	7 / 7	12 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	15 / 377 (3.98%)	29 / 391 (7.42%)	23 / 395 (5.82%)
occurrences causally related to treatment / all	15 / 15	29 / 29	23 / 23
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	7 / 377 (1.86%)	4 / 391 (1.02%)	9 / 395 (2.28%)
occurrences causally related to treatment / all	7 / 7	4 / 4	9 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	16 / 377 (4.24%)	8 / 391 (2.05%)	10 / 395 (2.53%)
occurrences causally related to treatment / all	16 / 16	8 / 8	10 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	0 / 395 (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
Pancytopenia			
subjects affected / exposed	5 / 377 (1.33%)	3 / 391 (0.77%)	5 / 395 (1.27%)
occurrences causally related to treatment / all	5 / 5	3 / 3	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 377 (0.00%)	3 / 391 (0.77%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal haemorrhage			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	0 / 395 (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
Constipation			
subjects affected / exposed	2 / 377 (0.53%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	1 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 377 (0.27%)	5 / 391 (1.28%)	3 / 395 (0.76%)
occurrences causally related to treatment / all	1 / 1	5 / 5	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal inflammation			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 377 (0.53%)	5 / 391 (1.28%)	5 / 395 (1.27%)
occurrences causally related to treatment / all	2 / 2	5 / 5	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic colitis			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	0 / 395 (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
Stomatitis			
subjects affected / exposed	1 / 377 (0.27%)	1 / 391 (0.26%)	2 / 395 (0.51%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 377 (0.27%)	5 / 391 (1.28%)	5 / 395 (1.27%)
occurrences causally related to treatment / all	1 / 1	5 / 5	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 377 (0.53%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash papular			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	0 / 395 (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
Osteonecrosis of jaw			
subjects affected / exposed	2 / 377 (0.53%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	2 / 377 (0.53%)	0 / 391 (0.00%)	2 / 395 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conjunctivitis			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	3 / 377 (0.80%)	4 / 391 (1.02%)	3 / 395 (0.76%)
occurrences causally related to treatment / all	1 / 3	1 / 4	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diverticulitis			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	0 / 395 (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
Erysipelas			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	0 / 395 (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
Febrile infection			
subjects affected / exposed	1 / 377 (0.27%)	1 / 391 (0.26%)	2 / 395 (0.51%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	1 / 377 (0.27%)	1 / 391 (0.26%)	2 / 395 (0.51%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 377 (0.00%)	3 / 391 (0.77%)	3 / 395 (0.76%)
occurrences causally related to treatment / all	0 / 0	2 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	2 / 377 (0.53%)	0 / 391 (0.00%)	0 / 395 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			

subjects affected / exposed	0 / 377 (0.00%)	3 / 391 (0.77%)	3 / 395 (0.76%)
occurrences causally related to treatment / all	0 / 0	3 / 3	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	2 / 377 (0.53%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral herpes			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paronychia			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	0 / 395 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	6 / 377 (1.59%)	1 / 391 (0.26%)	5 / 395 (1.27%)
occurrences causally related to treatment / all	5 / 6	1 / 1	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	0 / 395 (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
Respiratory tract infection			
subjects affected / exposed	1 / 377 (0.27%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonellosis			

subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	0 / 395 (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
Sinusitis			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	0 / 395 (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
Tooth abscess			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 377 (0.00%)	4 / 391 (1.02%)	0 / 395 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral pharyngitis			

subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	0 / 395 (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
Vulval abscess			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	0 / 395 (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			
Dehydration			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	1 / 395 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	nab-Paclitaxel d1,8 q22		
Total subjects affected by serious adverse events			
subjects affected / exposed	92 / 373 (24.66%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer			

subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Arterial occlusive disease			
subjects affected / exposed	1 / 373 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Circulatory collapse			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	1 / 373 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 373 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	2 / 373 (0.54%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Shock haemorrhagic			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subclavian vein thrombosis			

subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombophlebitis superficial				
subjects affected / exposed	1 / 373 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vena cava thrombosis				
subjects affected / exposed	1 / 373 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis				
subjects affected / exposed	2 / 373 (0.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Administration site extravasation				
subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest discomfort				
subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	1 / 373 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	1 / 373 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				

subjects affected / exposed	3 / 373 (0.80%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	12 / 373 (3.22%)		
occurrences causally related to treatment / all	11 / 12		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	11 / 373 (2.95%)		
occurrences causally related to treatment / all	8 / 11		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactoid reaction			
subjects affected / exposed	1 / 373 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	1 / 373 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Abortion missed			
subjects affected / exposed	1 / 373 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Alveolitis			
subjects affected / exposed	1 / 373 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cough			

subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	3 / 373 (0.80%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 373 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	2 / 373 (0.54%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device occlusion			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			

C-reactive protein increased			
subjects affected / exposed	1 / 373 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ejection fraction decreased			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anastomotic stenosis			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Atrial fibrillation				
subjects affected / exposed	1 / 373 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiovascular disorder				
subjects affected / exposed	4 / 373 (1.07%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Palpitations				
subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	1 / 373 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Acoustic neuritis				
subjects affected / exposed	1 / 373 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Facial paresis				
subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intercostal neuralgia				
subjects affected / exposed	1 / 373 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral motor neuropathy				
subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral sensory neuropathy				

subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Polyneuropathy				
subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	5 / 373 (1.34%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	21 / 373 (5.63%)			
occurrences causally related to treatment / all	21 / 21			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	2 / 373 (0.54%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	14 / 373 (3.75%)			
occurrences causally related to treatment / all	14 / 14			
deaths causally related to treatment / all	0 / 0			
Neutrophil count decreased				
subjects affected / exposed	1 / 373 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	3 / 373 (0.80%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				

subjects affected / exposed	2 / 373 (0.54%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain lower			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anal haemorrhage			
subjects affected / exposed	1 / 373 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	2 / 373 (0.54%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	3 / 373 (0.80%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		

Gastritis				
subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal inflammation				
subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematochezia				
subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 373 (0.54%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Neutropenic colitis				
subjects affected / exposed	1 / 373 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 373 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Rash				
subjects affected / exposed	1 / 373 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rash papular				

subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 373 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis of jaw			
subjects affected / exposed	1 / 373 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis perforated			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atypical pneumonia			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Conjunctivitis			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Device related infection			
subjects affected / exposed	4 / 373 (1.07%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	1 / 373 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 373 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile infection			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal infection			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			

subjects affected / exposed	2 / 373 (0.54%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nasopharyngitis				
subjects affected / exposed	1 / 373 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oral herpes				
subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paronychia				
subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 373 (0.54%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 373 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				

subjects affected / exposed	1 / 373 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Salmonellosis				
subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 373 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				
subjects affected / exposed	1 / 373 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tooth abscess				
subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	4 / 373 (1.07%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 373 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular device infection				

subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral pharyngitis			
subjects affected / exposed	1 / 373 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vulval abscess			
subjects affected / exposed	1 / 373 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 373 (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	Denosumab	no Denosumab	nab-Paclitaxel weekly
Total subjects affected by non-serious adverse events			
subjects affected / exposed	377 / 377 (100.00%)	391 / 391 (100.00%)	395 / 395 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 377 (6.90%)	30 / 391 (7.67%)	26 / 395 (6.58%)
occurrences (all)	26	30	26
Embolism			
subjects affected / exposed	14 / 377 (3.71%)	15 / 391 (3.84%)	14 / 395 (3.54%)
occurrences (all)	14	15	14
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	270 / 377 (71.62%)	273 / 391 (69.82%)	292 / 395 (73.92%)
occurrences (all)	270	273	292
Decreased appetite			
subjects affected / exposed	48 / 377 (12.73%)	51 / 391 (13.04%)	61 / 395 (15.44%)
occurrences (all)	48	51	61
Pyrexia			
subjects affected / exposed	66 / 377 (17.51%)	54 / 391 (13.81%)	76 / 395 (19.24%)
occurrences (all)	66	54	76
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	3 / 377 (0.80%)	0 / 391 (0.00%)	2 / 395 (0.51%)
occurrences (all)	3	0	2
Hypersensitivity			
subjects affected / exposed	10 / 377 (2.65%)	15 / 391 (3.84%)	13 / 395 (3.29%)
occurrences (all)	10	15	13
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	80 / 377 (21.22%)	78 / 391 (19.95%)	106 / 395 (26.84%)
occurrences (all)	80	78	106
Dyspnoea			
subjects affected / exposed	50 / 377 (13.26%)	46 / 391 (11.76%)	54 / 395 (13.67%)
occurrences (all)	50	46	54
Pneumonitis			

subjects affected / exposed	3 / 377 (0.80%)	0 / 391 (0.00%)	3 / 395 (0.76%)
occurrences (all)	3	0	3
Cough			
subjects affected / exposed	39 / 377 (10.34%)	46 / 391 (11.76%)	50 / 395 (12.66%)
occurrences (all)	39	46	50
Pulmonary toxicity			
subjects affected / exposed	2 / 377 (0.53%)	8 / 391 (2.05%)	5 / 395 (1.27%)
occurrences (all)	2	8	5
Investigations			
Ejection fraction decreased	Additional description: >= 10% decrease in LVEF from baseline and < 50%		
subjects affected / exposed	2 / 377 (0.53%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences (all)	2	1	1
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	10 / 377 (2.65%)	7 / 391 (1.79%)	10 / 395 (2.53%)
occurrences (all)	10	7	10
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 377 (0.00%)	1 / 391 (0.26%)	1 / 395 (0.25%)
occurrences (all)	0	1	1
Nervous system disorders			
Headache			
subjects affected / exposed	76 / 377 (20.16%)	80 / 391 (20.46%)	85 / 395 (21.52%)
occurrences (all)	76	80	85
Peripheral sensory neuropathy			
subjects affected / exposed	226 / 377 (59.95%)	245 / 391 (62.66%)	296 / 395 (74.94%)
occurrences (all)	226	245	296
Cranial nerve disorder			
subjects affected / exposed	1 / 377 (0.27%)	4 / 391 (1.02%)	5 / 395 (1.27%)
occurrences (all)	1	4	5
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	357 / 377 (94.69%)	379 / 391 (96.93%)	382 / 395 (96.71%)
occurrences (all)	357	379	382
Leukopenia			

subjects affected / exposed	355 / 377 (94.16%)	376 / 391 (96.16%)	380 / 395 (96.20%)
occurrences (all)	355	376	380
Neutropenia			
subjects affected / exposed	339 / 377 (89.92%)	354 / 391 (90.54%)	361 / 395 (91.39%)
occurrences (all)	339	354	361
Febrile neutropenia			
subjects affected / exposed	17 / 377 (4.51%)	32 / 391 (8.18%)	26 / 395 (6.58%)
occurrences (all)	17	32	26
Thrombocytopenia			
subjects affected / exposed	197 / 377 (52.25%)	210 / 391 (53.71%)	200 / 395 (50.63%)
occurrences (all)	197	210	200
Blood bilirubin increased			
subjects affected / exposed	12 / 377 (3.18%)	19 / 391 (4.86%)	22 / 395 (5.57%)
occurrences (all)	12	19	22
Blood alkaline phosphatase increased			
subjects affected / exposed	124 / 377 (32.89%)	144 / 391 (36.83%)	141 / 395 (35.70%)
occurrences (all)	124	144	141
Aspartate aminotransferase increased			
subjects affected / exposed	158 / 377 (41.91%)	151 / 391 (38.62%)	169 / 395 (42.78%)
occurrences (all)	158	151	169
Alanine aminotransferase increased			
subjects affected / exposed	234 / 377 (62.07%)	233 / 391 (59.59%)	256 / 395 (64.81%)
occurrences (all)	234	233	256
Blood creatinine increased			
subjects affected / exposed	40 / 377 (10.61%)	54 / 391 (13.81%)	45 / 395 (11.39%)
occurrences (all)	40	54	45
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	225 / 377 (59.68%)	238 / 391 (60.87%)	222 / 395 (56.20%)
occurrences (all)	225	238	222
Vomiting			
subjects affected / exposed	58 / 377 (15.38%)	51 / 391 (13.04%)	57 / 395 (14.43%)
occurrences (all)	58	51	57
Diarrhoea			

subjects affected / exposed	140 / 377 (37.14%)	148 / 391 (37.85%)	164 / 395 (41.52%)
occurrences (all)	140	148	164
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	327 / 377 (86.74%)	337 / 391 (86.19%)	345 / 395 (87.34%)
occurrences (all)	327	337	345
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	24 / 377 (6.37%)	23 / 391 (5.88%)	34 / 395 (8.61%)
occurrences (all)	24	23	34
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	94 / 377 (24.93%)	77 / 391 (19.69%)	100 / 395 (25.32%)
occurrences (all)	94	77	100
Myalgia			
subjects affected / exposed	63 / 377 (16.71%)	43 / 391 (11.00%)	56 / 395 (14.18%)
occurrences (all)	63	43	56
Osteonecrosis of jaw			
subjects affected / exposed	1 / 377 (0.27%)	0 / 391 (0.00%)	0 / 395 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Pneumonia			
subjects affected / exposed	10 / 377 (2.65%)	4 / 391 (1.02%)	12 / 395 (3.04%)
occurrences (all)	10	4	12
Infection	Additional description: other than pneumonia		
subjects affected / exposed	159 / 377 (42.18%)	157 / 391 (40.15%)	167 / 395 (42.28%)
occurrences (all)	159	157	167
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	193 / 377 (51.19%)	112 / 391 (28.64%)	160 / 395 (40.51%)
occurrences (all)	193	112	160

Non-serious adverse events	nab-Paclitaxel d1,8 q22		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	373 / 373 (100.00%)		
Vascular disorders			

Hypertension			
subjects affected / exposed	30 / 373 (8.04%)		
occurrences (all)	30		
Embolism			
subjects affected / exposed	15 / 373 (4.02%)		
occurrences (all)	15		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	251 / 373 (67.29%)		
occurrences (all)	251		
Decreased appetite			
subjects affected / exposed	38 / 373 (10.19%)		
occurrences (all)	38		
Pyrexia			
subjects affected / exposed	44 / 373 (11.80%)		
occurrences (all)	44		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 373 (0.27%)		
occurrences (all)	1		
Hypersensitivity			
subjects affected / exposed	12 / 373 (3.22%)		
occurrences (all)	12		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	52 / 373 (13.94%)		
occurrences (all)	52		
Dyspnoea			
subjects affected / exposed	42 / 373 (11.26%)		
occurrences (all)	42		
Pneumonitis			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	35 / 373 (9.38%)		
occurrences (all)	35		

Pulmonary toxicity			
subjects affected / exposed	5 / 373 (1.34%)		
occurrences (all)	5		
Investigations			
Ejection fraction decreased	Additional description: >= 10% decrease in LVEF from baseline and < 50%		
subjects affected / exposed	2 / 373 (0.54%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	7 / 373 (1.88%)		
occurrences (all)	7		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	71 / 373 (19.03%)		
occurrences (all)	71		
Peripheral sensory neuropathy			
subjects affected / exposed	175 / 373 (46.92%)		
occurrences (all)	175		
Cranial nerve disorder			
subjects affected / exposed	0 / 373 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	354 / 373 (94.91%)		
occurrences (all)	354		
Leukopenia			
subjects affected / exposed	351 / 373 (94.10%)		
occurrences (all)	351		
Neutropenia			
subjects affected / exposed	332 / 373 (89.01%)		
occurrences (all)	332		
Febrile neutropenia			

subjects affected / exposed	23 / 373 (6.17%)		
occurrences (all)	23		
Thrombocytopenia			
subjects affected / exposed	207 / 373 (55.50%)		
occurrences (all)	207		
Blood bilirubin increased			
subjects affected / exposed	9 / 373 (2.41%)		
occurrences (all)	9		
Blood alkaline phosphatase increased			
subjects affected / exposed	127 / 373 (34.05%)		
occurrences (all)	127		
Aspartate aminotransferase increased			
subjects affected / exposed	140 / 373 (37.53%)		
occurrences (all)	140		
Alanine aminotransferase increased			
subjects affected / exposed	211 / 373 (56.57%)		
occurrences (all)	211		
Blood creatinine increased			
subjects affected / exposed	49 / 373 (13.14%)		
occurrences (all)	49		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	241 / 373 (64.61%)		
occurrences (all)	241		
Vomiting			
subjects affected / exposed	52 / 373 (13.94%)		
occurrences (all)	52		
Diarrhoea			
subjects affected / exposed	124 / 373 (33.24%)		
occurrences (all)	124		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	319 / 373 (85.52%)		
occurrences (all)	319		
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	13 / 373 (3.49%)		
occurrences (all)	13		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	71 / 373 (19.03%)		
occurrences (all)	71		
Myalgia			
subjects affected / exposed	50 / 373 (13.40%)		
occurrences (all)	50		
Osteonecrosis of jaw			
subjects affected / exposed	1 / 373 (0.27%)		
occurrences (all)	1		
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 373 (0.54%)		
occurrences (all)	2		
Infection	Additional description: other than pneumonia		
subjects affected / exposed	149 / 373 (39.95%)		
occurrences (all)	149		
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	145 / 373 (38.87%)		
occurrences (all)	145		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 March 2017	Amendment 1 comprised the inclusion of a trastuzumab biosimilar replacing Herceptin® (and thus opening the study for patients with HER2-positive tumor), minor adjustments to the protocol and deletion of the PET-CT substudy.
18 June 2018	Amendment 2 implemented the change of the co-ordinating investigator and adjustments in the informed consent form (ICF) required due to several updates to the reference document for the investigational medicinal product Denosumab.
11 April 2019	Amendment 3 contained a clarification of end of study and timeframe from end of therapy until surgery. Moreover, several reformulations and additions in ICF, especially for the marketing authorization of the trastuzumab biosimilar were included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: