Clinical trial results:
Neo- / adjuvant phase III trial to compare intense dose-dense chemotherapy to tailored dose-dense chemotherapy in patients with high-risk early breast cancer (GAIN-2 trial)

Summary

EudraCT number	2011-005214-11
Trial protocol	DE
Global end of trial date	07 January 2019

Results information

Result version number	v1 (current)
This version publication date	27 October 2021
First version publication date	27 October 2021
Summary attachment (see zip file)	GAIN-2 CSR Synopsis (CSR_GAIN2_Synopsis Final_2.0_20200727.pdf)

Trial information

Trial identification

Sponsor protocol code	GBG-68

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01690702
WHO universal trial number (UTN)	-
Other trial identifiers	no: no

Notes:

Sponsors

Sponsor organisation name	GBG Forschungs GmbH
Sponsor organisation address	Martin-Behaim-Straße 12, Neu-Isenburg, Germany,
Public contact	Medicine and Research, GBG Forschungs GmbH, +49 610274800, publications@gbg.de
Scientific contact	Medicine and Research, GBG Forschungs GmbH, +49 610274800, publications@gbg.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 September 2018
Global end of trial reached?	Yes
Global end of trial date	07 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the invasive disease-free survival (IDFS) after neo- / adjuvant chemotherapy with EnPC or dtEC-dtD in patients with early node-positive or high-risk node-negative 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: -

Evidence for comparator: -

Actual start date of recruitment	09 April 2012
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: 2857
Worldwide total number of subjects	2857
EEA total number of subjects	2857

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)	2698
From 65 to 84 years	159
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Approximately 5 years (Q-IV 2012 –Q-III 2017) in 136 sites in Germany. 2887 patients were randomized, 2857 patients started treatment (iddEnPC 1429; dtEC-dtD 1428).

Pre-assignment

Screening details:

Female patients <18 - 70years, uni- or bilateral primary BC, Karnofsky index ≥ 80%, estimated life expectancy of >=10 years irresp. of BC. Centrally confirmed ER, PgR , HER2, and Ki-67 on surgical or core biopsy eligible. High risk BC defined as HER2+ or TNBC irresp. of nodal status or luminal B-like with N+ or luminal A-like with >=4 involved LN

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	EnPC

Arm description:

- intense dose-dense epirubicin for 3 cycles followed by
- intense dose-dense nab-paclitaxel for 3 cycles followed by
- intense dose-dense cyclophosphamide for 3 cycles.

Arm type	Experimental
Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Epirubicin was administered i.v. over 20 min via catheter to the subclavian vein or an implanted port system. The schedule of administration was 150 mg/m² (EnPC) given on day 1 every 2 weeks for 3 cycles (EnPC).

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cyclophosphamide was administered i.v. over 120 min (EnPC) . The schedule of administration was 2000 mg/m² (EnPC) given on day 1 every 2 weeks for 3 cycles (EnPC).

Investigational medicinal product name	nab-Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

nab-paclitaxel was administered i.v. over 30-60 min. The schedule of administration was 330 mg/m² (after determination during the run-in phase) given on day 1 q day 14 for 3 cycles

Arm title	dtEC-dtD

Arm description:

- dose-dense / dose-tailored epirubicin / cyclophosphamide for 4 cycles followed after 1 additional week of rest by
- dose-dense / dose-tailored docetaxel for 4 cycles.

Arm type	Experimental
Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Epirubicin was administered i.v. over 20 min via catheter to the subclavian vein or an implanted port system. The schedule of administration was 38-120 mg/m² (dtEC-dtD) given on day 1 every 2 weeks for 4 cycles (dtEC-dtD).

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel was administered i.v. over 60 min. The schedule of administration was 60-100 mg/m² (dtEC-dtD) given on day 1 every 2 weeks for 4 cycles.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cyclophosphamide was administered i.v. over 60 min (dtEC-dtD). The schedule of administration was 450-1200 mg/m² (dtEC-dtD) given on day 1 every 2 weeks for 4 cycles (dtEC-dtD).

Number of subjects in period 1	EnPC	dtEC-dtD
Started	1429	1428
Completed	1259	1258
Not completed	170	170
Physician decision	24	23
Consent withdrawn by subject	48	47
death	-	2
Adverse event, non-fatal	94	91
local progression	2	2
relapse	2	5

Baseline characteristics

Reporting groups	
Reporting group title	EnPC

Reporting group description:

- intense dose-dense epirubicin for 3 cycles followed by
- intense dose-dense nab-paclitaxel for 3 cycles followed by
- intense dose-dense cyclophosphamide for 3 cycles.

Reporting group title	dtEC-dtD

Reporting group description:

- dose-dense / dose-tailored epirubicin / cyclophosphamide for 4 cycles followed after 1 additional week of rest by
- dose-dense / dose-tailored docetaxel for 4 cycles.

Reporting group values	EnPC	dtEC-dtD	Total
Number of subjects	1429	1428	2857
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	51	51	
full range (min-max)	18 to 73	20 to 75	-
Gender categorical			
Units: Subjects			
Female	1429	1428	2857
Male	0	0	0

End points

End points reporting groups

Reporting group title	EnPC

Reporting group description:

- intense dose-dense epirubicin for 3 cycles followed by
- intense dose-dense nab-paclitaxel for 3 cycles followed by
- intense dose-dense cyclophosphamide for 3 cycles.

Reporting group title	dtEC-dtD

Reporting group description:

- dose-dense / dose-tailored epirubicin / cyclophosphamide for 4 cycles followed after 1 additional week of rest by
- dose-dense / dose-tailored docetaxel for 4 cycles.

Primary: iDFS rate

End point title	iDFS rate

End point description:

iDFS rate at 48months follow up

End point type	Primary

End point timeframe:

iDFS defined as the time period between randomization and first event (local, loco-regional or distant recurrence, death from breast cancer, death from non-breast cancer cause, death from unknown cause, second primary invasive cancer [non-breast])

End point values	EnPC	dtEC-dtD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1429	1428		
Units: percent				
number (confidence interval 95%)	84.3 (82.0 to 86.4)	84.3 (82.0 to 86.4)		

Statistical analyses

Statistical analysis title	Hazard ratio
Comparison groups	EnPC v dtEC-dtD
Number of subjects included in analysis	2857
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.23

Notes:

[1] - The non-inferiority margin of 5% prespecified in the protocol was crossed, i.e. the 95%-CI for hazard ratio excluded 1.05. Therefore, the non-inferiority could not be shown.

Statistical analysis title	Two-sided log-rank

Statistical analysis description:

The difference in iDFS time was tested using a two-sided log-rank test with significance level of α = 0.05.

Comparison groups	EnPC v dtEC-dtD
Number of subjects included in analysis	2857
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.9102 [3]
Method	Logrank

Notes:

[2] - A closed test procedure was used to test for non-inferiority and superiority.

[3] - The 4-year iDFS rate was identical in both arms with 84.3% (95% CI 82.0% to 86.4%) and a log-rank p=0.9102

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.
Free-text AEs are listed if occurring in >20%
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	20.1

Reporting groups

Reporting group title	EnPC

Reporting group description:

Analysis of safety and compliance to treatment was performed based on patients who were randomized and received at least once study treatment (2857 patients).
For safety and compliance, patients were analyzed according to the treatment which they actually received. One patient randomized to the dtEC-dtD arm was treated in the EnPC arm and was therefore analyzed in the EnPC arm in all safety analyses (safety set: EnPC: 1430 patients; dtEC-dtD: 1427 patients.

Reporting group title	dtEC-dtD

Reporting group description:

Analysis of safety and compliance to treatment was performed based on patients who were randomized and received at least once study treatment (2857 patients).
For safety and compliance, patients were analyzed according to the treatment which they actually received. One patient randomized to the dtEC-dtD arm was treated in the EnPC arm and was therefore analyzed in the EnPC arm in all safety analyses (safety set: EnPC: 1430 patients; dtEC-dtD: 1427 patients.

Serious adverse events	EnPC	dtEC-dtD	
Total subjects affected by serious adverse events			
subjects affected / exposed	546 / 1430 (38.18%)	394 / 1427 (27.61%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			

subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	5 / 1430 (0.35%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	5 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 1430 (0.14%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 1430 (0.14%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 1430 (0.07%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site thrombosis			

subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	10 / 1430 (0.70%)	7 / 1427 (0.49%)	
occurrences causally related to treatment / all	9 / 10	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	10 / 1430 (0.70%)	5 / 1427 (0.35%)	
occurrences causally related to treatment / all	7 / 10	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Administration site extravasation			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			

subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site extravasation			
subjects affected / exposed	1 / 1430 (0.07%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site inflammation			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site thrombosis			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 1430 (0.00%)	4 / 1427 (0.28%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 1430 (0.07%)	3 / 1427 (0.21%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	2 / 1430 (0.14%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related thrombosis			

subjects affected / exposed	2 / 1430 (0.14%)	3 / 1427 (0.21%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravasation			
subjects affected / exposed	3 / 1430 (0.21%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	19 / 1430 (1.33%)	17 / 1427 (1.19%)	
occurrences causally related to treatment / all	19 / 19	17 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	42 / 1430 (2.94%)	25 / 1427 (1.75%)	
occurrences causally related to treatment / all	40 / 42	25 / 25	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 1430 (0.07%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion device issue			

subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	3 / 1430 (0.21%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	7 / 1430 (0.49%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	7 / 7	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 1430 (0.00%)	3 / 1427 (0.21%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	7 / 1430 (0.49%)	5 / 1427 (0.35%)	
occurrences causally related to treatment / all	7 / 7	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	60 / 1430 (4.20%)	54 / 1427 (3.78%)	
occurrences causally related to treatment / all	59 / 60	49 / 54	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Swelling			

subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic pain			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			
subjects affected / exposed	1 / 1430 (0.07%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 1430 (0.07%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Haemorrhagic ovarian cyst			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Alveolitis			
subjects affected / exposed	1 / 1430 (0.07%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 1430 (0.07%)	3 / 1427 (0.21%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	7 / 1430 (0.49%)	5 / 1427 (0.35%)	
occurrences causally related to treatment / all	6 / 7	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 1430 (0.07%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 1430 (0.14%)	4 / 1427 (0.28%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary mass			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal inflammation			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Adjustment disorder with mixed anxiety and depressed mood			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	3 / 1430 (0.21%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	2 / 1430 (0.14%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	2 / 1430 (0.14%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Suicidal behaviour			
subjects affected / exposed	0 / 1430 (0.00%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 1430 (0.00%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	2 / 1430 (0.14%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Platelet count decreased			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 1430 (0.14%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 1430 (0.07%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 1430 (0.07%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular disorder			
subjects affected / exposed	3 / 1430 (0.21%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 1430 (0.00%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	2 / 1430 (0.14%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 1430 (0.07%)	3 / 1427 (0.21%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			

subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic hyperglycaemic coma			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	5 / 1430 (0.35%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	5 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	2 / 1430 (0.14%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	2 / 1430 (0.14%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic intolerance			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 1430 (0.28%)	3 / 1427 (0.21%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	3 / 1430 (0.21%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Restless legs syndrome			

subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	4 / 1430 (0.28%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 1430 (0.07%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	19 / 1430 (1.33%)	11 / 1427 (0.77%)	
occurrences causally related to treatment / all	19 / 19	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	143 / 1430 (10.00%)	49 / 1427 (3.43%)	
occurrences causally related to treatment / all	143 / 143	49 / 49	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			

subjects affected / exposed	3 / 1430 (0.21%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	55 / 1430 (3.85%)	42 / 1427 (2.94%)	
occurrences causally related to treatment / all	55 / 55	42 / 42	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocytosis			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	119 / 1430 (8.32%)	50 / 1427 (3.50%)	
occurrences causally related to treatment / all	119 / 119	50 / 50	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	5 / 1430 (0.35%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	26 / 1430 (1.82%)	3 / 1427 (0.21%)	
occurrences causally related to treatment / all	26 / 26	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	12 / 1430 (0.84%)	5 / 1427 (0.35%)	
occurrences causally related to treatment / all	12 / 12	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			

subjects affected / exposed	3 / 1430 (0.21%)	5 / 1427 (0.35%)	
occurrences causally related to treatment / all	3 / 3	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inner ear disorder			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden hearing loss			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tinnitus			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	5 / 1430 (0.35%)	5 / 1427 (0.35%)	
occurrences causally related to treatment / all	5 / 5	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye inflammation			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			

subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 1430 (0.21%)	5 / 1427 (0.35%)	
occurrences causally related to treatment / all	3 / 3	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	3 / 1430 (0.21%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	2 / 1430 (0.14%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	5 / 1430 (0.35%)	3 / 1427 (0.21%)	
occurrences causally related to treatment / all	5 / 5	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	18 / 1430 (1.26%)	14 / 1427 (0.98%)	
occurrences causally related to treatment / all	18 / 18	13 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			

subjects affected / exposed	5 / 1430 (0.35%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	4 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 1430 (0.00%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric disorder			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 1430 (0.00%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			

subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	21 / 1430 (1.47%)	9 / 1427 (0.63%)	
occurrences causally related to treatment / all	21 / 21	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 1430 (0.14%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	5 / 1430 (0.35%)	3 / 1427 (0.21%)	
occurrences causally related to treatment / all	5 / 5	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	22 / 1430 (1.54%)	20 / 1427 (1.40%)	
occurrences causally related to treatment / all	22 / 22	20 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder necrosis			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 1430 (0.00%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder disorder			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cyst			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis chronic active			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Cutis laxa			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis bullous			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epidermolysis			

subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			
subjects affected / exposed	0 / 1430 (0.00%)	3 / 1427 (0.21%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 1430 (0.00%)	7 / 1427 (0.49%)	
occurrences causally related to treatment / all	0 / 0	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin lesion			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin reaction			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	2 / 1430 (0.14%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	3 / 1430 (0.21%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal pain			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 1430 (0.14%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 1430 (0.14%)	4 / 1427 (0.28%)	
occurrences causally related to treatment / all	1 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			

subjects affected / exposed	6 / 1430 (0.42%)	9 / 1427 (0.63%)	
occurrences causally related to treatment / all	4 / 6	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 1430 (0.07%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Myalgia			
subjects affected / exposed	2 / 1430 (0.14%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			

subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 1430 (0.07%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 1430 (0.07%)	3 / 1427 (0.21%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 1430 (0.00%)	3 / 1427 (0.21%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			

subjects affected / exposed	1 / 1430 (0.07%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	5 / 1430 (0.35%)	5 / 1427 (0.35%)	
occurrences causally related to treatment / all	1 / 5	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 1430 (0.00%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 1430 (0.14%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			

subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	2 / 1430 (0.14%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital herpes			
subjects affected / exposed	2 / 1430 (0.14%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	0 / 1430 (0.00%)	157 / 1427 (11.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	5 / 1430 (0.35%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	5 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impetigo			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site infection			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected dermal cyst			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected seroma			

subjects affected / exposed	3 / 1430 (0.21%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	10 / 1430 (0.70%)	12 / 1427 (0.84%)	
occurrences causally related to treatment / all	9 / 10	11 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	5 / 1430 (0.35%)	3 / 1427 (0.21%)	
occurrences causally related to treatment / all	4 / 5	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site infection			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	5 / 1430 (0.35%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	4 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nail infection			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			

subjects affected / exposed	0 / 1430 (0.00%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 1430 (0.07%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii infection			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	14 / 1430 (0.98%)	19 / 1427 (1.33%)	
occurrences causally related to treatment / all	9 / 14	19 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 1430 (0.21%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	0 / 1430 (0.00%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 1430 (0.00%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 1430 (0.07%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 1430 (0.00%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 1430 (0.07%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 1430 (0.00%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 1430 (0.07%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethritis			
subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 1430 (0.21%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urogenital infection bacterial			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 1430 (0.14%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval abscess			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	3 / 1430 (0.21%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			

subjects affected / exposed	1 / 1430 (0.07%)	0 / 1427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 1430 (0.07%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 1430 (0.00%)	1 / 1427 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 1430 (0.00%)	2 / 1427 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	EnPC	dtEC-dtD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1429 / 1430 (99.93%)	1426 / 1427 (99.93%)	
Investigations			
Alanine aminotransferase increased	Additional description: ALAT increased		
subjects affected / exposed	977 / 1430 (68.32%)	842 / 1427 (59.00%)	
occurrences (all)	977	842	
Aspartate aminotransferase increased	Additional description: ASAT increased		
subjects affected / exposed	628 / 1430 (43.92%)	526 / 1427 (36.86%)	
occurrences (all)	628	526	
Blood bilirubin increased			
subjects affected / exposed	73 / 1430 (5.10%)	63 / 1427 (4.41%)	
occurrences (all)	73	63	
Blood creatinine increased			

subjects affected / exposed	168 / 1430 (11.75%)	164 / 1427 (11.49%)	
occurrences (all)	168	164	
Vascular disorders			
Embolism			
subjects affected / exposed	60 / 1430 (4.20%)	61 / 1427 (4.27%)	
occurrences (all)	60	61	
Epistaxis			
subjects affected / exposed	149 / 1430 (10.42%)	362 / 1427 (25.37%)	
occurrences (all)	149	362	
Hypertension			
subjects affected / exposed	165 / 1430 (11.54%)	140 / 1427 (9.81%)	
occurrences (all)	165	140	
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	8 / 1430 (0.56%)	7 / 1427 (0.49%)	
occurrences (all)	8	7	
Nervous system disorders			
Headache			
subjects affected / exposed	432 / 1430 (30.21%)	491 / 1427 (34.41%)	
occurrences (all)	432	491	
Peripheral sensory neuropathy			
subjects affected / exposed	1190 / 1430 (83.22%)	903 / 1427 (63.28%)	
occurrences (all)	1190	903	
Dysgeusia	Additional description: reported as free-text		
subjects affected / exposed	320 / 1430 (22.38%)	387 / 1427 (27.12%)	
occurrences (all)	320	387	
Blood and lymphatic system disorders			
Blood alkaline phosphatase increased	Additional description: Blood AP increased		
subjects affected / exposed	847 / 1430 (59.23%)	629 / 1427 (44.08%)	
occurrences (all)	847	629	
Anaemia			
subjects affected / exposed	1410 / 1430 (98.60%)	1408 / 1427 (98.67%)	
occurrences (all)	1410	1408	
Leukopenia			

subjects affected / exposed	1411 / 1430 (98.67%)	1401 / 1427 (98.18%)	
occurrences (all)	1411	1401	
Lymphopenia			
subjects affected / exposed	1389 / 1430 (97.13%)	1389 / 1427 (97.34%)	
occurrences (all)	1389	1389	
Neutropenia			
subjects affected / exposed	1350 / 1430 (94.41%)	1308 / 1427 (91.66%)	
occurrences (all)	1350	1308	
Thrombocytopenia			
subjects affected / exposed	1250 / 1430 (87.41%)	1041 / 1427 (72.95%)	
occurrences (all)	1250	1041	
General disorders and administration site conditions			
Febrile neutropenia			
subjects affected / exposed	174 / 1430 (12.17%)	73 / 1427 (5.12%)	
occurrences (all)	174	73	
Decreased appetite			
subjects affected / exposed	353 / 1430 (24.69%)	299 / 1427 (20.95%)	
occurrences (all)	353	299	
Fatigue			
subjects affected / exposed	1210 / 1430 (84.62%)	1220 / 1427 (85.49%)	
occurrences (all)	1210	1220	
Mucosal inflammation			
subjects affected / exposed	958 / 1430 (66.99%)	968 / 1427 (67.83%)	
occurrences (all)	958	968	
Pyrexia			
subjects affected / exposed	255 / 1430 (17.83%)	274 / 1427 (19.20%)	
occurrences (all)	255	274	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	168 / 1430 (11.75%)	193 / 1427 (13.52%)	
occurrences (all)	168	193	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	539 / 1430 (37.69%)	561 / 1427 (39.31%)	
occurrences (all)	539	561	
Nausea			
subjects affected / exposed	1057 / 1430 (73.92%)	1055 / 1427 (73.93%)	
occurrences (all)	1057	1055	
Vomiting			
subjects affected / exposed	390 / 1430 (27.27%)	322 / 1427 (22.56%)	
occurrences (all)	390	322	
Constipation	Additional description: reported as free-text		
subjects affected / exposed	544 / 1430 (38.04%)	451 / 1427 (31.60%)	
occurrences (all)	544	451	
Other gastrointestinal disorders	Additional description: reported as free-text		
subjects affected / exposed	338 / 1430 (23.64%)	361 / 1427 (25.30%)	
occurrences (all)	338	361	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	297 / 1430 (20.77%)	341 / 1427 (23.90%)	
occurrences (all)	297	341	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1313 / 1430 (91.82%)	1318 / 1427 (92.36%)	
occurrences (all)	1313	1318	
Nail disorder	Additional description: reported as free-text		
subjects affected / exposed	331 / 1430 (23.15%)	286 / 1427 (20.04%)	
occurrences (all)	331	286	
Other skin and subcutaneous tissue disorder	Additional description: reported as free-text		
subjects affected / exposed	380 / 1430 (26.57%)	417 / 1427 (29.22%)	
occurrences (all)	380	417	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	836 / 1430 (58.46%)	639 / 1427 (44.78%)	
occurrences (all)	836	639	

Myalgia			
subjects affected / exposed	642 / 1430 (44.90%)	533 / 1427 (37.35%)	
occurrences (all)	642	533	
Infections and infestations			
Infection			
subjects affected / exposed	384 / 1430 (26.85%)	408 / 1427 (28.59%)	
occurrences (all)	384	408	
Other infections and infestations	Additional description: reported as free-text		
subjects affected / exposed	311 / 1430 (21.75%)	280 / 1427 (19.62%)	
occurrences (all)	311	280	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 October 2012	The study protocol was amended to implement a change in the inclusion criteria. The definition of high risk breast cancer was expanded to also include patients with luminal A like tumors and 4 or more involved lymph nodes.
19 December 2012	The study protocol and informed consent form (ICF) were amended to implement changes in the design of the run-in phase. The number of patients additionally recruited into each dose-level to avoid interruption of accrual was increased from 10 to 20.
28 April 2016	Amendment 3 was a substantial amendment of the study protocol and ICF to open GAIN-2 for the neoadjuvant setting due to slow accrual. While endpoints of the study remained unchanged, an additional stratification factor was added (neoadjuvant vs adjuvant chemotherapy) and HER2-positive patients were now allowed to receive dual anti-HER2-blockade (Pertuzumab + Trastuzumab). Corresponding changes were implemented in all parts of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34450552