Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Study Comparing GW572016 and Letrozole versus Letrozole in Subjects with Estrogen/Progesterone Receptor- Positive Advanced or Metastatic Breast Cancer

Summary

EudraCT number	2004-003928-35
Trial protocol	IT
Global end of trial date	22 March 2018

Results information

Result version number	v1
This version publication date	04 April 2019
First version publication date	04 April 2019

Trial information

Trial identification

Sponsor protocol code	EGF30008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00073528
WHO universal trial number (UTN)	-
Other trial identifiers	Novartis: CLAP016A2308

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

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	22 March 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate and compare progression free survival (PFS) in subjects with Estrogen/Progesterone Receptor- Positive (ER+/PgR+), human epidermal growth factor receptor 2-positive (ErbB2+) advanced or metastatic breast cancer treated with GW572016 (lapatinib) and letrozole, versus letrozole and placebo.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 December 2013
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	Argentina: 13
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Brazil: 19
Country: Number of subjects enrolled	Bulgaria: 18
Country: Number of subjects enrolled	Canada: 29
Country: Number of subjects enrolled	Chile: 18
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Croatia: 5
Country: Number of subjects enrolled	Czech Republic: 20
Country: Number of subjects enrolled	Denmark: 20
Country: Number of subjects enrolled	France: 130
Country: Number of subjects enrolled	Germany: 104
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Ireland: 53
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Korea, Republic of: 19
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Netherlands: 33

Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Pakistan: 30
Country: Number of subjects enrolled	Peru: 47
Country: Number of subjects enrolled	Poland: 43
Country: Number of subjects enrolled	Russian Federation: 89
Country: Number of subjects enrolled	South Africa: 16
Country: Number of subjects enrolled	Spain: 77
Country: Number of subjects enrolled	Tunisia: 16
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	United Kingdom: 84
Country: Number of subjects enrolled	United States: 325
Worldwide total number of subjects	1286
EEA total number of subjects	634

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)	709
From 65 to 84 years	559
85 years and over	18

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was conducted at 212 centers in 29 countries (Argentina, Australia, Brazil, Bulgaria, Canada, Chile, Colombia, Croatia, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Italy, Republic of Korea, Mexico, Netherlands, New Zealand, Pakistan, Peru, Poland, Russian Federation, South-Africa, Spain, Tunisia, Turkey, UK, USA).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Letrozole 2.5 mg

Arm description:

Participants received 6 tablets of placebo, identical in appearance to lapatinib tablets, orally daily (approximately at the same time each day), either 1 hour (or more) before breakfast or 1 hour (or more) after breakfast. Participants also received 1 tablet of letrozole 2.5 milligrams (mg) orally daily, preferably with the daily dose of lapatinib.

Arm type	Placebo
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2.5 mg once daily orally

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Lapatinib matching placebo 1500 mg once daily orally

Arm title	Lapatinib 1500 mg + Letrozole 2.5 mg

Arm description:

Participants received 6 tablets of Lapatinib orally daily (250 mg lapatinib/tablet for a total of 1500 mg of lapatinib/day; approximately at the same time each day), either 1 hour (or more) before breakfast or 1 hour (or more) after breakfast. Participants also received 1 tablet of letrozole 2.5 mg orally daily, preferably with the daily dose of lapatinib.

Arm type	Experimental
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details: 2.5 mg once daily orally	
Investigational medicinal product name	Lapatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1500 mg once daily orally

Number of subjects in period 1	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg
Started	644	642
Completed	14	14
Not completed	630	628
Adverse event, serious fatal	488	473
Consent withdrawn by subject	50	45
Study terminated by Sponsor	10	29
Not Specified	18	19
Unknown	9	12
Lost to follow-up	52	45
Protocol deviation	3	5

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + Letrozole 2.5 mg
Reporting group description:	
Participants received 6 tablets of placebo, identical in appearance to lapatinib tablets, orally daily (approximately at the same time each day), either 1 hour (or more) before breakfast or 1 hour (or more) after breakfast. Participants also received 1 tablet of letrozole 2.5 milligrams (mg) orally daily, preferably with the daily dose of lapatinib.	
Reporting group title	Lapatinib 1500 mg + Letrozole 2.5 mg
Reporting group description:	
Participants received 6 tablets of Lapatinib orally daily (250 mg lapatinib/tablet for a total of 1500 mg of lapatinib/day; approximately at the same time each day), either 1 hour (or more) before breakfast or 1 hour (or more) after breakfast. Participants also received 1 tablet of letrozole 2.5 mg orally daily, preferably with the daily dose of lapatinib.	

Reporting group values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg	Total
Number of subjects	644	642	1286
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)	352	357	709
From 65-84 years	280	279	559
85 years and over	12	6	18
Sex: Female, Male Units: Subjects			
Female	644	642	1286
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
White	557	529	1086
Black	10	17	27
Asian	30	30	60
American Hispanic	44	57	101
Other	3	9	12
AgeContinuous Units: Years			
arithmetic mean	63.3	62.8	
standard deviation	± 9.95	± 9.70	-

End points

End points reporting groups

Reporting group title	Placebo + Letrozole 2.5 mg

Reporting group description:

Participants received 6 tablets of placebo, identical in appearance to lapatinib tablets, orally daily (approximately at the same time each day), either 1 hour (or more) before breakfast or 1 hour (or more) after breakfast. Participants also received 1 tablet of letrozole 2.5 milligrams (mg) orally daily, preferably with the daily dose of lapatinib.

Reporting group title	Lapatinib 1500 mg + Letrozole 2.5 mg

Reporting group description:

Participants received 6 tablets of Lapatinib orally daily (250 mg lapatinib/tablet for a total of 1500 mg of lapatinib/day; approximately at the same time each day), either 1 hour (or more) before breakfast or 1 hour (or more) after breakfast. Participants also received 1 tablet of letrozole 2.5 mg orally daily, preferably with the daily dose of lapatinib.

Primary: Number of participants with progression free survival (PFS) in the human epidermal growth factor receptor 2 (HER2)-Positive advanced or metastatic breast cancer as assessed by the Investigator

End point title	Number of participants with progression free survival (PFS) in the human epidermal growth factor receptor 2 (HER2)-Positive advanced or metastatic breast cancer as assessed by the Investigator

End point description:

PFS is defined as the time from randomization until the earliest date of disease progression (PD) or death due to any cause, if sooner. The date of documented PD is defined as the date of radiological PD as assessed by the investigator based on imaging data and also by the clinical assessment of symptomatic progression. Per Response Evaluation Criteria in Solid Tumors (RECIST 1.0), PD is defined as a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as a reference the smallest sum LD recorded since the treatment started, or the appearance of 1 or more new lesions.

End point type	Primary

End point timeframe:

From the date of randomization until the date of the first documented progression or date of death from any cause, whichever came first, assessed for up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	111		
Units: Participants	89	88		

Statistical analyses

Statistical analysis title	Number of participants with PFS in HER2+
Comparison groups	Placebo + Letrozole 2.5 mg v Lapatinib 1500 mg + Letrozole 2.5 mg

Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.019 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.96

Notes:

[1] - p-value is from stratified log-rank test, stratifying for site of disease and time since prior adjuvant endocrine therapy at screening

Primary: Progression free survival (PFS) of participants in the HER2-Positive Population as assessed by the Investigator

End point title	Progression free survival (PFS) of participants in the HER2-Positive Population as assessed by the Investigator

End point description:

PFS is defined as the time from randomization until the earliest date of disease progression or death due to any cause, if sooner. The date of documented disease progression is defined as the date of radiological disease progression as assessed by the investigator based on imaging data and also by the clinical assessment of symptomatic progression. Per RECIST 1.0, disease progression is defined as a 20% increase in the sum of the LD of target lesions, taking as a reference the smallest sum LD recorded since the treatment started, or the appearance of 1 or more new lesions.

End point type	Primary

End point timeframe:

From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	88		
Units: Weeks				
median (confidence interval 95%)	13.0 (12.0 to 23.7)	35.4 (24.1 to 39.4)		

Statistical analyses

Statistical analysis title	PFS of participants in the HER2-Positive
Comparison groups	Placebo + Letrozole 2.5 mg v Lapatinib 1500 mg + Letrozole 2.5 mg

Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.019 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.96

Notes:

[2] - p-value is from stratified log-rank test, stratifying for site of disease and time since prior adjuvant endocrine therapy at screening

Secondary: Number of participants with PFS in the Intent-To-Treat (ITT) Population as assessed by the Investigator

End point title	Number of participants with PFS in the Intent-To-Treat (ITT) Population as assessed by the Investigator

End point description:

PFS is defined as the time from randomization until the earliest date of disease progression or death due to any cause, if sooner. The date of documented disease progression is defined as the date of radiological disease progression as assessed by the investigator based on imaging data and also by the clinical assessment of symptomatic progression. Per RECIST 1.0, disease progression is defined as a 20% increase in the sum of the LD of target lesions, taking as a reference the smallest sum LD recorded since the treatment started, or the appearance of 1 or more new lesions.

End point type	Secondary

End point timeframe:

From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	644	642		
Units: Participants	476	413		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS in participants in the ITT Population as assessed by the Investigator

End point title	PFS in participants in the ITT Population as assessed by the Investigator

End point description:

PFS is defined as the time from randomization until the earliest date of disease progression or death due to any cause, if sooner. The date of documented disease progression is defined as the date of radiological disease progression as assessed by the investigator based on imaging data and also by the clinical assessment of symptomatic progression. Per RECIST 1.0, disease progression is defined as a

20% increase in the sum of the LD of target lesions, taking as a reference the smallest sum LD recorded since the treatment started, or the appearance of 1 or more new lesions.

End point type	Secondary

End point timeframe:

From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	413		
Units: Weeks				
median (confidence interval 95%)	47.0 (36.9 to 50.9)	51.7 (47.6 to 59.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival in the HER2-Positive Population

End point title	Overall survival in the HER2-Positive Population

End point description:

Overall survival was defined as the time from randomization until death due to any cause.

End point type	Secondary

End point timeframe:

From date of randomization until date of death due to any cause, assessed up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	111		
Units: Weeks				
median (confidence interval 95%)	140.3 (92.1 to 159.4)	144.7 (95.6 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall tumor response (OR) for participants with measurable and non-measurable disease, including bone scans, in the HER2-Positive Population as assessed by the Investigator

End point title	Overall tumor response (OR) for participants with measurable and non-measurable disease, including bone scans, in the HER2-Positive Population as assessed by the Investigator

End point description:

OR is defined as the percentage of participants achieving either a confirmed complete response (CR) or partial response (PR). Response was assessed via Response Evaluation criteria in Solid Tumors (RECIST). The percentage of participants with response was calculated by using the formula: 100 * (number of participants with CR + number of participants with PR)/total number of participants. CR: disappearance of all target lesions. PR: at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as a reference the baseline sum LD.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	111		
Units: Percent response rate				
number (confidence interval 95%)	14.8 (8.7 to 22.9)	27.9 (19.8 to 37.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with overall tumor response (OR) by stratification factors with measurable disease, including bone scans, in the HER2-Positive Population as assessed by the Investigator

End point title	Number of participants with overall tumor response (OR) by stratification factors with measurable disease, including bone scans, in the HER2-Positive Population as assessed by the Investigator

End point description:

Participants were stratified based on site of disease at screening (SDS) (soft tissue or visceral or bone-only disease) and prior adjuvant endocrine therapy (PAET) (discontinuation interval [DI] =>6 months or DI <6 months). OR is defined as the number of participants achieving either a confirmed CR or PR. Response was assessed via RECIST. CR: disappearance of all target lesions. PR: at least a 30% decrease in the sum of the LD of target lesions, taking as a reference the baseline sum LD. DI is defined as the time period from stopping the PEAT to the randomization date.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	93		
Units: Participants				
SDS, Soft tissue or visceral	14	31		
SDS, Bone-only disease	0	0		
PAET, DI =>6 months	12	24		
PAET, DI <6 months	2	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit (CB) in the HER2-Positive Population as assessed by the Investigator

End point title	Clinical benefit (CB) in the HER2-Positive Population as assessed by the Investigator

End point description:

CB is defined as the percentage of participants with evidence of confirmed CR, PR, or stable disease (SD) for at least 6 months. CR: disappearance of all target lesions. PR: at least a 30% decrease in the sum of the LD of target lesions, taking as a reference the baseline sum LD. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the baseline measurement.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	111		
Units: Months				
number (confidence interval 95%)	28.7 (20.4 to 38.2)	47.7 (38.2 to 57.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated best response from the participants with measurable and non-measurable disease, including bone scans, in the HER2-Positive Population as assessed by the Investigator.

End point title	Number of participants with the indicated best response from the participants with measurable and non-measurable disease, including bone scans, in the HER2-Positive Population as

	assessed by the Investigator.

End point description:

CR: disappearance of all target lesions. PR: at least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum LD since the baseline measurement. The best overall response is defined as the best response recorded from the start of treatment until disease progression/recurrence. PD: presence of target lesions, non-target lesions, and/or new lesions.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	111		
Units: Participants				
CR	4	5		
PR	12	26		
SD	35	44		
PD	49	30		
Unknown	8	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated best response from the participants with measurable and non-measurable disease, including bone scans, in the ITT Population as assessed by the Investigator.

End point title	Number of participants with the indicated best response from the participants with measurable and non-measurable disease, including bone scans, in the ITT Population as assessed by the Investigator.

End point description:

CR: disappearance of all target lesions. PR: at least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum LD since the baseline measurement. The best overall response is defined as the best response recorded from the start of treatment until disease progression/recurrence. PD: presence of target lesions, non-target lesions, and/or new lesions.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	644	642		
Units: Participants				
CR	26	28		
PR	153	168		
SD	243	280		
PD	174	113		
Unknown	48	53		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated time to response for CR or PR in the HER2-Positive Population as assessed by the Investigator

End point title	Number of participants with the indicated time to response for CR or PR in the HER2-Positive Population as assessed by the Investigator

End point description:

Time to response is defined as the time from randomization until the first documented evidence of CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sume of the LD of target lesions, taking as reference the baseline sum LD) (whichever status was recorded first). The assessments of CR or PR required confirmation using bone scans.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	31		
Units: Participants				
Week 12	11	23		
Week 16	1	3		
Week 24 or longer	4	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response for the participants with CR or PR in the HER2-Positive Population as assessed by the Investigator

End point title	Duration of response for the participants with CR or PR in the

	HER2-Positive Population as assessed by the Investigator

End point description:

Duration of response is defined as the time from the first documented evidence of CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of the LD of target lesions, taking as a reference the baseline sum LD) until the first documented sign of disease progression or death due to any cause. The assessments of CR or PR required confirmation using bone scans.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	31		
Units: weeks				
median (inter-quartile range (Q1-Q3))	84.4 (29.1 to 999)	47.4 (25.1 to 108.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with evidence of brain metastases in the HER2-Positive Population

End point title	Number of participants with evidence of brain metastases in the HER2-Positive Population

End point description:

The confirmation criteria for the evidence of brain metastases was the incidence of lesions occurring within any part of the central nervous system (CNS) as evidenced by radiological scans. Metastases are defined as the spread of cancer from one part of the body to another.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	111		
Units: participants	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression (TTP) for the HER2-Positive Population as assessed by the Investigator

End point title	Time to progression (TTP) for the HER2-Positive Population as assessed by the Investigator

End point description:

TTP is defined as the interval between the date of randomization and the earliest date of disease progression or death due to breast cancer. Disease progression was based on the assessments by the Investigator.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	87		
Units: weeks				
median (confidence interval 95%)	13.0 (12.0 to 23.7)	35.4 (24.1 to 39.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival in the ITT Population

End point title	Overall survival in the ITT Population

End point description:

Overall survival was defined as the time from randomization until death due to any cause.

End point type	Secondary

End point timeframe:

From date of randomization until date of death due to any cause, assessed up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	240		
Units: weeks				
median (confidence interval 95%)	176.3 (156.1 to 189.7)	170.9 (157.7 to 196.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall tumor response (OR) for participants with measurable and non-measurable disease, including bone scans, in the ITT Population as assessed by the Investigator

End point title	Overall tumor response (OR) for participants with measurable and non-measurable disease, including bone scans, in the ITT Population as assessed by the Investigator

End point description:

OR is defined as the percentage of participants achieving either a confirmed complete response (CR) or partial response (PR). Response was assessed via Response Evaluation criteria in Solid Tumors (RECIST). The percentage of participants with response was calculated by using the formula: 100 * (number of participants with CR + number of participants with PR)/total number of participants. CR: disappearance of all target lesions. PR: at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as a reference the baseline sum LD.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	644	642		
Units: percentage of participants				
number (not applicable)	27.8	30.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with overall tumor response (OR) by stratification factors with measurable disease, including bone scans, in the ITT Population as assessed by the Investigator

End point title	Number of participants with overall tumor response (OR) by stratification factors with measurable disease, including bone scans, in the ITT Population as assessed by the Investigator

End point description:

Participants were stratified based on site of disease at screening (SDS) (soft tissue or visceral or bone-only disease) and prior adjuvant endocrine therapy (PAET) (discontinuation interval [DI] =>6 months or DI <6 months). OR is defined as the number of participants achieving either a confirmed CR or PR. Response was assessed via RECIST. CR: disappearance of all target lesions. PR: at least a 30% decrease in the sum of the LD of target lesions, taking as a reference the baseline sum LD. DI is defined

as the time period from stopping the PEAT and the randomization date.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	486	480		
Units: participants				
SDS, Soft tissue or visceral (n=486,480)	170	190		
PAET, DI =>6 months (n=376,381)	151	168		
PAET, DI <6 months (n=110,99)	19	22		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit (CB) in the ITT Population as assessed by the Investigator

End point title	Clinical benefit (CB) in the ITT Population as assessed by the Investigator

End point description:

CB is defined as the percentage of participants with evidence of confirmed CR, PR, or stable disease (SD) for at least 6 months. CR: disappearance of all target lesions. PR: at least a 30% decrease in the sum of the LD of target lesions, taking as a reference the baseline sum LD. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the baseline measurement.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	644	642		
Units: percentage of participants				
number (not applicable)	50.6	55.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated time to response for CR or PR in the ITT Population as assessed by the Investigator

End point title	Number of participants with the indicated time to response for CR or PR in the ITT Population as assessed by the Investigator

End point description:

Time to response is defined as the time from randomization until the first documented evidence of CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sume of the LD of target lesions, taking as reference the baseline sum LD) (whichever status was recorded first). The assessments of CR or PR required confirmation using bone scans.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	196		
Units: participants				
Week 12	76	94		
Week 16	21	18		
Week 24	28	28		
Week 28	17	14		
Week 36 or longer	37	42		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response for the participants with CR or PR in the ITT Population as assessed by the Investigator

End point title	Duration of response for the participants with CR or PR in the ITT Population as assessed by the Investigator

End point description:

Duration of response is defined as the time from the first documented evidence of CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of the LD of target lesions, taking as a reference the baseline sum LD) until the first documented sign of disease progression or death due to any cause. The assessments of CR or PR required confirmation using bone scans.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	196		
Units: weeks				
median (inter-quartile range (Q1-Q3))	72.6 (39.1 to 145.7)	60.1 (36.0 to 138.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with evidence of brain metastases from the ITT Population

End point title	Number of participants with evidence of brain metastases from the ITT Population

End point description:

The confirmation criteria for the evidence of brain metastases was the incidence of lesions occurring within any part of the central nervous system (CNS) as evidenced by radiological scans. Metastases are defined as the spread of cancer from one part of the body to another.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	644	642		
Units: participants	4	6		

Statistical analyses

No statistical analyses for this end point

Secondary: TTP for participants from the ITT Population as assessed by the Investigator

End point title	TTP for participants from the ITT Population as assessed by the Investigator

End point description:

TTP is defined as the interval between the date of randomization and the earliest date of disease progression or death due to breast cancer. Disease progression was based on the assessments by the Investigator.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	469	409		
Units: weeks				
median (confidence interval 95%)	47.0 (36.9 to 50.9)	51.7 (47.6 to 59.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants completing the functional assessment of cancer therapy-breast (FACT-B) questionnaire at the scheduled visits

End point title	Number of participants completing the functional assessment of cancer therapy-breast (FACT-B) questionnaire at the scheduled visits

End point description:

Quality of Life (QOL) was assessed using the FACT-B questionnaire, which was a 37-item (27 general and 10 breast cancer-specific questions) self-reporting instrument consisting of 5 dimensions: physical-, social/family-, emotional-, functional-well being, and a breast cancer subscale. Higher scores on the FACT-B scales (each ranging from 0 [not at all] to 4 [very much]) indicate a higher QOL. The score is transformed for FACT-B and results in a total score ranging from 0 to 144. Complete: completing at least 1 question from FACT-B.

End point type	Secondary

End point timeframe:

Day 1 (baseline) visit; Week 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, and 192 visits; conclusion/withdrawal visit

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	644	642		
Units: Participants				
Day 1, baseline	605	605		
Week 12	460	476		
Week 24	350	382		
Week 36	291	294		
Week 48	254	243		
Week 60	199	183		
Week 72	181	153		
Week 84	144	119		
Week 96	117	98		
Week 108	80	62		
Week 120	59	56		

Week 132	43	43		
Week 144	33	33		
Week 156	22	21		
Week 168	15	11		
Week 180	11	5		
Week 192	6	1		
Conclusion/withdrawal	327	359		

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted mean change from baseline for the FACT-B total score using observed data

End point title	Adjusted mean change from baseline for the FACT-B total score using observed data

End point description:

Quality of Life (QOL) was assessed using the FACT-B questionnaire, which is a 37-item (27 general and 10 breast cancer-specific questions) self-reporting instrument consisting of 5 dimensions: physical-, social/family-, emotional-, functional-well being, and a breast cancer subscale. Higher scores on the FACT-B scales indicate a higher QOL; each ranging from 0 (not at all) to 4 (very much). The score is transformed for FACT-B and results in a total score ranging from 0 to 144. The FACT-B is designed to measure multidimensional QOL in participants with breast cancer.

End point type	Secondary

End point timeframe:

Week 12, 24, 36, and 48 visits; conclusion/withdrawal visit

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	78		
Units: Adjusted mean change				
number (not applicable)				
Week 12 (n=57,78)	1.5	3.3		
Week 24 (n=36,53)	3.8	1.9		
Week 36 (n=23,31)	3.3	1.4		
Week 48 (n=22,23)	2.9	0.3		
Conclusion/WD (n=61,69)	-9.4	-9.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted mean change from baseline for the Functional Assessment of Cancer Therapy-General (FACT-G) score using observed data

End point title	Adjusted mean change from baseline for the Functional Assessment of Cancer Therapy-General (FACT-G) score using observed data

End point description:

FACT-G is a subscale of the FACT-B QOL questionnaire and consists of 27 questions grouped into 4 domains that measure a participant's physical, functional, social and family, and emotional well-being. FACT-G is assessed on a five-point Likert-type scale, with scores ranging from 0 to 4 (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much). The total score is calculated as the sum of the item scores on the subscale; the total ranges from 0 to 108, with higher score indicating a better quality of life.

End point type	Secondary

End point timeframe:

Week 12, 24, 36, and 48 visits; conclusion/withdrawal visit

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	79		
Units: Adjusted mean change				
number (not applicable)				
Week 12 (n=60,79)	1.6	1.5		
Week 24 (n=37,54)	2.2	0.6		
Week 36 (n=24,33)	2.6	0.9		
Week 48 (n=23,25)	2.0	-0.9		
Conclusion/WD (n=63,71)	-7.8	-8.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted mean change from baseline for the trial outcome index (TOI) score using observed data

End point title	Adjusted mean change from baseline for the trial outcome index (TOI) score using observed data

End point description:

The TOI score is the sum of the physical well-being, functional well-being, and breast cancer unweighted subscale scores. The total TOI score ranges from 0 to 92, with higher scores representing a better quality of life.

End point type	Secondary

End point timeframe:

Week 12, 24, 36, and 48 visits; conclusion/withdrawal visit

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	77		
Units: Adjusted mean change				
number (not applicable)				
Week 12 (n=59,77)	-0.3	2.7		
Week 24 (n=37,52)	3.9	2.0		
Week 36 (n=24,28)	3.3	0.8		
Week 48 (n=22,23)	2.2	-0.7		
Conclusion/WD (n=62,67)	-6.2	-6.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants classified as QOL responders based on the FACT-B, FACT-G, and TOI total scores

End point title	Number of participants classified as QOL responders based on the FACT-B, FACT-G, and TOI total scores

End point description:

A minimally important difference (MID) is the smallest difference in a score for a measure of QOL that corresponds to a difference in function or clinical course. Responders are defined as participants with an MID => 8 for the FACT-B score, and an MID =>6 for the FACT-G and TOI scores.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	99		
Units: Participants				
FACT-B total, =>8 (MID upper bound) (n=85,98)	29	33		
FACT-G, =>6 (MID upper bound) (n=87,99)	29	38		
TOI, =>6 (MID upper bound) (n=87, 97)	29	33		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinical benefit categorized by HER2

fluorescence in situ hybridization (FISH) status

End point title	Number of participants with clinical benefit categorized by HER2 fluorescence in situ hybridization (FISH) status

End point description:

Clinical benefit: participants with CR, PR, or SD for =>6-month period. FISH testing measures the amount of the HER2 gene in each cell. This gene is responsible for the overproduction of the HER2 protein. FISH-positive: excessive amounts of the gene are present; FISH-negative: normal levels of the gene are present.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	644	642		
Units: Participants				
FISH status, Positive (n=96,97)	28	49		
FISH status, Negative (n=412,422)	237	245		
FISH status, missing (n=136,123)	61	64		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinical benefit categorized by HER2 ImmunoHistoChemistry (IHC) intensity

End point title	Number of participants with clinical benefit categorized by HER2 ImmunoHistoChemistry (IHC) intensity

End point description:

IHC is a commonly used test to assess the amount of the HER2 receptor protein on the surface of the cancer cells. The IHC test results in a score of 0 to 3+, which indicates the amount of HER2 receptor protein on the cells in a sample of breast cancer tissue. Tissue scores of 0 to 1+ indicate HER2 negativity; scores of 2+ and 3+ indicate HER2 positivity. Clinical benefit is defined as participants with CR, PR, or SD for =>6-month period.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	644	642		
Units: Participants				
IHC Intensity 0, (n=153,177)	74	106		

IHC Intensity 1 (n =189,190)	108	106		
IHC Intensity 2 (n=165,146)	94	85		
IHC Intensity 3 (n=64,61)	16	26		
IHC Intensity Missing, (n=73,68)	34	35		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with response in participants with baseline serum HER2 extracellular domain (ECD) baseline values greater than 15 nanograms per milliliter (ng/mL) and 15 ng/mL or lower

End point title	Number of participants with response in participants with baseline serum HER2 extracellular domain (ECD) baseline values greater than 15 nanograms per milliliter (ng/mL) and 15 ng/mL or lower

End point description:

The HER2 ECD is a glycoprotein that can be shed from the cell surface into the blood of normal individuals and can be elevated in different pathologic conditions. The serum HER2 ECD level generally reflects the tissue HER2 status. The HER2 ECD is quantified in serum with an enzyme-linked immunosorbent assay (ELISA). Non-Evaluable (NE): any participant who could not be classified as CR, PR, SD, or PD.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	111		
Units: Participants				
>15 ng/mL, CR/PR (n=53,34)	3	9		
>15 ng/mL, SD (n=53,34)	11	13		
>15 ng/mL, PD/NE (n=53,34)	39	12		
=<15 ng/mL, CR/PR (n=51,70)	12	17		
=<15 ng/mL, SD (n=51,70)	23	30		
=<15 ng/mL, PD/NE (n=51,70)	16	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of HER2-Negative participants at baseline with and without seroconversion to a status of HER2 Positive

End point title	Number of HER2-Negative participants at baseline with and without seroconversion to a status of HER2 Positive

End point description:

Participants who had a HER2-negative tumor status based on baseline tissue with baseline serum HER2 ECD values =<15 ng/mL but later had at least two consecutive serum HER2 ECD values >15 ng/mL experienced seroconversion.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	474	478		
Units: Participants				
Seroconversion, No	323	140		
Seroconversion, Yes	52	219		
Missing	99	119		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to seroconversion for participants who were HER2 Negative at baseline but became HER2 Positive

End point title	Time to seroconversion for participants who were HER2 Negative at baseline but became HER2 Positive

End point description:

Time to seroconversion was defined as the time from the date of randomization until the first instance of serum HER2 (>15 ng/mL) on two consecutive occasions.

End point type	Secondary

End point timeframe:

Up to 46 months

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	219		
Units: Weeks				
median (confidence interval 95%)	999 (999 to 999)	36.1 (24.0 to 48.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated expression of tumor by epidermal growth factor receptor (ErbB1/HER1/EGFR) at baseline

End point title	Number of participants with the indicated expression of tumor by epidermal growth factor receptor (ErbB1/HER1/EGFR) at baseline

End point description:

EGFR is a cell surface receptor tyrosine kinase expressed in certain types of tumors. Depending upon the staining intensity, EGFR was graded as follows: 0=absence of membrane staining above background in all tumor cells; EGFR-positive=staining is defined as any IHC staining of tumor cell membranes above background level, whether it is complete or incomplete circumferential staining (1+, 2+, 3+).

End point type	Secondary

End point timeframe:

Baseline

End point values	Placebo + Letrozole 2.5 mg	Lapatinib 1500 mg + Letrozole 2.5 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	644	642		
Units: Participants				
EGFR, 0	513	522		
EGFR, 1+	43	45		
EGFR, 2+	17	12		
EGFR, 3+	3	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious and Other (Not Including Serious) Adverse Events were collected for the maximum duration of participants' treatment exposure plus any follow up period, approximately 11 years.

Adverse event reporting additional description:

SAEs and AEs were collected for the Safety Population, which included all randomized participants who had received at least 1 dose of study treatment, based on the actual treatment received if this differed from that to which the participant was randomized.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Placebo + Letrozole 2.5mg

Reporting group description:

Placebo + Letrozole 2.5mg

Reporting group title	Lapatinib 1500mg + Letrozole 2.5mg

Reporting group description:

Lapatinib 1500mg + Letrozole 2.5mg

Serious adverse events	Placebo + Letrozole 2.5mg	Lapatinib 1500mg + Letrozole 2.5mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	103 / 624 (16.51%)	150 / 654 (22.94%)	
number of deaths (all causes)	23	18	
number of deaths resulting from adverse events	1	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer metastatic			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lymphoma			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Ovarian cyst			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 624 (0.00%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transitional cell carcinoma			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 624 (0.32%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 624 (0.16%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			

subjects affected / exposed	0 / 624 (0.00%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 624 (0.00%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids thrombosed			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lymphoedema			
subjects affected / exposed	2 / 624 (0.32%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			

subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 624 (0.00%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	3 / 624 (0.48%)	4 / 654 (0.61%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 624 (0.16%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	2 / 624 (0.32%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			

subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 624 (0.64%)	4 / 654 (0.61%)	
occurrences causally related to treatment / all	1 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Crohn's disease			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatomyositis			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast abscess			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian enlargement			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cellulitis			
subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			

subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 624 (0.00%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic pulmonary fibrosis			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 624 (0.16%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			

subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 624 (0.48%)	3 / 654 (0.46%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachypnoea			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, visual			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device breakage			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			

subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood urea increased			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	8 / 624 (1.28%)	17 / 654 (2.60%)	
occurrences causally related to treatment / all	7 / 8	16 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural			

complications				
Catheter site infection				
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Accidental poisoning				
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Head injury				
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hepatotoxicity				
subjects affected / exposed	2 / 624 (0.32%)	1 / 654 (0.15%)		
occurrences causally related to treatment / all	1 / 2	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Overdose				
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pelvic fracture				
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Post procedural complication				
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Post procedural infection				
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Road traffic accident				

subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Synovial rupture			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine perforation			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
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	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			

subjects affected / exposed	2 / 624 (0.32%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 624 (0.32%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 624 (0.32%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	5 / 624 (0.80%)	6 / 654 (0.92%)	
occurrences causally related to treatment / all	2 / 5	0 / 6	
deaths causally related to treatment / all	1 / 1	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 624 (0.16%)	7 / 654 (1.07%)	
occurrences causally related to treatment / all	0 / 1	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			

subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	3 / 624 (0.48%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar haemorrhage			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cerebrovascular disorder			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			

subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia Alzheimer's type			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			

subjects affected / exposed	2 / 624 (0.32%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 624 (0.32%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 624 (0.16%)	3 / 654 (0.46%)	
occurrences causally related to treatment / all	0 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 624 (0.32%)	5 / 654 (0.76%)	
occurrences causally related to treatment / all	2 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 624 (0.00%)	3 / 654 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			

subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 624 (0.00%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness bilateral			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye injury			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (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 pain			
subjects affected / exposed	3 / 624 (0.48%)	3 / 654 (0.46%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal strangulated hernia			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ascites			
subjects affected / exposed	0 / 624 (0.00%)	3 / 654 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 624 (0.32%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 624 (0.32%)	15 / 654 (2.29%)	
occurrences causally related to treatment / all	1 / 2	11 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	4 / 624 (0.64%)	5 / 654 (0.76%)	
occurrences causally related to treatment / all	1 / 4	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral infection			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis haemorrhagic			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal prolapse			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	7 / 624 (1.12%)	9 / 654 (1.38%)	
occurrences causally related to treatment / all	3 / 7	4 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
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 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder pain			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 624 (0.00%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Skin and subcutaneous tissue disorders			

Cellulitis			
subjects affected / exposed	0 / 624 (0.00%)	5 / 654 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Excessive granulation tissue			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site cellulitis			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			

subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash papular			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatorenal failure			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercreatininaemia			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvi-ureteric obstruction			

subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 624 (0.16%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal impairment			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Carcinoid tumour			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	2 / 624 (0.32%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Ankle fracture			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthritis			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 624 (0.00%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	7 / 624 (1.12%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 7	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 624 (0.16%)	3 / 654 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			

subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	2 / 624 (0.32%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercreatinaemia			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 624 (0.00%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			

subjects affected / exposed	0 / 624 (0.00%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spinal compression fracture			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (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			
Diverticulitis			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	2 / 624 (0.32%)	4 / 654 (0.61%)	
occurrences causally related to treatment / all	1 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 624 (0.32%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 624 (0.00%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 624 (0.00%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	4 / 624 (0.64%)	3 / 654 (0.46%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	2 / 624 (0.32%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	0 / 624 (0.00%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Tooth infection			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (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			
subjects affected / exposed	1 / 624 (0.16%)	6 / 654 (0.92%)	
occurrences causally related to treatment / all	1 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval abscess			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	2 / 624 (0.32%)	7 / 654 (1.07%)	
occurrences causally related to treatment / all	1 / 2	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 624 (0.16%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	0 / 624 (0.00%)	2 / 654 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 624 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 624 (0.32%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 624 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Letrozole 2.5mg	Lapatinib 1500mg + Letrozole 2.5mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	481 / 624 (77.08%)	589 / 654 (90.06%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	28 / 624 (4.49%)	58 / 654 (8.87%)	
occurrences (all)	33	81	
Aspartate aminotransferase increased			
subjects affected / exposed	24 / 624 (3.85%)	54 / 654 (8.26%)	
occurrences (all)	28	75	
Blood alkaline phosphatase increased			
subjects affected / exposed	15 / 624 (2.40%)	34 / 654 (5.20%)	
occurrences (all)	18	49	
Weight decreased			
subjects affected / exposed	13 / 624 (2.08%)	35 / 654 (5.35%)	
occurrences (all)	14	40	
Vascular disorders			
Hot flush			
subjects affected / exposed	80 / 624 (12.82%)	65 / 654 (9.94%)	
occurrences (all)	94	73	
Cardiac disorders			
Dyspnoea			
subjects affected / exposed	68 / 624 (10.90%)	58 / 654 (8.87%)	
occurrences (all)	83	71	
Nervous system disorders			

Dizziness			
subjects affected / exposed	46 / 624 (7.37%)	44 / 654 (6.73%)	
occurrences (all)	56	53	
Insomnia			
subjects affected / exposed	50 / 624 (8.01%)	41 / 654 (6.27%)	
occurrences (all)	60	52	
Headache			
subjects affected / exposed	79 / 624 (12.66%)	84 / 654 (12.84%)	
occurrences (all)	114	126	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	28 / 624 (4.49%)	52 / 654 (7.95%)	
occurrences (all)	35	74	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	62 / 624 (9.94%)	76 / 654 (11.62%)	
occurrences (all)	88	112	
Decreased appetite			
subjects affected / exposed	55 / 624 (8.81%)	80 / 654 (12.23%)	
occurrences (all)	65	95	
Fatigue			
subjects affected / exposed	98 / 624 (15.71%)	124 / 654 (18.96%)	
occurrences (all)	121	169	
Mucosal inflammation			
subjects affected / exposed	11 / 624 (1.76%)	37 / 654 (5.66%)	
occurrences (all)	20	45	
Pyrexia			
subjects affected / exposed	32 / 624 (5.13%)	42 / 654 (6.42%)	
occurrences (all)	42	54	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	28 / 624 (4.49%)	48 / 654 (7.34%)	
occurrences (all)	36	52	
Abdominal pain upper			
subjects affected / exposed	16 / 624 (2.56%)	36 / 654 (5.50%)	
occurrences (all)	17	41	

Constipation			
subjects affected / exposed	64 / 624 (10.26%)	45 / 654 (6.88%)	
occurrences (all)	81	49	
Diarrhoea			
subjects affected / exposed	109 / 624 (17.47%)	393 / 654 (60.09%)	
occurrences (all)	148	784	
Dyspepsia			
subjects affected / exposed	28 / 624 (4.49%)	56 / 654 (8.56%)	
occurrences (all)	46	71	
Nausea			
subjects affected / exposed	123 / 624 (19.71%)	190 / 654 (29.05%)	
occurrences (all)	162	274	
Stomatitis			
subjects affected / exposed	8 / 624 (1.28%)	34 / 654 (5.20%)	
occurrences (all)	8	41	
Vomiting			
subjects affected / exposed	69 / 624 (11.06%)	101 / 654 (15.44%)	
occurrences (all)	89	138	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	89 / 624 (14.26%)	71 / 654 (10.86%)	
occurrences (all)	116	92	
Epistaxis			
subjects affected / exposed	9 / 624 (1.44%)	61 / 654 (9.33%)	
occurrences (all)	10	88	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	4 / 624 (0.64%)	39 / 654 (5.96%)	
occurrences (all)	4	53	
Alopecia			
subjects affected / exposed	39 / 624 (6.25%)	74 / 654 (11.31%)	
occurrences (all)	40	77	
Dry skin			
subjects affected / exposed	25 / 624 (4.01%)	82 / 654 (12.54%)	
occurrences (all)	26	94	
Erythema			

subjects affected / exposed	9 / 624 (1.44%)	33 / 654 (5.05%)	
occurrences (all)	13	39	
Paronychia			
subjects affected / exposed	1 / 624 (0.16%)	39 / 654 (5.96%)	
occurrences (all)	1	64	
Nail disorder			
subjects affected / exposed	6 / 624 (0.96%)	63 / 654 (9.63%)	
occurrences (all)	6	79	
Pruritus			
subjects affected / exposed	50 / 624 (8.01%)	76 / 654 (11.62%)	
occurrences (all)	58	112	
Rash			
subjects affected / exposed	56 / 624 (8.97%)	223 / 654 (34.10%)	
occurrences (all)	68	338	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	91 / 624 (14.58%)	99 / 654 (15.14%)	
occurrences (all)	110	118	
Arthralgia			
subjects affected / exposed	135 / 624 (21.63%)	112 / 654 (17.13%)	
occurrences (all)	184	176	
Muscle spasms			
subjects affected / exposed	22 / 624 (3.53%)	33 / 654 (5.05%)	
occurrences (all)	23	42	
Bone pain			
subjects affected / exposed	48 / 624 (7.69%)	26 / 654 (3.98%)	
occurrences (all)	59	29	
Musculoskeletal chest pain			
subjects affected / exposed	34 / 624 (5.45%)	30 / 654 (4.59%)	
occurrences (all)	35	34	
Musculoskeletal pain			
subjects affected / exposed	49 / 624 (7.85%)	52 / 654 (7.95%)	
occurrences (all)	63	60	
Myalgia			

subjects affected / exposed	41 / 624 (6.57%)	26 / 654 (3.98%)	
occurrences (all)	53	31	
Pain in extremity			
subjects affected / exposed	65 / 624 (10.42%)	67 / 654 (10.24%)	
occurrences (all)	85	87	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	44 / 624 (7.05%)	50 / 654 (7.65%)	
occurrences (all)	54	61	
Upper respiratory tract infection			
subjects affected / exposed	32 / 624 (5.13%)	31 / 654 (4.74%)	
occurrences (all)	38	43	
Urinary tract infection			
subjects affected / exposed	44 / 624 (7.05%)	35 / 654 (5.35%)	
occurrences (all)	58	45	
Metabolism and nutrition disorders			
Oedema peripheral			
subjects affected / exposed	46 / 624 (7.37%)	28 / 654 (4.28%)	
occurrences (all)	51	40	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2004	Amendment 1 was issued to provide further clarification to study design and update relevant sections to reflect current clinical practice.
11 January 2005	Amendment 2 was a country specific amendment for Italy. This amendment was for the pharmacogenetic research to be conducted on blood samples collected from consenting subjects as part of study EGF30008 and complied with the "Italian Proposed Guideline for the Evaluation of Pharmacogenetic Research."
27 October 2005	Amendment 3 was issued to: revise the eligibility criteria to include only those subjects with Stage IV disease, remove Interim Analysis and add an extension to the study to include additional subjects to ensure adequate power to see a difference in both the original population as well as ErbB2-positive population.
31 October 2007	Amendment 4 was issued to: revise the statistical analysis plan for the primary endpoint, provide further clarification on the data collection and to decrease the frequency of visits for subjects that had reached 108 Weeks on study treatment.
27 May 2008	Amendment 5 was issued to: update the safety monitoring for hepatic events and refine ITT and modified populations.
11 June 2013	Amendment 6 was a country specific amendment for France. Protocol updated to include the Diarrhea Management Guidelines and Dermatological Assessment Guidelines.
13 April 2015	Amendment 7 was issued to allow subjects currently on study treatment to continue access to treatment with alteration to study/clinical assessments. Subject assessments and disease management were performed as indicated by local medical standard of care and local approved labeling for lapatinib and letrozole. All subjects in overall survival follow up were permitted to withdraw from the study. Subjects might be withdrawn from EGF30008 study treatment, and continue therapy via alternative means such as commercial availability and local approved labelling for this indication.
03 October 2016	Amendment 8 was issue to: delete or replace references to GSK or its staff with that of Novartis/Novartis and its authorized agents. Administrative changes were made to align with Novartis processes and procedures. References to the source of investigational product supply were changed from non-commercial to commercial supply.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: