Clinical trial results:
TH v THL: A phase III randomized study of TH (Paclitaxel and Trastuzumab) versus THL (Paclitaxel, Trastuzumab and Lapatinib) in first line treatment of HER2-positive metastatic breast cancer.

Summary

EudraCT number	2011-005189-39
Trial protocol	IE DE FI PT ES IT GB
Global end of trial date	17 February 2023

Results information

Result version number	v1 (current)
This version publication date	04 January 2026
First version publication date	04 January 2026

Trial information

Trial identification

Sponsor protocol code	CTRIAL-IE 11-10

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01526369
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cancer Trials Ireland
Sponsor organisation address	RCSI House, Dublin 2, Ireland, D02 H903
Public contact	Clinical Trial Information, Cancer Trials Ireland, 00353 016677211, info@cancertrials.ie
Scientific contact	Clinical Trial Information, Cancer Trials Ireland, 00353 016677211, info@cancertrials.ie

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	23 April 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 February 2023
Global end of trial reached?	Yes
Global end of trial date	17 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of THL versus TH in first line treatment of metastatic HER2 positive breast cancer

Protection of trial subjects:

This clinical study was conducted in accordance with the EU Directive 2001/20/EC and International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP) and the appropriate regulatory requirements. The trial was also conducted in accordance with ethical principles founded in the Declaration of Helsinki.

Background therapy:

N/A

Evidence for comparator:

The primary objective is to compare 2 regimens, Arm A TH (Paclitaxel + Trastuzumab) versus Arm B THL (Paclitaxel + Trastuzumab + Lapatinib).

Actual start date of recruitment	13 February 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Ireland: 34
Worldwide total number of subjects	75
EEA total number of subjects	75

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)	63
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

304 patients were planned to be enrolled in this trial over a 60 month period. On the 2nd of February 2015, recruitment was stopped due to the slow rate of accrual. At the time that recruitment was terminated, 75 patients from 23 international centres had been randomised to the study.

Pre-assignment

Screening details:

Patients with histologically or cytologically confirmed invasive metastatic breast cancer and who fulfil all inclusion criteria and none of the exclusion criteria outlined in protocol.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A TH

Arm description:

Paclitaxel* administered weekly (80 mg/m² IV day 1, for 3 weeks of a 4 week cycle) and trastuzumab administered every two weeks (8 mg/kg loading dose IV and 4 mg/kg every 2 weeks thereafter) until disease progression, unacceptable toxicity or consent withdrawal.
If the patient discontinues paclitaxel:
Trastuzumab (6 mg/kg) will be administered every 3 weeks until disease progression, unacceptable toxicity or consent withdrawal.

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

Dosage and administration details:

80 mg/m² IV day 1, for 3 weeks of a 4 week cycle

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

Dosage and administration details:

8 mg/kg loading dose IV and 4 mg/kg every 2 weeks thereafter
If the patient discontinues paclitaxel:
Trastuzumab (6 mg/kg) will be administered every 3 weeks until disease progression, unacceptable toxicity or consent withdrawal.

Arm title	Arm B THL

Arm description:

Paclitaxel* administered weekly (80 mg/m² IV day 1, for 3 weeks of a 4 week cycle), trastuzumab administered every two weeks (8 mg/kg loading dose IV and 4 mg/kg every 2 weeks thereafter) and lapatinib (1,000 mg PO daily) until disease progression, unacceptable toxicity or consent withdrawal.
If the patient discontinues paclitaxel:
Trastuzumab (6 mg/kg) will be administered every 3 weeks and Lapatinib (1,000 mg PO daily) until disease progression, unacceptable toxicity or consent withdrawal.

Arm type	Active comparator

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

Dosage and administration details:

administered weekly (80 mg/m² IV day 1, for 3 weeks of a 4 week cycle)

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

Dosage and administration details:

administered every two weeks (8 mg/kg loading dose IV and 4 mg/kg every 2 weeks thereafter)
If the patient discontinues paclitaxel:
Trastuzumab (6 mg/kg) will be administered every 3 weeks

Investigational medicinal product name	Lapatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

lapatinib (1,000 mg PO daily) until disease progression, unacceptable toxicity or consent withdrawal.
If the patient discontinues paclitaxel:
Lapatinib (1,000 mg PO daily) until disease progression, unacceptable toxicity or consent withdrawal.

Number of subjects in period 1[1]	Arm A TH	Arm B THL
Started	38	34
Completed	0	0
Not completed	38	34
Consent withdrawn by subject	5	5
investigator discretional	2	-
End of Study	11	10
Adverse event, non-fatal	-	1
Death	18	18
Disease Progression	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Seventy-five patients (THL:37, TH: 38) were registered, of which seventy two (THL:34, TH:38) received study treatment. Of the three who did not receive treatment, one patient withdrew consent, one patient was withdrawn prior to treatment due to investigator’s decision with a noted clinically significant ALT reading at the withdrawal visit. The final patient not treated was withdrawn due to elevated ALT and AST

Baseline characteristics

Reporting groups	
Reporting group title	Arm A TH
Reporting group description:	
Paclitaxel* administered weekly (80 mg/m² IV day 1, for 3 weeks of a 4 week cycle) and trastuzumab administered every two weeks (8 mg/kg loading dose IV and 4 mg/kg every 2 weeks thereafter) until disease progression, unacceptable toxicity or consent withdrawal. If the patient discontinues paclitaxel: Trastuzumab (6 mg/kg) will be administered every 3 weeks until disease progression, unacceptable toxicity or consent withdrawal.	
Reporting group title	Arm B THL
Reporting group description:	
Paclitaxel* administered weekly (80 mg/m² IV day 1, for 3 weeks of a 4 week cycle), trastuzumab administered every two weeks (8 mg/kg loading dose IV and 4 mg/kg every 2 weeks thereafter) and lapatinib (1,000 mg PO daily) until disease progression, unacceptable toxicity or consent withdrawal. If the patient discontinues paclitaxel: Trastuzumab (6 mg/kg) will be administered every 3 weeks and Lapatinib (1,000 mg PO daily) until disease progression, unacceptable toxicity or consent withdrawal.	

Reporting group values	Arm A TH	Arm B THL	Total
Number of subjects	38	34	72
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	34	26	60
From 65-84 years	4	8	12
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	38	34	72
Male	0	0	0
Ethnic Origin Units: Subjects			
Black	0	1	1
Caucasian	37	33	70
Hispanic	1	0	1
Asian	0	0	0
ER Status Units: Subjects			
Negative	15	17	32
Positive	23	17	40
PR Status Units: Subjects			
Negative	22	23	45

Positive	15	11	26
Not Recorded	1	0	1

Weight at Screening			
Units: kilogram(s)			
arithmetic mean	68.35	68.25	
full range (min-max)	51.6 to 104.0	43.9 to 95.0	-
Duration of Exposure			
Overall duration of exposure for treatment			
Units: day			
arithmetic mean	446.7	552.3	
full range (min-max)	44 to 2437	6 to 3440	-
Trastuzumab of Duration of Exposure			
Units: day			
arithmetic mean	445.7	543.2	
full range (min-max)	44 to 2437	1 to 3440	-
Lapatinib of Duration of Exposure			
Units: day			
arithmetic mean	0	551.4	
full range (min-max)	0 to 0	6 to 3440	-
Duration of Paclitaxel Exposure			
Units: day			
arithmetic mean	264.2	248.3	
full range (min-max)	44 to 743	1 to 1002	-
Height at Screening			
Units: cm			
arithmetic mean	161.9	161.1	
full range (min-max)	148 to 175	144 to 175	-

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set (FAS): The FAS includes all eligible patients who received at least one dose of study treatment and have some post-baseline assessment of efficacy. The FAS will be used for all efficacy analyses.

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Set (Safety): The Safety Set includes all patients who receive at least one dose of study treatment. The Safety Set will be used for all safety analyses.

Reporting group values	Full Analysis Set	Safety Set	
Number of subjects	66	72	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	

Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	55	60	
From 65-84 years	11	12	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	66	72	
Male	0	0	
Ethnic Origin Units: Subjects			
Black			
Caucasian			
Hispanic			
Asian			
ER Status Units: Subjects			
Negative	29	32	
Positive	37	40	
PR Status Units: Subjects			
Negative	42	45	
Positive	23	26	
Not Recorded	1	1	
Weight at Screening Units: kilogram(s) arithmetic mean full range (min-max)			
Duration of Exposure			
Overall duration of exposure for treatment			
Units: day arithmetic mean full range (min-max)			
Trastuzumab of Duration of Exposure Units: day arithmetic mean full range (min-max)			
Lapatinib of Duration of Exposure Units: day arithmetic mean full range (min-max)			
Duration of Paclitaxel Exposure Units: day arithmetic mean full range (min-max)			
Height at Screening Units: cm arithmetic mean full range (min-max)			

End points

End points reporting groups

Reporting group title	Arm A TH

Reporting group description:

Paclitaxel* administered weekly (80 mg/m² IV day 1, for 3 weeks of a 4 week cycle) and trastuzumab administered every two weeks (8 mg/kg loading dose IV and 4 mg/kg every 2 weeks thereafter) until disease progression, unacceptable toxicity or consent withdrawal.
If the patient discontinues paclitaxel:
Trastuzumab (6 mg/kg) will be administered every 3 weeks until disease progression, unacceptable toxicity or consent withdrawal.

Reporting group title	Arm B THL

Reporting group description:

Paclitaxel* administered weekly (80 mg/m² IV day 1, for 3 weeks of a 4 week cycle), trastuzumab administered every two weeks (8 mg/kg loading dose IV and 4 mg/kg every 2 weeks thereafter) and lapatinib (1,000 mg PO daily) until disease progression, unacceptable toxicity or consent withdrawal.
If the patient discontinues paclitaxel:
Trastuzumab (6 mg/kg) will be administered every 3 weeks and Lapatinib (1,000 mg PO daily) until disease progression, unacceptable toxicity or consent withdrawal.

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set (FAS): The FAS includes all eligible patients who received at least one dose of study treatment and have some post-baseline assessment of efficacy. The FAS will be used for all efficacy analyses.

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Set (Safety): The Safety Set includes all patients who receive at least one dose of study treatment. The Safety Set will be used for all safety analyses.

Primary: Summary of Progression-Free Survival

End point title	Summary of Progression-Free Survival

End point description:

Patients who did not progress or die are censored at the date of their last disease assessment. In addition, patients with no disease progression who started another anticancer therapy were censored at the date of starting the new therapy.

Progression-free probabilities over time were estimated using the Kaplan-Meier method (Kaplan. 1958), presenting estimates of median survival with 95% confidence intervals (CIs) and estimates of survival (95% CI) at 9 months. Comparison between the two treatment arms is made using the Log-rank test, and the hazard ratio for the comparison is calculated with 95% CIs. Kaplan-Meier plots were produced including 95% Hall-Wellner Bands.

Given the small sample size, the study is not powered for treatment comparisons for the primary endpoint, so care should be taken in interpreting these results. To this end p values will not be presented within the report.

End point type	Primary

End point timeframe:

The primary endpoint of this study is progression free survival (PFS), defined as the time from randomisation until objective tumour progression or death

End point values	Arm A TH	Arm B THL	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	34	32	66	
Units: Subjects				
Number of Patients with Event	14	13	27	
Number of Patients Censored	20	19	39	

Statistical analyses

Statistical analysis title	Median Survival and PFS at 9 months

Statistical analysis description:

Progression-free probabilities over time are estimated using the Kaplan-Meier method (Kaplan. 1958), presenting estimates of median survival with 95% confidence intervals (CIs) and estimates of survival (95% CI) at 9 months. Comparison between the two treatment arms is made using the Log-rank test, and the hazard ratio for the comparison is calculated with 95% CIs. Kaplan-Meier plots were produced including 95% Hall-Wellner Bands.

Comparison groups	Arm A TH v Arm B THL
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.6448 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.82
Variability estimate	Standard deviation

Notes:

[1] - Median (95% CI) PFS in the THL treatment group was 33.35 months (8.67 to 51.12 months) with an estimated rate (95% CI) for PFS at 9 months of 69.7% (44.3 to 85.2%).
Median (95% CI) PFS in the TH treatment group was 19.29 months (8.05 to 22.31 months) compared to 33.25 months (8.67 to 15.12 months) in the THL group with a Hazard Ratio (95% CI) for THL vs TH of 0.83 (0.38 to 1.81). The estimated rate (95% CI) for PFS at 9 months was 65.4% (44.7 to 79.9%).

[2] - Given the small sample size, the study is not powered for treatment comparisons for the primary endpoint, so care should be taken in interpreting the results. Therefore p-values will be presented but significance will not be concluded.

Secondary: Overall Survival

End point title	Overall Survival

End point description:

OS was analysed similarly to progression-free survival, presenting estimates of survival and 95% CIs at 30 months and accompanied by a Kaplan-Meier plots including 95% Hall-Wellner Bands.

End point type	Secondary

End point timeframe:

The time from randomisation until death from any cause.

End point values	Arm A TH	Arm B THL	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	34	32	66	
Units: Subject				
Number of Patients with Event	17	18	35	
Number of Patients Censored	17	14	31	

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Tumour Response

End point title	Objective Tumour Response

End point description:

The proportions of patients with objective tumour response (complete or partial response), as defined by RECIST criteria version 1.1, is presented by treatment arm with accompanying CIs. The chi-squared test, or Fisher's Exact test (for small counts) was used to compare objective response between treatment arms.
The objective tumour response rate (i.e. complete response or partial response) in the THL treatment group was 88.9% versus 76.5% in the TH treatment group (p=0.317). Of these 18.5% achieved a complete response (CR) and 70.4% achieved a partial response (PR) in the THL treatment group versus 14.7% with a CR and 61.8% with a PR in the TH treatment group. Of the remaining patients who did not achieve an objective response 7.4% had stable disease (SD) and 3.7% had progressive disease (PD) in the THL treatment group versus 20.6% with stable disease (SD) and 2.9% with progressive disease (PD) in the TH treatment group.

End point type	Secondary

End point timeframe:

Complete or partial response

End point values	Arm A TH	Arm B THL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	32		
Units: Subject				
Best Overall Response	34	27		
Objective Tumour Response Time	26	24		
Complete Response	5	5		
Partial Response	21	19		
Stable Disease	7	2		
Progression Disease	1	1		
Non-Target lesion Stable Disease	28	21		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE
Adverse events, both serious and non-serious that occur during the patient's study participation, defined as beginning on or after the start date of study drug administration and up to 30 days after last administration.

Adverse event reporting additional description:

Version of MedDRA used was dependent on the time the coding was undertaken during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21 to 26

Reporting groups

Reporting group title	Arm A: TH
Reporting group description: -	
Reporting group title	Arm B: THL

Reporting group description: -

Serious adverse events	Arm A: TH	Arm B: THL	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 38 (28.95%)	15 / 34 (44.12%)	
number of deaths (all causes)	18	18	
number of deaths resulting from adverse events	0	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system	Additional description: Metastases to central nervous system		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Surgical and medical procedures			
Axillary lymphadenectomy	Additional description: Axillary lymphadenectomy		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast conserving surgery	Additional description: Breast conserving surgery		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mastectomy	Additional description: Mastectomy		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue	Additional description: Fatigue		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance	Additional description: Gait disturbance		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation	Additional description: Inflammation		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	2 / 38 (5.26%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction	Additional description: Anaphylactic reaction		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity	Additional description: Bronchial hyperreactivity		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea	Additional description: Dyspnoea		

subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain	Additional description: Pleuritic pain		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous	Additional description: Pneumothorax spontaneous		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure	Additional description: Respiratory failure		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Confusional state	Additional description: Confusional state		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Biopsy lymph gland abnormal	Additional description: Biopsy lymph gland abnormal		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased	Additional description: Ejection fraction decreased		
subjects affected / exposed	2 / 38 (5.26%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Mitral valve disease	Additional description: Mitral valve disease		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (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			
Disturbance in attention	Additional description: Disturbance in attention		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis	Additional description: Facial paralysis		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache	Additional description: Headache		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke	Additional description: Ischaemic stroke		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis	Additional description: Leukocytosis		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neutrophilia	Additional description: Neutrophilia		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort	Additional description: Abdominal discomfort		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	0 / 38 (0.00%)	4 / 34 (11.76%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis	Additional description: Gastritis		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea	Additional description: Nausea		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis	Additional description: Oesophagitis		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis	Additional description: Pancreatitis		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Erythema	Additional description: Erythema		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Breast abscess	Additional description: Breast abscess		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective	Additional description: Bursitis infective		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection	Additional description: Catheter site infection		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis	Additional description: Cellulitis		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection	Additional description: Device related infection		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza	Additional description: Influenza		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection	Additional description: Urinary tract infection		

subjects affected / exposed	2 / 38 (5.26%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration	Additional description: Dehydration		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia	Additional description: Hyponatraemia		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Arm A: TH	Arm B: THL	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 38 (100.00%)	34 / 34 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer fatigue	Additional description: Cancer fatigue		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Metastases to central nervous system	Additional description: Metastases to central nervous system		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Pyogenic granuloma	Additional description: Pyogenic granuloma		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Vascular disorders			

Flushing	Additional description: Flushing		
subjects affected / exposed	1 / 38 (2.63%)	3 / 34 (8.82%)	
occurrences (all)	1	3	
Haematoma	Additional description: Haematoma		
subjects affected / exposed	2 / 38 (5.26%)	2 / 34 (5.88%)	
occurrences (all)	3	3	
Haemorrhage	Additional description: Haemorrhage		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Hot flush	Additional description: Hot flush		
subjects affected / exposed	6 / 38 (15.79%)	4 / 34 (11.76%)	
occurrences (all)	10	6	
Hypertension	Additional description: Hypertension		
subjects affected / exposed	2 / 38 (5.26%)	4 / 34 (11.76%)	
occurrences (all)	2	6	
Lymphoedema	Additional description: Lymphoedema		
subjects affected / exposed	4 / 38 (10.53%)	2 / 34 (5.88%)	
occurrences (all)	4	3	
Vascular pain	Additional description: Vascular pain		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Cataract operation	Additional description: Cataract operation		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	
Axillary lymphadenectomy	Additional description: Axillary lymphadenectomy		
subjects affected / exposed	2 / 38 (5.26%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
Mastectomy	Additional description: Mastectomy		
subjects affected / exposed	2 / 38 (5.26%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Adverse drug reaction	Additional description: Adverse drug reaction		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Catheter site injury	Additional description: Catheter site injury		

subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Chest pain	Additional description: Chest pain		
subjects affected / exposed	2 / 38 (5.26%)	2 / 34 (5.88%)	
occurrences (all)	2	5	
Chills	Additional description: Chills		
subjects affected / exposed	2 / 38 (5.26%)	4 / 34 (11.76%)	
occurrences (all)	2	8	
Asthenia	Additional description: Asthenia		
subjects affected / exposed	9 / 38 (23.68%)	12 / 34 (35.29%)	
occurrences (all)	41	76	
Axillary pain	Additional description: Axillary pain		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Fatigue	Additional description: Fatigue		
subjects affected / exposed	21 / 38 (55.26%)	15 / 34 (44.12%)	
occurrences (all)	46	31	
Extravasation	Additional description: Extravasation		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Influenza like illness	Additional description: Influenza like illness		
subjects affected / exposed	5 / 38 (13.16%)	3 / 34 (8.82%)	
occurrences (all)	5	3	
Infusion site erythema	Additional description: Infusion site erythema		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Infusion site extravasation	Additional description: Infusion site extravasation		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Malaise	Additional description: Malaise		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Mucosal inflammation	Additional description: Mucosal inflammation		
subjects affected / exposed	8 / 38 (21.05%)	5 / 34 (14.71%)	
occurrences (all)	20	15	
Nodule	Additional description: Nodule		

subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Oedema	Additional description: Oedema		
subjects affected / exposed	2 / 38 (5.26%)	2 / 34 (5.88%)	
occurrences (all)	3	3	
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	5 / 38 (13.16%)	5 / 34 (14.71%)	
occurrences (all)	7	15	
Pain	Additional description: Pain		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Peripheral swelling	Additional description: Peripheral swelling		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	4 / 38 (10.53%)	6 / 34 (17.65%)	
occurrences (all)	6	11	
Suprapubic pain	Additional description: Suprapubic pain		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Xerosis	Additional description: Xerosis		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	3	
Immune system disorders			
Drug hypersensitivity	Additional description: Drug hypersensitivity		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Hypersensitivity	Additional description: Hypersensitivity		
subjects affected / exposed	1 / 38 (2.63%)	2 / 34 (5.88%)	
occurrences (all)	2	3	
Seasonal allergy	Additional description: Seasonal allergy		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			

Amenorrhoea	Additional description: Amenorrhoea		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	
Breast discomfort	Additional description: Breast discomfort		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Breast inflammation	Additional description: Breast inflammation		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Breast pain	Additional description: Breast pain		
subjects affected / exposed	4 / 38 (10.53%)	6 / 34 (17.65%)	
occurrences (all)	6	9	
Breast ulceration	Additional description: Breast ulceration		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	3	
Intermenstrual bleeding	Additional description: Intermenstrual bleeding		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Menstruation irregular	Additional description: Menstruation irregular		
subjects affected / exposed	2 / 38 (5.26%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
Ovarian cyst	Additional description: Ovarian cyst		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Pelvic pain	Additional description: Pelvic pain		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	
Vaginal haemorrhage	Additional description: Vaginal haemorrhage		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal dryness	Additional description: Vulvovaginal dryness		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	3	
Vulvovaginal pruritus	Additional description: Vulvovaginal pruritus		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	

Vaginal discharge	Additional description: Vaginal discharge		
subjects affected / exposed	0 / 38 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
Aphonia	Additional description: Aphonia		
subjects affected / exposed	2 / 38 (5.26%)	1 / 34 (2.94%)	
occurrences (all)	2	1	
Catarrh	Additional description: Catarrh		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
Cough	Additional description: Cough		
subjects affected / exposed	10 / 38 (26.32%)	8 / 34 (23.53%)	
occurrences (all)	15	16	
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	9 / 38 (23.68%)	11 / 34 (32.35%)	
occurrences (all)	16	31	
Dyspnoea exertional	Additional description: Dyspnoea exertional		
subjects affected / exposed	0 / 38 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	4	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	5 / 38 (13.16%)	4 / 34 (11.76%)	
occurrences (all)	8	13	
Dysphonia	Additional description: Dysphonia		
subjects affected / exposed	1 / 38 (2.63%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Nasal crusting	Additional description: Nasal crusting		
subjects affected / exposed	0 / 38 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	4	
Nasal discomfort	Additional description: Nasal discomfort		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Nasal dryness	Additional description: Nasal dryness		
subjects affected / exposed	3 / 38 (7.89%)	5 / 34 (14.71%)	
occurrences (all)	7	12	
Nasal congestion	Additional description: Nasal congestion		

subjects affected / exposed	2 / 38 (5.26%)	3 / 34 (8.82%)	
occurrences (all)	3	3	
Pharyngeal inflammation	Additional description: Pharyngeal inflammation		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Pleuritic pain	Additional description: Pleuritic pain		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain	Additional description: Oropharyngeal pain		
subjects affected / exposed	7 / 38 (18.42%)	2 / 34 (5.88%)	
occurrences (all)	7	3	
Productive cough	Additional description: Productive cough		
subjects affected / exposed	1 / 38 (2.63%)	3 / 34 (8.82%)	
occurrences (all)	1	7	
Pulmonary hypertension	Additional description: Pulmonary hypertension		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Rhinitis allergic	Additional description: Rhinitis allergic		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	3	
Rhinorrhoea	Additional description: Rhinorrhoea		
subjects affected / exposed	6 / 38 (15.79%)	3 / 34 (8.82%)	
occurrences (all)	9	3	
Upper-airway cough syndrome	Additional description: Upper-airway cough syndrome		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Psychiatric disorders			
Abnormal dreams	Additional description: Abnormal dreams		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Agoraphobia	Additional description: Agoraphobia		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Anxiety	Additional description: Anxiety		
subjects affected / exposed	5 / 38 (13.16%)	6 / 34 (17.65%)	
occurrences (all)	6	7	

Disorientation	Additional description: Disorientation		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Depressive symptom	Additional description: Depressive symptom		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Depression	Additional description: Depression		
subjects affected / exposed	1 / 38 (2.63%)	2 / 34 (5.88%)	
occurrences (all)	2	2	
Insomnia	Additional description: Insomnia		
subjects affected / exposed	5 / 38 (13.16%)	13 / 34 (38.24%)	
occurrences (all)	8	26	
Irritability	Additional description: Irritability		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Mood altered	Additional description: Mood altered		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Panic attack	Additional description: Panic attack		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Stress	Additional description: Stress		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		
subjects affected / exposed	1 / 38 (2.63%)	5 / 34 (14.71%)	
occurrences (all)	1	10	
Aspartate aminotransferase increased	Additional description: Aspartate aminotransferase increased		
subjects affected / exposed	2 / 38 (5.26%)	4 / 34 (11.76%)	
occurrences (all)	2	6	
Blood alkaline phosphatase increased	Additional description: Blood alkaline phosphatase increased		
subjects affected / exposed	2 / 38 (5.26%)	1 / 34 (2.94%)	
occurrences (all)	3	2	
Blood bilirubin increased	Additional description: Blood bilirubin increased		

subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	
Blood phosphorus decreased	Additional description: Blood phosphorus decreased		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Body temperature increased	Additional description: Body temperature increased		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Ejection fraction decreased	Additional description: Ejection fraction decreased		
subjects affected / exposed	2 / 38 (5.26%)	1 / 34 (2.94%)	
occurrences (all)	2	2	
Haemoglobin decreased	Additional description: Haemoglobin decreased		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased	Additional description: Neutrophil count decreased		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Weight decreased	Additional description: Weight decreased		
subjects affected / exposed	0 / 38 (0.00%)	5 / 34 (14.71%)	
occurrences (all)	0	8	
Weight increased	Additional description: Weight increased		
subjects affected / exposed	2 / 38 (5.26%)	1 / 34 (2.94%)	
occurrences (all)	3	2	
Injury, poisoning and procedural complications			
Breast injury	Additional description: Breast injury		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
Chillblains	Additional description: Chillblains		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Contusion	Additional description: Contusion		

subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Foot fracture	Additional description: Foot fracture		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	3 / 38 (7.89%)	2 / 34 (5.88%)	
occurrences (all)	3	2	
Nail injury	Additional description: Nail injury		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Nasal injury	Additional description: Nasal injury		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Post procedural diarrhoea	Additional description: Post procedural diarrhoea		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Procedural pain	Additional description: Procedural pain		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Procedural site reaction	Additional description: Procedural site reaction		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Thermal burn	Additional description: Thermal burn		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Thermal burns of eye	Additional description: Thermal burns of eye		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Tooth fracture	Additional description: Tooth fracture		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Traumatic haematoma	Additional description: Traumatic haematoma		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Wound complication	Additional description: Wound complication		

subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Wound decomposition	Additional description: Wound decomposition		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
Wrist fracture	Additional description: Wrist fracture		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Muscular dystrophy	Additional description: Muscular dystrophy		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Angina pectoris	Additional description: Angina pectoris		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Palpitations	Additional description: Palpitations		
subjects affected / exposed	1 / 38 (2.63%)	3 / 34 (8.82%)	
occurrences (all)	2	3	
Tachycardia	Additional description: Tachycardia		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Allodynia	Additional description: Allodynia		
subjects affected / exposed	1 / 38 (2.63%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Anosmia	Additional description: Anosmia		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	3	
Aphasia	Additional description: Aphasia		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Ataxia	Additional description: Ataxia		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	
Balance disorder	Additional description: Balance disorder		

subjects affected / exposed	2 / 38 (5.26%)	2 / 34 (5.88%)	
occurrences (all)	2	2	
Dysarthria	Additional description: Dysarthria		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Dysgeusia	Additional description: Dysgeusia		
subjects affected / exposed	1 / 38 (2.63%)	10 / 34 (29.41%)	
occurrences (all)	5	21	
Dyslexia	Additional description: Dyslexia		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Dizziness	Additional description: Dizziness		
subjects affected / exposed	5 / 38 (13.16%)	6 / 34 (17.65%)	
occurrences (all)	5	9	
Disturbance in attention	Additional description: Disturbance in attention		
subjects affected / exposed	2 / 38 (5.26%)	2 / 34 (5.88%)	
occurrences (all)	2	2	
Headache	Additional description: Headache		
subjects affected / exposed	11 / 38 (28.95%)	11 / 34 (32.35%)	
occurrences (all)	21	49	
Hyperaesthesia	Additional description: Hyperaesthesia		
subjects affected / exposed	1 / 38 (2.63%)	2 / 34 (5.88%)	
occurrences (all)	1	3	
Hypoaesthesia	Additional description: Hypoaesthesia		
subjects affected / exposed	4 / 38 (10.53%)	2 / 34 (5.88%)	
occurrences (all)	6	4	
Hyposmia	Additional description: Hyposmia		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	4	
Hypokinesia	Additional description: Hypokinesia		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Memory impairment	Additional description: Memory impairment		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Migraine	Additional description: Migraine		

subjects affected / exposed	0 / 38 (0.00%)	4 / 34 (11.76%)	
occurrences (all)	0	10	
Neuralgia	Additional description: Neuralgia		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Neuropathy peripheral	Additional description: Neuropathy peripheral		
subjects affected / exposed	17 / 38 (44.74%)	14 / 34 (41.18%)	
occurrences (all)	30	30	
Ophthalmic migraine	Additional description: Ophthalmic migraine		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed	6 / 38 (15.79%)	10 / 34 (29.41%)	
occurrences (all)	18	13	
Peripheral motor neuropathy	Additional description: Peripheral motor neuropathy		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Peripheral sensory neuropathy	Additional description: Peripheral sensory neuropathy		
subjects affected / exposed	7 / 38 (18.42%)	1 / 34 (2.94%)	
occurrences (all)	9	1	
Restless legs syndrome	Additional description: Restless legs syndrome		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	3	
Seizure	Additional description: Seizure		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Presyncope	Additional description: Presyncope		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Syncope	Additional description: Syncope		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Taste disorder	Additional description: Taste disorder		
subjects affected / exposed	6 / 38 (15.79%)	4 / 34 (11.76%)	
occurrences (all)	7	6	
Tremor	Additional description: Tremor		

subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	7	1	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	7 / 38 (18.42%)	7 / 34 (20.59%)	
occurrences (all)	10	11	
Febrile neutropenia	Additional description: Febrile neutropenia		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Lymphadenopathy	Additional description: Lymphadenopathy		
subjects affected / exposed	3 / 38 (7.89%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	7 / 38 (18.42%)	11 / 34 (32.35%)	
occurrences (all)	15	18	
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear pain	Additional description: Ear pain		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Ear congestion	Additional description: Ear congestion		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Hypoacusis	Additional description: Hypoacusis		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Tinnitus	Additional description: Tinnitus		
subjects affected / exposed	2 / 38 (5.26%)	2 / 34 (5.88%)	
occurrences (all)	2	2	
Vertigo	Additional description: Vertigo		
subjects affected / exposed	2 / 38 (5.26%)	3 / 34 (8.82%)	
occurrences (all)	6	4	
Eye disorders			

Cataract	Additional description: Cataract		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Blindness	Additional description: Blindness		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Dry eye	Additional description: Dry eye		
subjects affected / exposed	3 / 38 (7.89%)	5 / 34 (14.71%)	
occurrences (all)	3	7	
Conjunctivitis allergic	Additional description: Conjunctivitis allergic		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Eye pruritus	Additional description: Eye pruritus		
subjects affected / exposed	1 / 38 (2.63%)	2 / 34 (5.88%)	
occurrences (all)	1	3	
Eye discharge	Additional description: Eye discharge		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Eczema eyelids	Additional description: Eczema eyelids		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Lacrimation increased	Additional description: Lacrimation increased		
subjects affected / exposed	3 / 38 (7.89%)	2 / 34 (5.88%)	
occurrences (all)	4	6	
Macular degeneration	Additional description: Macular degeneration		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Ocular hyperaemia	Additional description: Ocular hyperaemia		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Ocular toxicity	Additional description: Ocular toxicity		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Periorbital oedema	Additional description: Periorbital oedema		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	

Periorbital swelling	Additional description: Periorbital swelling		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	4	
Photophobia	Additional description: Photophobia		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	
Retinopathy	Additional description: Retinopathy		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Ulcerative keratitis	Additional description: Ulcerative keratitis		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Vision blurred	Additional description: Vision blurred		
subjects affected / exposed	3 / 38 (7.89%)	3 / 34 (8.82%)	
occurrences (all)	5	3	
Visual acuity reduced	Additional description: Visual acuity reduced		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	5 / 38 (13.16%)	10 / 34 (29.41%)	
occurrences (all)	5	36	
Abdominal distension	Additional description: Abdominal distension		
subjects affected / exposed	3 / 38 (7.89%)	4 / 34 (11.76%)	
occurrences (all)	3	4	
Abdominal pain upper	Additional description: Abdominal pain upper		
subjects affected / exposed	4 / 38 (10.53%)	4 / 34 (11.76%)	
occurrences (all)	7	5	
Abnormal faeces	Additional description: Abnormal faeces		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Anal inflammation	Additional description: Anal inflammation		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Anal pruritus	Additional description: Anal pruritus		

subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Angular cheilitis	Additional description: Angular cheilitis		
subjects affected / exposed	0 / 38 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	4	
Anorectal discomfort	Additional description: Anorectal discomfort		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	5	
Aphthous ulcer	Additional description: Aphthous ulcer		
subjects affected / exposed	2 / 38 (5.26%)	4 / 34 (11.76%)	
occurrences (all)	4	14	
Abdominal discomfort	Additional description: Abdominal discomfort		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Abdominal pain lower	Additional description: Abdominal pain lower		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Colitis	Additional description: Colitis		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Dry mouth	Additional description: Dry mouth		
subjects affected / exposed	2 / 38 (5.26%)	3 / 34 (8.82%)	
occurrences (all)	5	5	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	16 / 38 (42.11%)	30 / 34 (88.24%)	
occurrences (all)	56	236	
Defaecation urgency	Additional description: Defaecation urgency		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Constipation	Additional description: Constipation		
subjects affected / exposed	12 / 38 (31.58%)	14 / 34 (41.18%)	
occurrences (all)	28	27	
Gastritis	Additional description: Gastritis		
subjects affected / exposed	0 / 38 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	3	
Faeces soft	Additional description: Faeces soft		

subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Dysphagia	Additional description: Dysphagia		
subjects affected / exposed	1 / 38 (2.63%)	4 / 34 (11.76%)	
occurrences (all)	2	6	
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	5 / 38 (13.16%)	4 / 34 (11.76%)	
occurrences (all)	5	6	
Flatulence	Additional description: Flatulence		
subjects affected / exposed	1 / 38 (2.63%)	4 / 34 (11.76%)	
occurrences (all)	2	9	
Gastrointestinal pain	Additional description: Gastrointestinal pain		
subjects affected / exposed	1 / 38 (2.63%)	3 / 34 (8.82%)	
occurrences (all)	1	3	
Gastrooesophageal reflux disease	Additional description: Gastrooesophageal reflux disease		
subjects affected / exposed	2 / 38 (5.26%)	7 / 34 (20.59%)	
occurrences (all)	17	12	
Gingival bleeding	Additional description: Gingival bleeding		
subjects affected / exposed	0 / 38 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	8	
Gingival pain	Additional description: Gingival pain		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	3	
Haemorrhoids	Additional description: Haemorrhoids		
subjects affected / exposed	1 / 38 (2.63%)	7 / 34 (20.59%)	
occurrences (all)	1	27	
Hypoaesthesia oral	Additional description: Hypoaesthesia oral		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia teeth	Additional description: Hypoaesthesia teeth		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Lip dry	Additional description: Lip dry		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Lip pain	Additional description: Lip pain		

subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Melaena	Additional description: Melaena		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Mouth ulceration	Additional description: Mouth ulceration		
subjects affected / exposed	2 / 38 (5.26%)	7 / 34 (20.59%)	
occurrences (all)	4	10	
Oral pain	Additional description: Oral pain		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Nausea	Additional description: Nausea		
subjects affected / exposed	18 / 38 (47.37%)	19 / 34 (55.88%)	
occurrences (all)	53	61	
Noninfective sialoadenitis	Additional description: Noninfective sialoadenitis		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Odynophagia	Additional description: Odynophagia		
subjects affected / exposed	2 / 38 (5.26%)	2 / 34 (5.88%)	
occurrences (all)	2	2	
Oral toxicity	Additional description: Oral toxicity		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	3	
Paraesthesia oral	Additional description: Paraesthesia oral		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Rectal haemorrhage	Additional description: Rectal haemorrhage		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Stomatitis	Additional description: Stomatitis		
subjects affected / exposed	3 / 38 (7.89%)	4 / 34 (11.76%)	
occurrences (all)	8	11	
Tongue pruritus	Additional description: Tongue pruritus		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Tooth disorder	Additional description: Tooth disorder		

subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Toothache	Additional description: Toothache		
subjects affected / exposed	1 / 38 (2.63%)	3 / 34 (8.82%)	
occurrences (all)	3	4	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	11 / 38 (28.95%)	15 / 34 (44.12%)	
occurrences (all)	11	48	
Skin and subcutaneous tissue disorders			
Acne	Additional description: Acne		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Alopecia	Additional description: Alopecia		
subjects affected / exposed	20 / 38 (52.63%)	17 / 34 (50.00%)	
occurrences (all)	27	26	
Dry skin	Additional description: Dry skin		
subjects affected / exposed	2 / 38 (5.26%)	6 / 34 (17.65%)	
occurrences (all)	3	9	
Dermatitis acneiform	Additional description: Dermatitis acneiform		
subjects affected / exposed	4 / 38 (10.53%)	13 / 34 (38.24%)	
occurrences (all)	8	25	
Dermatitis	Additional description: Dermatitis		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	2	
Decubitus ulcer	Additional description: Decubitus ulcer		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	
Erythema	Additional description: Erythema		
subjects affected / exposed	1 / 38 (2.63%)	8 / 34 (23.53%)	
occurrences (all)	1	15	
Eczema	Additional description: Eczema		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	4	
Hand dermatitis	Additional description: Hand dermatitis		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	4	

Hyperhidrosis	Additional description: Hyperhidrosis		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Ingrowing nail	Additional description: Ingrowing nail		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Nail ridging	Additional description: Nail ridging		
subjects affected / exposed	2 / 38 (5.26%)	4 / 34 (11.76%)	
occurrences (all)	2	4	
Nail discolouration	Additional description: Nail discolouration		
subjects affected / exposed	2 / 38 (5.26%)	3 / 34 (8.82%)	
occurrences (all)	2	3	
Nail disorder	Additional description: Nail disorder		
subjects affected / exposed	7 / 38 (18.42%)	6 / 34 (17.65%)	
occurrences (all)	9	6	
Nail dystrophy	Additional description: Nail dystrophy		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Nail toxicity	Additional description: Nail toxicity		
subjects affected / exposed	2 / 38 (5.26%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
Onychalgia	Additional description: Onychalgia		
subjects affected / exposed	3 / 38 (7.89%)	1 / 34 (2.94%)	
occurrences (all)	4	1	
Onychoclasis	Additional description: Onychoclasis		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Onycholysis	Additional description: Onycholysis		
subjects affected / exposed	1 / 38 (2.63%)	6 / 34 (17.65%)	
occurrences (all)	1	13	
Onychomadesis	Additional description: Onychomadesis		
subjects affected / exposed	1 / 38 (2.63%)	3 / 34 (8.82%)	
occurrences (all)	1	4	
Pain of skin	Additional description: Pain of skin		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	

Palmar-plantar erythrodysaesthesia syndrome	Additional description: Palmar-plantar erythrodysaesthesia syndrome		
subjects affected / exposed	2 / 38 (5.26%)	2 / 34 (5.88%)	
occurrences (all)	2	4	
Photosensitivity reaction	Additional description: Photosensitivity reaction		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	2	
Skin fissures	Additional description: Skin fissures		
subjects affected / exposed	1 / 38 (2.63%)	5 / 34 (14.71%)	
occurrences (all)	1	7	
Pruritus	Additional description: Pruritus		
subjects affected / exposed	3 / 38 (7.89%)	7 / 34 (20.59%)	
occurrences (all)	5	10	
Psoriasis	Additional description: Psoriasis		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Rash	Additional description: Rash		
subjects affected / exposed	6 / 38 (15.79%)	15 / 34 (44.12%)	
occurrences (all)	11	22	
Rash erythematous	Additional description: Rash erythematous		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Rash macular	Additional description: Rash macular		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Rash maculo-papular	Additional description: Rash maculo-papular		
subjects affected / exposed	1 / 38 (2.63%)	3 / 34 (8.82%)	
occurrences (all)	1	6	
Rash pruritic	Additional description: Rash pruritic		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Scar pain	Additional description: Scar pain		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Skin disorder	Additional description: Skin disorder		

subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Skin lesion	Additional description: Skin lesion		
subjects affected / exposed	2 / 38 (5.26%)	1 / 34 (2.94%)	
occurrences (all)	2	1	
Skin ulcer	Additional description: Skin ulcer		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	3	
Umbilical discharge	Additional description: Umbilical discharge		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Skin irritation	Additional description: Skin irritation		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Xeroderma	Additional description: Xeroderma		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Cystitis noninfective	Additional description: Cystitis noninfective		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Dysuria	Additional description: Dysuria		
subjects affected / exposed	2 / 38 (5.26%)	2 / 34 (5.88%)	
occurrences (all)	3	2	
Nocturia	Additional description: Nocturia		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Pollakiuria	Additional description: Pollakiuria		
subjects affected / exposed	2 / 38 (5.26%)	2 / 34 (5.88%)	
occurrences (all)	3	2	
Endocrine disorders			
Hypothyroidism	Additional description: Hypothyroidism		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			

Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	14 / 38 (36.84%)	13 / 34 (38.24%)	
occurrences (all)	39	25	
Arthritis	Additional description: Arthritis		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Back pain	Additional description: Back pain		
subjects affected / exposed	7 / 38 (18.42%)	11 / 34 (32.35%)	
occurrences (all)	14	23	
Bone pain	Additional description: Bone pain		
subjects affected / exposed	2 / 38 (5.26%)	5 / 34 (14.71%)	
occurrences (all)	2	9	
Chondritis	Additional description: Chondritis		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Flank pain	Additional description: Flank pain		
subjects affected / exposed	1 / 38 (2.63%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Groin pain	Additional description: Groin pain		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Joint stiffness	Additional description: Joint stiffness		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Joint swelling	Additional description: Joint swelling		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Limb discomfort	Additional description: Limb discomfort		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed	1 / 38 (2.63%)	6 / 34 (17.65%)	
occurrences (all)	5	23	
Muscular weakness	Additional description: Muscular weakness		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	

Musculoskeletal chest pain	Additional description: Musculoskeletal chest pain		
subjects affected / exposed	3 / 38 (7.89%)	2 / 34 (5.88%)	
occurrences (all)	3	9	
Musculoskeletal pain	Additional description: Musculoskeletal pain		
subjects affected / exposed	2 / 38 (5.26%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal stiffness	Additional description: Musculoskeletal stiffness		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Myalgia	Additional description: Myalgia		
subjects affected / exposed	8 / 38 (21.05%)	7 / 34 (20.59%)	
occurrences (all)	14	15	
Myopathy	Additional description: Myopathy		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Neck pain	Additional description: Neck pain		
subjects affected / exposed	1 / 38 (2.63%)	4 / 34 (11.76%)	
occurrences (all)	2	14	
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	9 / 38 (23.68%)	8 / 34 (23.53%)	
occurrences (all)	14	22	
Pain in jaw	Additional description: Pain in jaw		
subjects affected / exposed	0 / 38 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	5	
Sacral pain	Additional description: Sacral pain		
subjects affected / exposed	1 / 38 (2.63%)	2 / 34 (5.88%)	
occurrences (all)	2	3	
Spinal pain	Additional description: Spinal pain		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Trismus	Additional description: Trismus		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis	Additional description: Bronchitis		

subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Carbuncle	Additional description: Carbuncle		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Catheter site infection	Additional description: Catheter site infection		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Cellulitis	Additional description: Cellulitis		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	8	
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	7 / 38 (18.42%)	4 / 34 (11.76%)	
occurrences (all)	11	14	
Clostridium difficile infection	Additional description: Clostridium difficile infection		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Device related infection	Additional description: Device related infection		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Cystitis	Additional description: Cystitis		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
COVID-19	Additional description: COVID-19		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Folliculitis	Additional description: Folliculitis		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	3	
Fungal foot infection	Additional description: Fungal foot infection		
subjects affected / exposed	0 / 38 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	3	
Fungal infection	Additional description: Fungal infection		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Gastroenteritis	Additional description: Gastroenteritis		

subjects affected / exposed	1 / 38 (2.63%)	2 / 34 (5.88%)	
occurrences (all)	1	5	
Escherichia urinary tract infection	Additional description: Escherichia urinary tract infection		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Enterovirus infection	Additional description: Enterovirus infection		
subjects affected / exposed	1 / 38 (2.63%)	3 / 34 (8.82%)	
occurrences (all)	4	5	
Gastroenteritis viral	Additional description: Gastroenteritis viral		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	3	
Genital herpes	Additional description: Genital herpes		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	8	
Gingival abscess	Additional description: Gingival abscess		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Gingivitis	Additional description: Gingivitis		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Herpes ophthalmic	Additional description: Herpes ophthalmic		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Herpes virus infection	Additional description: Herpes virus infection		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	5	
Herpes zoster	Additional description: Herpes zoster		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Lower respiratory tract infection	Additional description: Lower respiratory tract infection		
subjects affected / exposed	4 / 38 (10.53%)	0 / 34 (0.00%)	
occurrences (all)	5	0	
Impetigo	Additional description: Impetigo		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Infected skin ulcer	Additional description: Infected skin ulcer		

subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Influenza	Additional description: Influenza		
subjects affected / exposed	2 / 38 (5.26%)	2 / 34 (5.88%)	
occurrences (all)	2	4	
Laryngitis	Additional description: Laryngitis		
subjects affected / exposed	1 / 38 (2.63%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Localised infection	Additional description: Localised infection		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Mastitis	Additional description: Mastitis		
subjects affected / exposed	0 / 38 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	3	
Medical device site infection	Additional description: Medical device site infection		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Nail infection	Additional description: Nail infection		
subjects affected / exposed	1 / 38 (2.63%)	3 / 34 (8.82%)	
occurrences (all)	1	3	
Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	7 / 38 (18.42%)	6 / 34 (17.65%)	
occurrences (all)	9	9	
Nipple infection	Additional description: Nipple infection		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis	Additional description: Oral candidiasis		
subjects affected / exposed	1 / 38 (2.63%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Oral herpes	Additional description: Oral herpes		
subjects affected / exposed	2 / 38 (5.26%)	7 / 34 (20.59%)	
occurrences (all)	2	16	
Post procedural infection	Additional description: Post procedural infection		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Otitis externa	Additional description: Otitis externa		

subjects affected / exposed	2 / 38 (5.26%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
Paronychia	Additional description: Paronychia		
subjects affected / exposed	0 / 38 (0.00%)	7 / 34 (20.59%)	
occurrences (all)	0	18	
Parotitis	Additional description: Parotitis		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Pharyngitis	Additional description: Pharyngitis		
subjects affected / exposed	2 / 38 (5.26%)	3 / 34 (8.82%)	
occurrences (all)	2	6	
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Postoperative abscess	Additional description: Postoperative abscess		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
Respiratory tract infection	Additional description: Respiratory tract infection		
subjects affected / exposed	3 / 38 (7.89%)	1 / 34 (2.94%)	
occurrences (all)	4	1	
Rhinitis	Additional description: Rhinitis		
subjects affected / exposed	2 / 38 (5.26%)	5 / 34 (14.71%)	
occurrences (all)	7	21	
Sinusitis	Additional description: Sinusitis		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	2	1	
Skin infection	Additional description: Skin infection		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	6 / 38 (15.79%)	2 / 34 (5.88%)	
occurrences (all)	6	3	
Superinfection	Additional description: Superinfection		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Tinea infection	Additional description: Tinea infection		

subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Tooth infection	Additional description: Tooth infection		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	3	1	
Tracheitis	Additional description: Tracheitis		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Tracheobronchitis bacterial	Additional description: Tracheobronchitis bacterial		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	6 / 38 (15.79%)	6 / 34 (17.65%)	
occurrences (all)	11	13	
Vestibular neuronitis	Additional description: Vestibular neuronitis		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Viral infection	Additional description: Viral infection		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	2	
Viral pharyngitis	Additional description: Viral pharyngitis		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Viral tonsillitis	Additional description: Viral tonsillitis		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection	Additional description: Viral upper respiratory tract infection		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	2	
Vulvovaginal candidiasis	Additional description: Vulvovaginal candidiasis		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Vulvovaginal mycotic infection	Additional description: Vulvovaginal mycotic infection		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	3	
Wound infection	Additional description: Wound infection		

subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Appetite disorder	Additional description: Appetite disorder		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Dehydration	Additional description: Dehydration		
subjects affected / exposed	1 / 38 (2.63%)	4 / 34 (11.76%)	
occurrences (all)	1	4	
Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed	5 / 38 (13.16%)	13 / 34 (38.24%)	
occurrences (all)	8	23	
Dyslipidaemia	Additional description: Dyslipidaemia		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Hypercholesterolaemia	Additional description: Hypercholesterolaemia		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Hyperglycaemia	Additional description: Hyperglycaemia		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Hyperuricaemia	Additional description: Hyperuricaemia		
subjects affected / exposed	0 / 38 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Hypocalcaemia	Additional description: Hypocalcaemia		
subjects affected / exposed	0 / 38 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	3	
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	2 / 38 (5.26%)	3 / 34 (8.82%)	
occurrences (all)	3	5	
Hypomagnesaemia	Additional description: Hypomagnesaemia		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	5	3	
Hyponatraemia	Additional description: Hyponatraemia		
subjects affected / exposed	1 / 38 (2.63%)	1 / 34 (2.94%)	
occurrences (all)	1	1	

Increased appetite	Additional description: Increased appetite		
subjects affected / exposed	1 / 38 (2.63%)	0 / 34 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 February 2012	Protocol V2_13Jan2012 - Updates included -Clarification to timing of assessments -Rewording of eligibility criteria -Revision to discontinuation of study drugs -Update to concomitant medications -Addition of definition of non-evaluable patients added to statistical consideration -Other administrative changes
24 November 2014	Protocol Version 3_17Apr2014- Updates included: -Update to study treatment schedule -Addition of exclusion criteria -Reduction in sample size -Update to translational research analysis -Update to assessment schedule -Update to contraception requirements -Other additional updates
22 June 2015	Protocol Version 4.0_18Mar2015- Updates included -Update to study design -Halt to recruitment as of 2nd Feb 2015 -Update to assessments -Update to timing of primary endpoint analysis -Other additional changes
13 June 2016	Protocol version 5_05May2016- updates included -Update to wording of duration of patient participation -Other administrative changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 February 2015	On the 2nd of February 2015, recruitment was stopped due to the slow rate of accrual. It was considered that the length of time required to complete accrual would result in a delay which would impact on the scientific value of the study. Patients receiving lapatinib could remain on lapatinib for as long as they were receiving benefit from the treatment and continue to be followed for AEs for as long as they were on lapatinib. At the time that recruitment was terminated, 75 patients from 23 international centres had been randomised to the study.	-

Notes:

Limitations and caveats

None reported