Clinical trial results:
A Randomized, Open-Label, Phase III Study of Taxane Based Chemotherapy with Lapatinib or Trastuzumab as First-Line Therapy for Women with HER2/neu Positive Metastatic Breast Cancer

Summary

EudraCT number	2007-004568-27
Trial protocol	DE NL ES IT BE GB FR
Global end of trial date	27 July 2022

Results information

Result version number	v1
This version publication date	07 June 2023
First version publication date	07 June 2023

Trial information

Trial identification

Sponsor protocol code	108919

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00667251
WHO universal trial number (UTN)	-
Other trial identifiers	Novartis: CLAP016A2303, NCI US - Physician Data Query: CAN-NCIC-MA31, PDQ: CDR0000594764

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, 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	27 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the progression-free survival of taxane based chemotherapy plus lapatinib for 24 weeks followed by single agent lapatinib therapy to taxane based chemotherapy plus trastuzumab for 24 weeks followed by single agent trastuzumab therapy, in women with human epidermal growth factor receptor 2 (HER2)/neu positive breast cancer (by local or central laboratory testing) which is metastatic, and with no prior chemotherapy and/or HER2/neu targeted therapy in the metastatic setting.

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	07 October 2008
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: 12
Country: Number of subjects enrolled	Australia: 30
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Canada: 75
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 66
Country: Number of subjects enrolled	India: 8
Country: Number of subjects enrolled	Israel: 31
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	Japan: 42
Country: Number of subjects enrolled	Korea, Republic of: 36
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Russian Federation: 101
Country: Number of subjects enrolled	Spain: 38
Country: Number of subjects enrolled	Ukraine: 8

Country: Number of subjects enrolled	United Kingdom: 65
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	Taiwan: 22
Country: Number of subjects enrolled	Thailand: 21
Worldwide total number of subjects	652
EEA total number of subjects	169

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)	523
From 65 to 84 years	128
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was conducted at 167 centers in 21 countries worldwide.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lapatinib (LTax/L)

Arm description:

Lapatinib 1250 mg once daily. Taxane based chemotherapy: Paclitaxel 80 mg/m2 IV once weekly (Days 1, 8, and 15 of a 4-week cycle) OR Docetaxel 75 mg/m2 IV once every 3 weeks (Day 1 of a 3-week cycle) plus G-CSF: according to institutional standards. Followed by Lapatinib 1500 mg once daily until disease progression.

Arm type	Active comparator
Investigational medicinal product name	lapatinib ditosylate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1250 mg once daily (while given with taxane).
1500mg once daily (when given alone after taxane completion).

Investigational medicinal product name	trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

IV q weekly (loading dose 4mg/kg; subsequent doses 2mg/kg) or IV q 3 weekly (loading dose 8mg/kg, subsequent doses 6mg/kg).

Investigational medicinal product name	docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

75mg/m2 IV q 3 weekly, day 1 of a 3 week cycle for 8 cycles plus G-CSF (when given together with lapatinib).

Investigational medicinal product name	paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

80mg/m2 IV q weekly days 1, 8 and 15 of a 4-week cycle for 6 cycles.

Arm title	Trastuzumab (TTax/T)

Arm description:

Trastuzumab IV once weekly (loading dose 4 mg/kg, subsequent doses 2 mg/kg) and Paclitaxel 80 mg/m2 IV once weekly (Days 1, 8, and 15 of a 4-week cycle) OR Trastuzumab IV once every 3 weeks (loading dose 8 mg/kg, subsequent doses 6 mg/kg) and Docetaxel 75 mg/m2 IV once every 3 weeks (Day 1 of a 3-week cycle). Followed by Trastuzumab 6 mg/kg IV once every 3 weeks until disease progression.

Arm type	Active comparator
Investigational medicinal product name	paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

80mg/m2 IV q weekly days 1, 8 and 15 of a 4-week cycle for 6 cycles.

Investigational medicinal product name	docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

75mg/m2 IV q 3 weekly, day 1 of a 3 week cycle for 8 cycles plus G-CSF (when given together with lapatinib).

Number of subjects in period 1	Lapatinib (LTax/L)	Trastuzumab (TTax/T)
Started	326	326
Randomized not Treated	4	1
Central HER2 positive	270	267
Safety Population	322	325
Completed	0	0
Not completed	326	326
Adverse event, serious fatal	6	11
Disease progression	232	203
Toxicity	44	23
Refused further treatment (not due to toxicity)	8	7
Intercurrent illness	5	6
Primary reason for withdrawal = missing	1	1
Subject Reached Protocol-Defined Stopping Criteria	18	70
Symptomatic progression	8	4

Randomized not Treated	4	1

Baseline characteristics

Reporting groups	
Reporting group title	Lapatinib (LTax/L)
Reporting group description:	
Lapatinib 1250 mg once daily. Taxane based chemotherapy: Paclitaxel 80 mg/m2 IV once weekly (Days 1, 8, and 15 of a 4-week cycle) OR Docetaxel 75 mg/m2 IV once every 3 weeks (Day 1 of a 3-week cycle) plus G-CSF: according to institutional standards. Followed by Lapatinib 1500 mg once daily until disease progression.	
Reporting group title	Trastuzumab (TTax/T)
Reporting group description:	
Trastuzumab IV once weekly (loading dose 4 mg/kg, subsequent doses 2 mg/kg) and Paclitaxel 80 mg/m2 IV once weekly (Days 1, 8, and 15 of a 4-week cycle) OR Trastuzumab IV once every 3 weeks (loading dose 8 mg/kg, subsequent doses 6 mg/kg) and Docetaxel 75 mg/m2 IV once every 3 weeks (Day 1 of a 3-week cycle). Followed by Trastuzumab 6 mg/kg IV once every 3 weeks until disease progression.	

Reporting group values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)	Total
Number of subjects	326	326	652
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	260	263	523
>=65 years	66	63	129
Age Continuous Units: years			
median	55.4	54.4	
full range (min-max)	26.6 to 87.1	29.3 to 84.3	-
Sex: Female, Male Units: Participants			
Female	326	326	652
Male	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	34	34	68
Not Hispanic or Latino	288	283	571
Unknown or Not Reported	4	9	13
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	4	4	8
Asian	67	74	141
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	5	8	13
White	246	234	480
More than one race	0	0	0
Unknown or Not Reported	3	6	9
Region of Enrollment Units: Subjects			
United States	10	13	23
Taiwan	11	11	22

Thailand	9	12	21
Spain	19	19	38
Ukraine	4	4	8
Russian Federation	55	46	101
Israel	16	15	31
United Kingdom	33	32	65
Italy	5	8	13
India	4	4	8
France	5	5	10
Mexico	3	6	9
Canada	39	36	75
Argentina	8	4	12
Poland	7	12	19
Belgium	3	6	9
Australia	17	13	30
Netherlands	7	7	14
Germany	32	34	66
Japan	22	20	42
Korea, Republic of	17	19	36
Number of Participants with the Indicated Eastern Cooperative Oncology Group Performance Status			
Eastern Cooperative Oncology Group (ECOG) Performance Status classifies participants according to their functional impairment, and scores indicate: 0, fully active; 1, ambulatory, restricted strenuous activity; 2, ambulatory, no work activity; 3, partially confined to bed; 4, totally confined in bed; 5, death.			
Units: Subjects			
0, fully active	196	204	400
1, ambulatory, restricted strenuous activity	118	112	230
2, ambulatory, no work activity	12	10	22
Disease Status Units: Subjects			
Primary diagnosis	138	138	276
Progression after therapy	187	187	374
Missing	1	1	2
Central review human epidermal growth factor receptor 2 (HER2) status Units: Subjects			
Positive IHC or FISH	270	267	537
Equivocal IHC and FISH	9	5	14
Negative IHC and FISH	36	46	82
Unknown	11	8	19
Central review estrogen receptor (ER) status Units: Subjects			
Positive (>0)	213	208	421
Negative	96	107	203
Missing	17	11	28
Central review progesterone receptor (PgR) status Units: Subjects			
Positive (>0)	116	104	220
Negative	190	204	394

Missing	20	18	38
Central Review of Cytokeratin 5 (CK5) Status Units: Subjects			
Positive (>0)	58	41	99
Negative	210	218	428
Missing	58	67	125
Central Review of epidermal growth factor receptor (EGFR) Status Units: Subjects			
Positive (>0)	71	77	148
Negative	194	181	375
Missing	61	68	129
Prior (neo)adjuvant HER2 targeted therapy Units: Subjects			
Prior (neo)adjuvant HER2 targeted therapy = Yes	59	59	118
Prior (neo)adjuvant HER2 targeted therapy = No	267	267	534
Prior (neo)adjuvant taxane chemotherapy Units: Subjects			
Prior (neo)adjuvant taxane chemotherapy = Yes	65	69	134
Prior (neo)adjuvant taxane chemotherapy = No	261	257	518
Planned taxane treatment Units: Subjects			
Weekly paclitaxel	146	146	292
3-weekly docetaxel	180	180	360
Liver metastasis Units: Subjects			
Liver metastasis = Yes	149	150	299
Liver metastasis = No	177	176	353
Prior neoadjuvant therapy/Other chemotherapy Units: Subjects			
Prior neoadjuvant therapy/Other chemotherapy = Yes	146	161	307
Prior neoadjuvant therapy/Other chemotherapy = No	180	165	345
Prior neoadjuvant therapy/Anthracyclines Units: Subjects			
Prior neoadjuvant therapy/Anthracyclines = Yes	128	140	268
Prior neoadjuvant therapy/Anthracyclines = No	198	186	384
Prior neoadjuvant therapy/Other therapy Units: Subjects			
Prior neoadjuvant therapy/Other therapy = Yes	5	2	7
Prior neoadjuvant therapy/Other therapy = No	321	323	644

Prior neoadjuvant therapy/Other therapy = Missing	0	1	1
Prior neoadjuvant/Metastatic radiotherapy Units: Subjects			
Prior neoadjuvant/Metastatic radiotherapy = Yes	138	149	287
Prior neoadjuvant/Metastatic radiotherapy = No	187	176	363
Prior neoadjuvant/Metastatic radiotherapy= Missing	1	1	2
Prior neoadjuvant/Metastatic endocrine therapy Units: Subjects			
Prior nad/Metastatic endocrine therapy = Yes	122	127	249
Prior nad/Metastatic endocrine therapy = No	204	198	402
Prior nad/Metastatic endocrine therapy = Missing	0	1	1
Central Review of Antigen KI-67 (ki67) Units: % cells positive			
geometric mean	33.33	31.43	
full range (min-max)	0 to 100	0 to 90	-

End points

End points reporting groups

Reporting group title	Lapatinib (LTax/L)

Reporting group description:

Lapatinib 1250 mg once daily. Taxane based chemotherapy: Paclitaxel 80 mg/m2 IV once weekly (Days 1, 8, and 15 of a 4-week cycle) OR Docetaxel 75 mg/m2 IV once every 3 weeks (Day 1 of a 3-week cycle) plus G-CSF: according to institutional standards. Followed by Lapatinib 1500 mg once daily until disease progression.

Reporting group title	Trastuzumab (TTax/T)

Reporting group description:

Trastuzumab IV once weekly (loading dose 4 mg/kg, subsequent doses 2 mg/kg) and Paclitaxel 80 mg/m2 IV once weekly (Days 1, 8, and 15 of a 4-week cycle) OR Trastuzumab IV once every 3 weeks (loading dose 8 mg/kg, subsequent doses 6 mg/kg) and Docetaxel 75 mg/m2 IV once every 3 weeks (Day 1 of a 3-week cycle). Followed by Trastuzumab 6 mg/kg IV once every 3 weeks until disease progression.

Subject analysis set title	Crossed over to Trastuzumab (TTax/T) after IA results
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Crossed over to Trastuzumab (TTax/T) after IA results

Subject analysis set title	Overall TTax/T
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Overall TTax/T

Subject analysis set title	Crossed over to Trastuzumab (TTax/T) after IA results
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Crossed over to Trastuzumab (TTax/T) after IA results

Subject analysis set title	Overall TTax/T
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Overall TTax/T

Subject analysis set title	Crossed over to Trastuzumab (TTax/T) after IA results
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Crossed over to Trastuzumab (TTax/T) after Interim Analysis (IA) results

Primary: Progression Free Survival (PFS) at the time of Primary Results

End point title	Progression Free Survival (PFS) at the time of Primary Results

End point description:

Progression free survival (PFS) was defined as the interval of time between the date of randomization and the earliest date of RECIST 1.0 assessment of disease progression (with radiological evidence) or death from any cause, or to the date of censor. Disease progression was based on assessments by the Investigator.

End point type	Primary

End point timeframe:

From date of randomization until date of progression or date of death from any cause, whichever comes first, assessed up to approximately 39 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326	326		
Units: Months				
median (full range (min-max))				
Intent-to-Treat (ITT) population (n=326, 326)	8.97 (0.30 to 32.69)	11.30 (0.30 to 38.54)		
centrally-confirmed HER2+ population (n=270, 267)	9.13 (0.30 to 32.69)	13.63 (0.30 to 38.54)		

Statistical analyses

Statistical analysis title	PFS at Primary Analysis (Central HER2+ population)
Comparison groups	Lapatinib (LTax/L) v Trastuzumab (TTax/T)
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0002
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.484
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.204
upper limit	1.829

Statistical analysis title	PFS at Primary Analysis (IIT population)
Comparison groups	Lapatinib (LTax/L) v Trastuzumab (TTax/T)
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.367
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.133
upper limit	1.648

Secondary: Progression Free Survival (PFS) at the time of Final Analysis

End point title	Progression Free Survival (PFS) at the time of Final Analysis

End point description:

Progression free survival (PFS) was defined as the interval of time between the date of randomization and the earliest date of RECIST 1.0 assessment of disease progression (with radiological evidence) or death from any cause, or to the date of censor. Subjects who crossover the treatment to Trastuzumab (TTax/T) after interim analysis, were censored at the last PFS assessment before crossover. Disease progression was based on assessments by the Investigator.

End point type	Secondary

End point timeframe:

From date of randomization until date of progression or date of death from any cause, whichever comes first, assessed up to approximately 45 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326	326		
Units: Months				
median (full range (min-max))				
Intent-to-Treat (ITT) population (n=326, 326)	9.1 (8.5 to 10.8)	11.5 (10.9 to 13.8)		
centrally-confirmed HER2+ population (n=270, 267)	9.4 (8.5 to 11.0)	13.8 (11.2 to 14.2)		

Statistical analyses

Statistical analysis title	PFS at Final Analysis (Central HER2+ population)
Comparison groups	Lapatinib (LTax/L) v Trastuzumab (TTax/T)
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.4968
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2251
upper limit	1.8288

Statistical analysis title	PFS at Final Analysis (IIT population)
Comparison groups	Lapatinib (LTax/L) v Trastuzumab (TTax/T)
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.3722

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1466
upper limit	1.6422

Secondary: Overall Survival (OS) (Central HER2+ population)

End point title	Overall Survival (OS) (Central HER2+ population)

End point description:

Overall Survival (OS) was defined as the time interval between the date of randomization and the date of death from any cause. Subjects who were still alive at the time of the final analysis or became lost to follow-up, were censored at their last contact date. Subjects who crossover the treatment to Trastuzumab (TTax/T) after interim analysis, were censored at last known alive date prior to crossover.

End point type	Secondary

End point timeframe:

From date of randomization until date of death from any cause, assessed up approximately 165 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	267		
Units: Months				
median (confidence interval 95%)	30.0 (24.2 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	Overall Survival (OS) (Central HER2+ population)
Comparison groups	Lapatinib (LTax/L) v Trastuzumab (TTax/T)
Number of subjects included in analysis	537
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.5818
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1181
upper limit	2.2379

Secondary: Overall Survival (OS) (IIT population)

End point title	Overall Survival (OS) (IIT population)

End point description:

Overall Survival (OS) was defined as the time interval between the date of randomization and the date of death from any cause. Subjects who were still alive at the time of the final analysis or became lost to follow-up, were censored at their last contact date. Subjects who crossover the treatment to Trastuzumab (TTax/T) after interim analysis, were censored at last known alive date prior to crossover.

End point type	Secondary

End point timeframe:

From date of randomization until date of death from any cause, assessed up approximately 165 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326	326		
Units: Months				
median (confidence interval 95%)	30.0 (24.2 to 999)	38.3 (31.0 to 999)		

Statistical analyses

Statistical analysis title	Overall Survival (OS) (IIT population)
Comparison groups	Lapatinib (LTax/L) v Trastuzumab (TTax/T)
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.3786
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.0246
upper limit	1.8549

Secondary: Incidence of Central Nervous System (CNS) metastasis at first progression (IIT population)

End point title	Incidence of Central Nervous System (CNS) metastasis at first progression (IIT population)

End point description:

The incidence of Central Nervous System (CNS) metastasis at first progression was defined as the ratio of the number of subjects with CNS metastasis at progression over the total number of subjects.

End point type	Secondary

End point timeframe:

From date of randomization to CNS metastases at time of first progression, assessed up approximately 45 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)	Crossed over to Trastuzumab (TTax/T) after IA results	Overall TTax/T
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	326	326	5	331
Units: Participants				
CNS metastasis at first progression = Yes	47	55	1	56
CNS metastasis at first progression = No	155	119	4	123
CNS metastasis at first progression = Unknown	66	62	0	62

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Central Nervous System (CNS) metastasis at first progression (Central HER2+ population)

End point title	Incidence of Central Nervous System (CNS) metastasis at first progression (Central HER2+ population)

End point description:

The incidence of Central Nervous System (CNS) metastasis at first progression was defined as the ratio of the number of subjects with CNS metastasis at progression over the total number of subjects.

End point type	Secondary

End point timeframe:

From date of randomization to CNS metastases at time of first progression, assessed up approximately 45 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)	Crossed over to Trastuzumab (TTax/T) after IA results	Overall TTax/T
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	270	267	4	271
Units: Participants				
CNS metastasis at first progression = Yes	43	50	1	51
CNS metastasis at first progression = No	128	92	3	95
CNS metastasis at first progression = Unknown	53	44	0	44

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Central Nervous System (CNS) metastasis (IIT population)	
End point title	Time to Central Nervous System (CNS) metastasis (IIT population)

End point description:

Time to Central Nervous System (CNS) metastasis was defined as the time from randomization until disease progression where CNS metastasis was documented at the time of first breast cancer progression. Subjects who crossed over the treatment to Trastuzumab (TTax/T) after interim analysis, were censored at RECIST assessment prior to crossover.

End point type	Secondary

End point timeframe:

From date of randomization to CNS metastases at time of first progression, assessed up approximately 45 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326	326		
Units: Months				
median (full range (min-max))	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	Time to CNS metastasis (IIT population)
Comparison groups	Lapatinib (LTax/L) v Trastuzumab (TTax/T)
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.0916
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7271
upper limit	1.6389

Secondary: Time to Central Nervous System (CNS) metastasis (Central HER2+ population)	
End point title	Time to Central Nervous System (CNS) metastasis (Central HER2+ population)

End point description:

Time to Central Nervous System (CNS) metastasis was defined as the time from randomization until disease progression where CNS metastasis was documented at the time of first breast cancer progression. Subjects who crossed over the treatment to Trastuzumab (TTax/T) after interim analysis, were censored at RECIST assessment prior to crossover.

End point type	Secondary

End point timeframe:

From date of randomization to CNS metastases at time of first progression, assessed up approximately 45 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	267		
Units: Months				
median (full range (min-max))	999 (25.4 to 999)	999 (27.7 to 999)		

Statistical analyses

Statistical analysis title	Time to CNS metastasis (Central HER2+ population)
Comparison groups	Lapatinib (LTax/L) v Trastuzumab (TTax/T)
Number of subjects included in analysis	537
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.0951
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7144
upper limit	1.6787

Secondary: Overall Response Rate (ORR) (IIT population)

End point title	Overall Response Rate (ORR) (IIT population)

End point description:

Overall Response Rate (ORR) was defined as the proportion of participants with Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR). The ORR was calculated from the Investigator’s assessment of response based on RECIST 1.1. Subjects with an unknown or missing response were treated as non-responders; i.e. they were included in the denominator when calculating the percentages.

End point type	Secondary

End point timeframe:

From date of randomization until date of progression or date of death from any cause, whichever comes first, assessed up approximately 45 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326	326		
Units: Percentage of Participants				
number (confidence interval 95%)	64.2 (58.0 to 70.1)	63.3 (57.3 to 69.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) (Central HER2+ population)

End point title	Overall Response Rate (ORR) (Central HER2+ population)

End point description:

Overall Response Rate (ORR) was defined as the proportion of participants with Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR). The ORR was calculated from the Investigator's assessment of response based on RECIST 1.1. Subjects with an unknown or missing response were treated as non-responders; i.e. they were included in the denominator when calculating the percentages.

End point type	Secondary

End point timeframe:

From date of randomization until date of progression or date of death from any cause, whichever comes first, assessed up approximately 45 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	267		
Units: Percentage of Participants				
number (confidence interval 95%)	66.7 (60.0 to 72.9)	67.4 (60.8 to 73.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Response (CBR) (Central HER2+ population)

End point title	Clinical Benefit Response (CBR) (Central HER2+ population)

End point description:

Clinical Benefit Response (CBR) was defined as the percentage with evidence of Complete Response (CR), Partial Response (PR) (participants with at least 1 measurable lesion at baseline), or maintaining Stable Disease (SD) for at least 24 weeks (all subjects, with or without measurable disease at baseline) while on study, according to the investigator assessment of response per RECIST 1.1 criteria. Participants were considered to be positive (Yes) for CBR if they experienced any CR or PR for any duration prior to progressive disease. Participants were considered to be negative (No) for CBR if they had progressive disease prior to Week 24 without prior confirmed CR or PR.

End point type	Secondary

End point timeframe:

From date of randomization until date of progression or date of death from any cause, whichever comes first, assessed up approximately 45 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	267		
Units: Percentage of Participants				
number (confidence interval 95%)	61.1 (55.0 to 67.0)	65.2 (59.1 to 70.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Response (CBR) (IIT population)

End point title	Clinical Benefit Response (CBR) (IIT population)

End point description:

Clinical Benefit Response (CBR) was defined as the percentage with evidence of Complete Response (CR), Partial Response (PR) (participants with at least 1 measurable lesion at baseline), or maintaining Stable Disease (SD) for at least 24 weeks (all subjects, with or without measurable disease at baseline) while on study, according to the investigator assessment of response per RECIST 1.1 criteria. Participants were considered to be positive (Yes) for CBR if they experienced any CR or PR for any duration prior to progressive disease. Participants were considered to be negative (No) for CBR if they had progressive disease prior to Week 24 without prior confirmed CR or PR.

End point type	Secondary

End point timeframe:

From date of randomization until date of progression or date of death from any cause, whichever comes first, assessed up approximately 45 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326	326		
Units: Percentage of Participants				
number (confidence interval 95%)	60.4 (54.9 to 65.8)	62.0 (56.5 to 67.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR) (Central HER2+ population)

End point title	Time to Response (TTR) (Central HER2+ population)

End point description:

Time to Response was defined as the time from randomization to the earliest date of Complete Response (CR) or Partial Response (PR). The event of first response was the first CR or PR; censoring was at PD date for those who progressed or at the last RECIST date if no progression occurred.

End point type	Secondary

End point timeframe:

From date of randomization until date of progression or date of death from any cause, whichever comes first, assessed up approximately 45 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	267		
Units: Months				
median (confidence interval 95%)	2.9 (2.8 to 3.0)	2.9 (2.8 to 3.0)		

Statistical analyses

Statistical analysis title	Time to Response (TTR) (Central HER2+ population)
Comparison groups	Lapatinib (LTax/L) v Trastuzumab (TTax/T)
Number of subjects included in analysis	537
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9573
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7544
upper limit	1.2148

Secondary: Time to Response (TTR) (IIT population)

End point title	Time to Response (TTR) (IIT population)

End point description:

Time to Response was defined as the time from randomization to the earliest date of Complete Response (CR) or Partial Response (PR). The event of first response was the first CR or PR; censoring was at PD date for those who progressed or at the last RECIST date if no progression occurred.

End point type	Secondary

End point timeframe:

From date of randomization until date of first response, assessed up approximately 45 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326	326		
Units: Months				
median (confidence interval 95%)	2.9 (2.8 to 3.0)	2.9 (2.8 to 3.0)		

Statistical analyses

Statistical analysis title	Time to Response (TTR) (IIT population)
Comparison groups	Lapatinib (LTax/L) v Trastuzumab (TTax/T)
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.0091
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.809
upper limit	1.2586

Secondary: Duration of Response (DoR) (IIT population)

End point title	Duration of Response (DoR) (IIT population)

End point description:

Duration of Response (DOR) was defined as the duration between the date of first documented Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) and the date of first documented sign of Progressive Disease or Death, with censoring at the last RECIST date if no progression occurred.

End point type	Secondary

End point timeframe:

From first documented evidence of CR or PR (the response prior to confirmation) until time of documented disease progression or death due to any cause, whichever comes first, assessed up approximately 165 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	171		
Units: Months				
median (confidence interval 95%)	8.3 (7.6 to 9.4)	11.1 (9.6 to 12.5)		

Statistical analyses

Statistical analysis title	DoR (IIT population)
Comparison groups	Lapatinib (LTax/L) v Trastuzumab (TTax/T)
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.4866
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1479
upper limit	1.9251

Secondary: Duration of Response (DoR) (Central HER2+ population)

End point title	Duration of Response (DoR) (Central HER2+ population)

End point description:

Duration of Response (DOR) was defined as the duration between the date of first documented Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) and the date of first documented sign of Progressive Disease or Death, with censoring at the last RECIST date if no progression occurred.

End point type	Secondary

End point timeframe:

From first documented evidence of CR or PR (the response prior to confirmation) until time of documented disease progression or death due to any cause, whichever comes first, assessed up approximately 165 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	151		
Units: Months				
median (confidence interval 95%)	8.3 (7.2 to 9.9)	11.1 (10.6 to 13.8)		

Statistical analyses

Statistical analysis title	DoR (Central HER2+ population)
Comparison groups	Lapatinib (LTax/L) v Trastuzumab (TTax/T)

Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.5594
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1767
upper limit	2.0666

Secondary: Number of Participants achieving European Quality of Life (EuroQol) – 5 Domain (EQ-5D) score (Canadian and Australian centers only)

End point title	Number of Participants achieving European Quality of Life (EuroQol) – 5 Domain (EQ-5D) score (Canadian and Australian centers only)

End point description:

The European Quality of Life (EuroQol) – 5 Domain (EQ-5D) self-administered questionnaire consists of two pages comprising the EQ-5D descriptive system and the EQ Visual Analogue Scale (VAS). The EQ-5D descriptive system comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and each dimension comprises three levels (no problems, some problems, extreme problems, unable to perform the activity).

End point type	Secondary

End point timeframe:

Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 120, Week 144

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	49		
Units: Participants				
Mobility @ Week 12|No Problems	29	27		
Self-Care @ Week 12|No Problems	41	32		
Usual Activities @ Week 12|No Problems	16	22		
Pain/Discomfort @ Week 12|No Problems	16	16		
Anxiety/Depression @Week 12|No Problems	24	22		
Mobility @ Week 24|No Problems	26	20		
Self-Care @ Week 24|No Problems	38	31		
Usual Activities @ Week 24|No Problems	18	18		
Pain/Discomfort @ Week 24|No Problems	10	12		
Anxiety/Depression @ Week 24|No Problems	23	18		
Mobility @ Week 36|No Problems	21	26		
Self-Care @ Week 36|No Problems	28	30		
Usual Activities @ Week 36|No Problems	17	16		
Pain/Discomfort @ Week 36|No Problems	9	13		

Anxiety/Depression @Week 36|No Problems	18	18		
Mobility @ Week 48|No Problems	14	18		
Self-Care @ Week 48|No Problems	18	26		
Usual Activities @ Week 48|No Problems	15	16		
Pain/Discomfort @ Week 48|No Problems	6	12		
Anxiety/Depression @ Week 48|No Problems	10	20		
Mobility @ Week 60|No Problems	8	16		
Self-Care @ Week 60|No Problems	8	20		
Usual Activities @ Week 60|No Problems	7	12		
Pain/Discomfort @ Week 60|No Problems	5	11		
Anxiety/Depression @ Week 60|No Problems	5	12		
Mobility @ Week 72|No Problems	7	13		
Self-Care @ Week 72|No Problems	8	15		
Usual Activities @ Week 72|No Problems	7	8		
Pain/Discomfort @ Week 72|No Problems	6	9		
Anxiety/Depression @ Week 72|No Problems	4	8		
Mobility @ Week 84|No Problems	5	6		
Self-Care @ Week 84|No Problems	6	8		
Usual Activities @ Week 84|No Problems	5	5		
Pain/Discomfort @ Week 84|No Problems	4	2		
Anxiety/Depression @ Week 84|No Problems	3	4		
Mobility @ Week 96|No Problems	5	3		
Self-Care @ Week 96|No Problems	5	5		
Usual Activities @ Week 96|No Problems	3	3		
Pain/Discomfort @ Week 96|No Problems	2	1		
Anxiety/Depression @ Week 96|No Problems	1	3		
Mobility @ Week 120|No Problems	4	2		
Self-Care @ Week 120|No Problems	4	3		
Usual Activities @ Week 120|No Problems	4	2		
Pain/Discomfort @ Week 120|No Problems	3	2		
Anxiety/Depression @ Week 120|No Problems	1	3		
Mobility @ Week 144|No Problems	1	1		
Self-Care @ Week 144|No Problems	1	1		
Usual Activities @ Week 144|No Problems	1	1		
Pain/Discomfort @ Week 144|No Problems	1	1		
Anxiety/Depression @ Week 144|No Problems	0	1		
Mobility @ Week 12|Some problems	16	9		
Self-Care @ Week 12|Some problems	4	2		
Usual Activities @ Week 12|Some problems	25	13		

Pain/Discomfort @ Week 12|Some problems	28	20		
Anxiety/Depression @ Week 12|Some problems	20	14		
Mobility @ Week 24|Some problems	14	14		
Self-Care @ Week 24|Some problems	3	3		
Usual Activities @ Week 24|Some problems	22	14		
Pain/Discomfort @ Week 24|Some problems	30	21		
Anxiety/Depression @ Week 24|Some problems	18	15		
Mobility @ Week 36|Some problems	10	5		
Self-Care @ Week 36|Some problems	2	1		
Usual Activities @ Week 36|Some problems	13	14		
Pain/Discomfort @ Week 36|Some problems	18	16		
Anxiety/Depression @ Week 36|Some problems	12	13		
Mobility @ Week 48|Some problems	4	9		
Self-Care @ Week 48|Some problems	0	1		
Usual Activities @ Week 48|Some problems	3	11		
Pain/Discomfort @ Week 48|Some problems	11	14		
Anxiety/Depression @ Week 48|Some problems	7	6		
Mobility @ Week 60|Some problems	0	5		
Self-Care @ Week 60|Some problems	0	1		
Usual Activities @ Week 60|Some problems	1	7		
Pain/Discomfort @ Week 60|Some problems	3	8		
Anxiety/Depression @ Week 60|Some problems	3	9		
Mobility @ Week 72|Some problems	1	2		
Self-Care @ Week 72|Some problems	0	0		
Usual Activities @ Week 72|Some problems	1	7		
Pain/Discomfort @ Week 72|Some problems	2	6		
Anxiety/Depression @ Week 72|Some problems	4	6		
Mobility @ Week 84|Some problems	1	2		
Self-Care @ Week 84|Some problems	0	0		
Usual Activities @ Week 84|Some problems	1	2		
Pain/Discomfort @ Week 84|Some problems	2	6		
Anxiety/Depression @ Week 84|Some problems	3	4		
Mobility @ Week 96|Some problems	0	2		
Self-Care @ Week 96|Some problems	0	0		
Usual Activities @ Week 96|Some problems	2	2		
Pain/Discomfort @ Week 96|Some problems	2	4		

Anxiety/Depression @ Week 96|Some problems	4	2		
Mobility @ Week 120|Some problems	0	1		
Self-Care @ Week 120|Some problems	0	0		
Usual Activities @ Week 120|Some problems	0	1		
Pain/Discomfort @ Week 120|Some problems	1	1		
Anxiety/Depression @ Week 120|Some problems	3	0		
Mobility @ Week 144|Some problems	0	0		
Self-Care @ Week 144|Some problems	0	0		
Usual Activities @ Week 144|Some problems	0	0		
Pain/Discomfort @ Week 144|Some problems	0	0		
Anxiety/Depression @ Week 144|Some problems	1	0		
Mobility @ Week 12|Unable to perform the activity	1	0		
Self-Care @ Wk 12|Unable to perform the activity	1	1		
Usual Activities@Wk 12|Unable to perform activity	5	1		
Pain/Discomfort @ Wk 12|Unable to perform activity	1	0		
Anxiety/Depr. @ Wk 12|Unable to perform activity	2	0		
Mobility @ Week 24|Unable to perform the activity	1	0		
Self-Care @ Wk 24|Unable to perform the activity	0	0		
Usual Activities@Wk 24|Unable to perform activity	1	2		
Pain/Discomfort @ Wk 24|Unable to perform activity	1	1		
Anxiety/Depr. @ Wk 24|Unable to perform activity	0	1		
Mobility @ Week 36|Unable to perform the activity	0	0		
Self-Care @ Wk 36|Unable to perform the activity	0	0		
Usual Activities@Wk 36|Unable to perform activity	0	1		
Pain/Discomfort @ Wk 36|Unable to perform activity	3	1		
Anxiety/Depr. @ Wk 36|Unable to perform activity	0	0		
Mobility @ Week 48|Unable to perform the activity	0	0		
Self-Care @ Wk 48|Unable to perform the activity	0	0		
Usual Activities@Wk 48|Unable to perform activity	0	0		
Pain/Discomfort @ Wk 48|Unable to perform activity	1	0		
Anxiety/Depr. @ Wk 48|Unable to perform activity	0	1		
Mobility @ Week 60|Unable to perform the activity	0	0		

Self-Care @ Wk 60|Unable to perform the activity	0	0		
Usual Activities@Wk 60|Unable to perform activity	0	2		
Pain/Discomfort @ Wk 60|Unable to perform activity	0	2		
Anxiety/Depr. @ Wk 60|Unable to perform activity	0	0		
Mobility @ Week 72|Unable to perform the activity	0	0		
Self-Care @ Wk 72|Unable to perform the activity	0	0		
Usual Activities@Wk 72|Unable to perform activity	0	0		
Pain/Discomfort @ Wk 72|Unable to perform activity	0	0		
Anxiety/Depr. @ Wk 72|Unable to perform activity	0	1		
Mobility @ Week 84|Unable to perform the activity	0	0		
Self-Care @ Wk 84|Unable to perform the activity	0	0		
Usual Activities@Wk 84|Unable to perform activity	0	1		
Pain/Discomfort @ Wk 84|Unable to perform activity	0	0		
Anxiety/Depr.@Wk 84|Unable to perform activity	0	0		
Mobility @ Week 96|Unable to perform the activity	0	0		
Self-Care @ Wk 96|Unable to perform the activity	0	0		
Usual Activities@Wk 96|Unable to perform activity	0	0		
Pain/Discomfort @ Wk 96|Unable to perform activity	1	0		
Anxiety/Depr. @ Wk 96|Unable to perform activity	0	0		
Mobility @ Week 120|Unable to perform the activity	0	0		
Self-Care @ Wk 120|Unable to perform the activity	0	0		
Usual Activities@Wk 120|Unable to perform activity	0	0		
Pain/Discomfort@Wk 120|Unable to perform activity	0	0		
Anxiety/Depr. @ Wk 120|Unable to perform activity	0	0		
Mobility @ Week 144|Unable to perform the activity	0	0		
Self-Care @ Wk 144|Unable to perform the activity	0	0		
Usual Activities@Wk 144|Unable to perform activity	0	0		
Pain/Discomfort@Wk 144|Unable to perform activity	0	0		
Anxiety/Depr. @ Wk 144|Unable to perform activity	0	0		
Mobility @ Week 12|Missing	0	0		
Self-Care @ Week 12|Missing	0	1		
Usual Activities @ Week 12|Missing	0	0		

Pain/Discomfort @ Week 12|Missing	1	0		
Anxiety/Depression @ Week 12|Missing	0	0		
Mobility @ Week 24|Missing	0	0		
Self-Care @ Week 24|Missing	0	0		
Usual Activities @ Week 24|Missing	0	0		
Pain/Discomfort @ Week 24|Missing	0	0		
Anxiety/Depression @ Week 24|Missing	0	0		
Mobility @ Week 36|Missing	0	0		
Self-Care @ Week 36|Missing	0	0		
Usual Activities @ Week 36|Missing	0	0		
Pain/Discomfort @ Week 36|Missing	0	1		
Anxiety/Depression @ Week 36|Missing	0	0		
Mobility @ Week 48|Missing	0	0		
Self-Care @ Week 48|Missing	0	0		
Usual Activities @ Week 48|Missing	0	0		
Pain/Discomfort @ Week 48|Missing	0	1		
Anxiety/Depression @ Week 48|Missing	1	0		
Mobility @ Week 60|Missing	0	0		
Self-Care @ Week 60|Missing	0	0		
Usual Activities @ Week 60|Missing	0	0		
Pain/Discomfort @ Week 60|Missing	0	0		
Anxiety/Depression @ Week 60|Missing	0	0		
Mobility @ Week 72|Missing	0	0		
Self-Care @ Week 72|Missing	0	0		
Usual Activities @ Week 72|Missing	0	0		
Pain/Discomfort @ Week 72|Missing	0	0		
Anxiety/Depression @ Week 72|Missing	0	0		
Mobility @ Week 84|Missing	0	0		
Self-Care @ Week 84|Missing	0	0		
Usual Activities @ Week 84|Missing	0	0		
Pain/Discomfort @ Week 84|Missing	0	0		
Anxiety/Depression @ Week 84|Missing	0	0		
Mobility @ Week 96|Missing	0	0		
Self-Care @ Week 96|Missing	0	0		
Usual Activities @ Week 96|Missing	0	0		
Pain/Discomfort @ Week 96|Missing	0	0		
Anxiety/Depression @ Week 96|Missing	0	0		
Mobility @ Week 120|Missing	0	0		
Self-Care @ Week 120|Missing	0	0		
Usual Activities @ Week 120|Missing	0	0		
Pain/Discomfort @ Week 120|Missing	0	0		
Anxiety/Depression @ Week 120|Missing	0	0		
Mobility @ Week 144|Missing	0	0		
Self-Care @ Week 144|Missing	0	0		
Usual Activities @ Week 144|Missing	0	0		
Pain/Discomfort @ Week 144|Missing	0	0		
Anxiety/Depression @ Week 144|Missing	0	0		
Mobility @ Week 12|Not Done	0	0		
Self-Care @ Week 12|Not Done	0	0		
Usual Activities @ Week 12|Not Done	0	0		

Pain/Discomfort @ Week 12|Not Done	0	0		
Anxiety/Depression @ Week 12|Not Done	0	0		
Mobility @ Week 24|Not Done	0	0		
Self-Care @ Week 24|Not Done	0	0		
Usual Activities @ Week 24|Not Done	0	0		
Pain/Discomfort @ Week 24|Not Done	0	0		
Anxiety/Depression @ Week 24|Not Done	0	0		
Mobility @ Week 36|Not Done	0	0		
Self-Care @ Week 36|Not Done	1	0		
Usual Activities @ Week 36|Not Done	1	0		
Pain/Discomfort @ Week 36|Not Done	1	0		
Anxiety/Depression @ Week 36|Not Done	1	0		
Mobility @ Week 48|Not Done	0	0		
Self-Care @ Week 48|Not Done	0	0		
Usual Activities @ Week 48|Not Done	0	0		
Pain/Discomfort @ Week 48|Not Done	0	0		
Anxiety/Depression @ Week 48|Not Done	0	0		
Mobility @ Week 60|Not Done	0	0		
Self-Care @ Week 60|Not Done	0	0		
Usual Activities @ Week 60|Not Done	0	0		
Pain/Discomfort @ Week 60|Not Done	0	0		
Anxiety/Depression @ Week 60|Not Done	0	0		
Mobility @ Week 72|Not Done	0	0		
Self-Care @ Week 72|Not Done	0	0		
Usual Activities @ Week 72|Not Done	0	0		
Pain/Discomfort @ Week 72|Not Done	0	0		
Anxiety/Depression @ Week 72|Not Done	0	0		
Mobility @ Week 84|Not Done	0	0		
Self-Care @ Week 84|Not Done	0	0		
Usual Activities @ Week 84|Not Done	0	0		
Pain/Discomfort @ Week 84|Not Done	0	0		
Anxiety/Depression @ Week 84|Not Done	0	0		
Mobility @ Week 96|Not Done	0	0		
Self-Care @ Week 96|Not Done	0	0		
Usual Activities @ Week 96|Not Done	0	0		
Pain/Discomfort @ Week 96|Not Done	0	0		
Anxiety/Depression @ Week 96|Not Done	0	0		
Mobility @ Week 120|Not Done	0	0		
Self-Care @ Week 120|Not Done	0	0		
Usual Activities @ Week 120|Not Done	0	0		
Pain/Discomfort @ Week 120|Not Done	0	0		
Anxiety/Depression @ Week 120|Not Done	0	0		
Mobility @ Week 144|Not Done	0	0		
Self-Care @ Week 144|Not Done	0	0		
Usual Activities @ Week 144|Not Done	0	0		
Pain/Discomfort @ Week 144|Not Done	0	0		

Anxiety/Depression @ Week 144|Not Done	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in EORTC QLQ-C30 Global Score from Baseline to 12 Weeks

End point title	Change in EORTC QLQ-C30 Global Score from Baseline to 12 Weeks

End point description:

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQC-30) is a questionnaire developed to assess the quality of life of cancer patients. The global score ranges from 0-100, with higher values representing a better quality of life.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	260	266		
Units: Score on global scale				
arithmetic mean (standard deviation)	61.67 (± 20.93)	64.41 (± 20.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the EQ-VAS score (Canadian and Australian centers only)

End point title	Change from Baseline in the EQ-VAS score (Canadian and Australian centers only)

End point description:

The European Quality of Life (EuroQol) – 5 Domain (EQ-5D) self-administered questionnaire consists of two pages comprising the EQ-5D descriptive system and the EQ Visual Analogue Scale (VAS). The EQ VAS records the patient's self-rated health on a vertical visual analogue 0-100 scale, where the endpoints are labelled 'The best health you can imagine' (100) and 'The worst health you can imagine' (0).

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 120, Week 144

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	43		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 12	1.6 (± 17.16)	7.0 (± 19.30)		
Week 24	-1.5 (± 21.98)	1.3 (± 21.56)		
Week 36	0.4 (± 21.86)	5.9 (± 22.53)		
Week 48	5.2 (± 23.17)	6.5 (± 25.37)		
Week 60	5.8 (± 10.51)	7.9 (± 28.29)		
Week 72	10.1 (± 7.36)	11.8 (± 29.96)		
Week 84	5.2 (± 6.46)	4.9 (± 25.08)		
Week 96	3.0 (± 19.90)	-10.0 (± 10.80)		
Week 120	10.3 (± 5.91)	-11.0 (± 13.11)		
Week 144	13.0 (± 999)	4.0 (± 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participant hospitalized (Canadian and Australian centers only)

End point title	Number of participant hospitalized (Canadian and Australian centers only)
End point description:	
The number of hospitalizations were categorized: >0 and =<2, >2 and =<4 and >4.	
End point type	Secondary
End point timeframe:	
From date of randomization till 28 days safety follow-up, assessed up to 40 months	

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	49		
Units: Participants				
> 0 and =< 2	27	16		
> 2 and =< 4	1	0		
> 4	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Healthcare Utilization (Canadian and Australian centers only)

End point title	Number of Participants with Healthcare Utilization (Canadian and Australian centers only)

End point description:

The measures of healthcare resource utilization collected were categorized: hospitalization/inpatient visit, Institutionalized, Outpatient visit.

End point type	Secondary

End point timeframe:

From date of randomization till 28 days safety follow-up, assessed up to 40 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	49		
Units: Participants				
Hospitalization/Inpatient visit	29	17		
Institutionalized	0	2		
Outpatient Visit	52	45		

Statistical analyses

No statistical analyses for this end point

Secondary: Reasons for hospitalization (Canadian and Australian centers only)

End point title	Reasons for hospitalization (Canadian and Australian centers only)

End point description:

The reasons for hospitalization were categorized: Breast Cancer, Febrile Neutropenia, Infection, Other and Pneumonia.

End point type	Secondary

End point timeframe:

From date of randomization till 28 days safety follow-up, assessed up to 40 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	49		
Units: Participants				
Breast Cancer	3	3		
Febrile neutropenia	10	1		
Infection	5	4		

Other	14	9		
Pneumonia	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Total and average duration of hospitalization (Canadian and Australian centers only)

End point title	Total and average duration of hospitalization (Canadian and Australian centers only)

End point description:

The total duration of hospitalization in days and average duration of each hospitalization in days were summarized using descriptive statistics.

End point type	Secondary

End point timeframe:

From date of randomization till 28 days safety follow-up, assessed up to 40 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	49		
Units: Days				
arithmetic mean (standard deviation)				
Total duration of hospitalization	10.38 (± 10.63)	16.18 (± 38.63)		
Average duration of each hospitalization	6.6 (± 5.46)	6.5 (± 4.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Type of ward (hospital unit) (Canadian and Australian centers only)

End point title	Type of ward (hospital unit) (Canadian and Australian centers only)

End point description:

The type of ward (hospital unit) were categorized: general ward, intensive care unit, oncology ward, rehabilitation unit and other.

End point type	Secondary

End point timeframe:

From date of randomization till 28 days safety follow-up, assessed up to 40 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	49		
Units: Participants				
General ward	12	9		
Intensive care unit	1	1		
Oncology ward	13	9		
Other	6	3		
Rehabilitation unit	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Discharge Destinations (Canadian and Australian centers only)

End point title	Discharge Destinations (Canadian and Australian centers only)

End point description:

The discharge destinations were categorized: died, home, rehabilitation facility and transfer to other hospital.

End point type	Secondary

End point timeframe:

From date of randomization till 28 days safety follow-up, assessed up to 40 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	49		
Units: Participants				
Died	1	1		
Home	26	14		
Rehabilitation facility	0	1		
Transfer to other hospital	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Estrogen receptor (ER) and Progesterone receptor (PgR) status

End point title	Estrogen receptor (ER) and Progesterone receptor (PgR) status

End point description:

Immunohistochemistry (IHC) analysis of estrogen receptor (ER) and progesterone receptor (PgR) were performed as part of the mandatory central laboratory testing for protocol-specified biomarkers.

End point type	Secondary

End point timeframe:

Up to approximately 39 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326	326		
Units: Percentage of Participants				
estrogen receptor (ER) positive	65	64		
progesterone receptor (PgR) negative	58	63		

Statistical analyses

No statistical analyses for this end point

Post-hoc: All collected deaths

End point title	All collected deaths

End point description:

On-treatment deaths were collected from first dose of study medication to 28 days after the last dose of study medication, for a maximum duration of approximately 165 months.
Post-treatment survival follow-up deaths were collected from day 29 after last dose of study medication to end of study, up to approximately 166 months.
All deaths refer to the sum of on-treatment deaths and post-treatment survival follow-up deaths.

End point type	Post-hoc

End point timeframe:

On-treatment deaths: Up to approximately 165 months. Post-treatment survival follow-up deaths: Up to approximately 166 months

End point values	Lapatinib (LTax/L)	Trastuzumab (TTax/T)	Crossed over to Trastuzumab (TTax/T) after IA results	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	322	325	5	
Units: Participants				
On-treatment deaths	21	13	0	
Post-treatment survival follow-up deaths	82	73	0	
All deaths	103	86	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus 28 days, up to a maximum duration of approximately 165 months.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	LTax/L [1]

Reporting group description:

LTax/L [1]

Reporting group title	Crossed over to TTax/T after IA results [2]

Reporting group description:

Crossed over to TTax/T after IA results [2]

Reporting group title	TTax/T

Reporting group description:

TTax/T

Serious adverse events	LTax/L [1]	Crossed over to TTax/T after IA results [2]	TTax/T
Total subjects affected by serious adverse events			
subjects affected / exposed	106 / 322 (32.92%)	2 / 5 (40.00%)	66 / 325 (20.31%)
number of deaths (all causes)	21	0	13
number of deaths resulting from adverse events	2	0	1
Vascular disorders			
Syncope			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			

subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	5 / 322 (1.55%)	0 / 5 (0.00%)	4 / 325 (1.23%)
occurrences causally related to treatment / all	4 / 7	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Cerebral ischaemia			
subjects affected / exposed	2 / 322 (0.62%)	1 / 5 (20.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Uterine haemorrhage			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	2 / 322 (0.62%)	0 / 5 (0.00%)	2 / 325 (0.62%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 2
Ulcer			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	7 / 322 (2.17%)	0 / 5 (0.00%)	9 / 325 (2.77%)
occurrences causally related to treatment / all	5 / 8	0 / 0	6 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	16 / 322 (4.97%)	0 / 5 (0.00%)	8 / 325 (2.46%)
occurrences causally related to treatment / all	18 / 18	0 / 0	10 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	5 / 322 (1.55%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	7 / 8	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	2 / 322 (0.62%)	0 / 5 (0.00%)	3 / 325 (0.92%)
occurrences causally related to treatment / all	0 / 2	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 322 (0.62%)	0 / 5 (0.00%)	3 / 325 (0.92%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Sexual dysfunction			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	5 / 322 (1.55%)	0 / 5 (0.00%)	2 / 325 (0.62%)
occurrences causally related to treatment / all	4 / 6	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			

subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	3 / 325 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oropharyngeal pain			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 322 (0.62%)	0 / 5 (0.00%)	4 / 325 (1.23%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 322 (0.62%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			

subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental disorder			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase			
subjects affected / exposed	14 / 322 (4.35%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	10 / 15	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase			
subjects affected / exposed	7 / 322 (2.17%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	7 / 7	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin			
subjects affected / exposed	7 / 322 (2.17%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	2 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	2 / 322 (0.62%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count			
subjects affected / exposed	6 / 322 (1.86%)	0 / 5 (0.00%)	3 / 325 (0.92%)
occurrences causally related to treatment / all	6 / 6	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase			

subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	2 / 325 (0.62%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	3 / 322 (0.93%)	0 / 5 (0.00%)	2 / 325 (0.62%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal anastomotic leak			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site reaction			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seroma			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound complication			

subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 322 (0.93%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	2 / 325 (0.62%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorder			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial ischaemia			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Right ventricular dysfunction			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	2 / 325 (0.62%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			

subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 1
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multifocal motor neuropathy			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Platelet disorder			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	3 / 325 (0.92%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric ulcer			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	2 / 322 (0.62%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fistula of small intestine			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	23 / 322 (7.14%)	0 / 5 (0.00%)	5 / 325 (1.54%)
occurrences causally related to treatment / all	37 / 39	0 / 0	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	2 / 325 (0.62%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			

subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	2 / 322 (0.62%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			
subjects affected / exposed	3 / 322 (0.93%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal perforation			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	12 / 322 (3.73%)	0 / 5 (0.00%)	3 / 325 (0.92%)
occurrences causally related to treatment / all	15 / 19	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	3 / 322 (0.93%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	2 / 322 (0.62%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal haemorrhage			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	6 / 322 (1.86%)	0 / 5 (0.00%)	4 / 325 (1.23%)
occurrences causally related to treatment / all	7 / 9	0 / 0	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine infection			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	2 / 322 (0.62%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatobiliary disease			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			

subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin infection			
subjects affected / exposed	3 / 322 (0.93%)	0 / 5 (0.00%)	4 / 325 (1.23%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	2 / 322 (0.62%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus			
subjects affected / exposed	4 / 322 (1.24%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	3 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Petechiae			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain of skin			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 322 (0.62%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pollakiuria			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney infection			

subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	2 / 322 (0.62%)	0 / 5 (0.00%)	2 / 325 (0.62%)
occurrences causally related to treatment / all	0 / 3	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	2 / 322 (0.62%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	3 / 322 (0.93%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	2 / 325 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pain in extremity			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal disorder			
subjects affected / exposed	1 / 322 (0.31%)	1 / 5 (20.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	2 / 322 (0.62%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Paronychia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	10 / 322 (3.11%)	0 / 5 (0.00%)	2 / 325 (0.62%)
occurrences causally related to treatment / all	4 / 11	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	5 / 322 (1.55%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	1 / 6	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	7 / 322 (2.17%)	0 / 5 (0.00%)	3 / 325 (0.92%)
occurrences causally related to treatment / all	3 / 11	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sepsis			

subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	4 / 325 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper aerodigestive tract infection			
subjects affected / exposed	0 / 322 (0.00%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	3 / 322 (0.93%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	2 / 5	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	4 / 322 (1.24%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	1 / 4	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	3 / 322 (0.93%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	4 / 322 (1.24%)	0 / 5 (0.00%)	1 / 325 (0.31%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			

subjects affected / exposed	3 / 322 (0.93%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cachexia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 5 (0.00%)	0 / 325 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	LTax/L [1]	Crossed over to TTax/T after IA results [2]	TTax/T
Total subjects affected by non-serious adverse events			
subjects affected / exposed	316 / 322 (98.14%)	1 / 5 (20.00%)	319 / 325 (98.15%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	16 / 322 (4.97%)	0 / 5 (0.00%)	22 / 325 (6.77%)
occurrences (all)	17	0	23
Vascular disorders			
Hot flush			
subjects affected / exposed	27 / 322 (8.39%)	0 / 5 (0.00%)	32 / 325 (9.85%)
occurrences (all)	28	0	35
Lymphoedema			
subjects affected / exposed	17 / 322 (5.28%)	0 / 5 (0.00%)	12 / 325 (3.69%)
occurrences (all)	23	0	13
Epistaxis			
subjects affected / exposed	63 / 322 (19.57%)	0 / 5 (0.00%)	43 / 325 (13.23%)
occurrences (all)	91	0	59
Hypertension			
subjects affected / exposed	22 / 322 (6.83%)	0 / 5 (0.00%)	37 / 325 (11.38%)
occurrences (all)	25	0	39
Flushing			
subjects affected / exposed	19 / 322 (5.90%)	0 / 5 (0.00%)	14 / 325 (4.31%)
occurrences (all)	34	0	24
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	51 / 322 (15.84%)	0 / 5 (0.00%)	54 / 325 (16.62%)
occurrences (all)	68	0	65
Fatigue			
subjects affected / exposed	225 / 322 (69.88%)	0 / 5 (0.00%)	212 / 325 (65.23%)
occurrences (all)	345	0	390
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	30 / 322 (9.32%)	1 / 5 (20.00%)	45 / 325 (13.85%)
occurrences (all)	37	1	63
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	24 / 322 (7.45%)	0 / 5 (0.00%)	29 / 325 (8.92%)
occurrences (all)	26	0	32
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	75 / 322 (23.29%)	0 / 5 (0.00%)	85 / 325 (26.15%)
occurrences (all)	102	0	107
Cough			
subjects affected / exposed	69 / 322 (21.43%)	0 / 5 (0.00%)	94 / 325 (28.92%)
occurrences (all)	80	0	113
Rhinitis allergic			
subjects affected / exposed	30 / 322 (9.32%)	0 / 5 (0.00%)	21 / 325 (6.46%)
occurrences (all)	32	0	26
Oropharyngeal pain			
subjects affected / exposed	15 / 322 (4.66%)	0 / 5 (0.00%)	30 / 325 (9.23%)
occurrences (all)	18	0	33
Influenza			
subjects affected / exposed	23 / 322 (7.14%)	0 / 5 (0.00%)	30 / 325 (9.23%)
occurrences (all)	35	0	51
Psychiatric disorders			
Insomnia			
subjects affected / exposed	65 / 322 (20.19%)	0 / 5 (0.00%)	72 / 325 (22.15%)
occurrences (all)	75	0	99
Dysphonia			

subjects affected / exposed	8 / 322 (2.48%)	0 / 5 (0.00%)	21 / 325 (6.46%)
occurrences (all)	8	0	34
Depressed mood			
subjects affected / exposed	27 / 322 (8.39%)	0 / 5 (0.00%)	30 / 325 (9.23%)
occurrences (all)	31	0	33
Anxiety			
subjects affected / exposed	34 / 322 (10.56%)	0 / 5 (0.00%)	34 / 325 (10.46%)
occurrences (all)	36	0	38
Investigations			
Weight increased			
subjects affected / exposed	6 / 322 (1.86%)	0 / 5 (0.00%)	17 / 325 (5.23%)
occurrences (all)	6	0	19
Weight decreased			
subjects affected / exposed	29 / 322 (9.01%)	0 / 5 (0.00%)	14 / 325 (4.31%)
occurrences (all)	30	0	15
Gamma-glutamyltransferase			
subjects affected / exposed	20 / 322 (6.21%)	0 / 5 (0.00%)	10 / 325 (3.08%)
occurrences (all)	24	0	12
Cardiac disorders			
Chest pain			
subjects affected / exposed	9 / 322 (2.80%)	0 / 5 (0.00%)	21 / 325 (6.46%)
occurrences (all)	12	0	23
Oedema peripheral			
subjects affected / exposed	86 / 322 (26.71%)	0 / 5 (0.00%)	113 / 325 (34.77%)
occurrences (all)	107	0	147
Left ventricular dysfunction			
subjects affected / exposed	9 / 322 (2.80%)	0 / 5 (0.00%)	25 / 325 (7.69%)
occurrences (all)	11	0	26
Nervous system disorders			
Vision blurred			
subjects affected / exposed	16 / 322 (4.97%)	0 / 5 (0.00%)	17 / 325 (5.23%)
occurrences (all)	17	0	17
Peripheral sensory neuropathy			
subjects affected / exposed	168 / 322 (52.17%)	0 / 5 (0.00%)	165 / 325 (50.77%)
occurrences (all)	204	0	197
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	30 / 322 (9.32%)	0 / 5 (0.00%)	10 / 325 (3.08%)
occurrences (all)	34	0	11
Multifocal motor neuropathy			
subjects affected / exposed	16 / 322 (4.97%)	0 / 5 (0.00%)	21 / 325 (6.46%)
occurrences (all)	18	0	22
Headache			
subjects affected / exposed	66 / 322 (20.50%)	0 / 5 (0.00%)	72 / 325 (22.15%)
occurrences (all)	106	0	112
Dizziness			
subjects affected / exposed	36 / 322 (11.18%)	0 / 5 (0.00%)	51 / 325 (15.69%)
occurrences (all)	41	0	61
Eye disorders			
Lacrimation increased			
subjects affected / exposed	26 / 322 (8.07%)	0 / 5 (0.00%)	37 / 325 (11.38%)
occurrences (all)	31	0	42
Gastrointestinal disorders			
Taste disorder			
subjects affected / exposed	55 / 322 (17.08%)	0 / 5 (0.00%)	51 / 325 (15.69%)
occurrences (all)	74	0	68
Stomatitis			
subjects affected / exposed	138 / 322 (42.86%)	0 / 5 (0.00%)	106 / 325 (32.62%)
occurrences (all)	233	0	215
Nausea			
subjects affected / exposed	157 / 322 (48.76%)	0 / 5 (0.00%)	139 / 325 (42.77%)
occurrences (all)	290	0	232
Dyspepsia			
subjects affected / exposed	67 / 322 (20.81%)	0 / 5 (0.00%)	61 / 325 (18.77%)
occurrences (all)	90	0	87
Dry mouth			
subjects affected / exposed	19 / 322 (5.90%)	0 / 5 (0.00%)	12 / 325 (3.69%)
occurrences (all)	27	0	15
Diarrhoea			
subjects affected / exposed	250 / 322 (77.64%)	0 / 5 (0.00%)	130 / 325 (40.00%)
occurrences (all)	689	0	275
Constipation			

subjects affected / exposed	74 / 322 (22.98%)	0 / 5 (0.00%)	85 / 325 (26.15%)
occurrences (all)	101	0	115
Abdominal pain upper			
subjects affected / exposed	21 / 322 (6.52%)	0 / 5 (0.00%)	14 / 325 (4.31%)
occurrences (all)	25	0	17
Abdominal pain			
subjects affected / exposed	51 / 322 (15.84%)	0 / 5 (0.00%)	40 / 325 (12.31%)
occurrences (all)	62	0	54
Abdominal distension			
subjects affected / exposed	18 / 322 (5.59%)	0 / 5 (0.00%)	8 / 325 (2.46%)
occurrences (all)	21	0	8
Vomiting			
subjects affected / exposed	92 / 322 (28.57%)	0 / 5 (0.00%)	75 / 325 (23.08%)
occurrences (all)	161	0	109
Skin and subcutaneous tissue disorders			
Skin infection			
subjects affected / exposed	12 / 322 (3.73%)	0 / 5 (0.00%)	19 / 325 (5.85%)
occurrences (all)	17	0	20
Skin disorder			
subjects affected / exposed	25 / 322 (7.76%)	0 / 5 (0.00%)	20 / 325 (6.15%)
occurrences (all)	36	0	31
Rash			
subjects affected / exposed	192 / 322 (59.63%)	0 / 5 (0.00%)	127 / 325 (39.08%)
occurrences (all)	321	0	194
Pruritus			
subjects affected / exposed	47 / 322 (14.60%)	0 / 5 (0.00%)	38 / 325 (11.69%)
occurrences (all)	61	0	60
Nail disorder			
subjects affected / exposed	129 / 322 (40.06%)	0 / 5 (0.00%)	88 / 325 (27.08%)
occurrences (all)	135	0	96
Dry skin			
subjects affected / exposed	59 / 322 (18.32%)	0 / 5 (0.00%)	40 / 325 (12.31%)
occurrences (all)	67	0	45
Alopecia			
subjects affected / exposed	212 / 322 (65.84%)	0 / 5 (0.00%)	238 / 325 (73.23%)
occurrences (all)	216	0	245

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	75 / 322 (23.29%)	0 / 5 (0.00%)	99 / 325 (30.46%)
occurrences (all)	112	0	154
Chills			
subjects affected / exposed	7 / 322 (2.17%)	0 / 5 (0.00%)	22 / 325 (6.77%)
occurrences (all)	7	0	22
Bone pain			
subjects affected / exposed	69 / 322 (21.43%)	0 / 5 (0.00%)	79 / 325 (24.31%)
occurrences (all)	86	0	110
Back pain			
subjects affected / exposed	55 / 322 (17.08%)	0 / 5 (0.00%)	72 / 325 (22.15%)
occurrences (all)	61	0	90
Myalgia			
subjects affected / exposed	79 / 322 (24.53%)	1 / 5 (20.00%)	78 / 325 (24.00%)
occurrences (all)	114	1	140
Pain in extremity			
subjects affected / exposed	37 / 322 (11.49%)	0 / 5 (0.00%)	52 / 325 (16.00%)
occurrences (all)	48	0	61
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	38 / 322 (11.80%)	0 / 5 (0.00%)	43 / 325 (13.23%)
occurrences (all)	43	0	66
Paronychia			
subjects affected / exposed	29 / 322 (9.01%)	0 / 5 (0.00%)	11 / 325 (3.38%)
occurrences (all)	39	0	12
Cystitis			
subjects affected / exposed	15 / 322 (4.66%)	0 / 5 (0.00%)	22 / 325 (6.77%)
occurrences (all)	16	0	27
Rhinitis			
subjects affected / exposed	27 / 322 (8.39%)	0 / 5 (0.00%)	31 / 325 (9.54%)
occurrences (all)	30	0	40
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	107 / 322 (33.23%)	0 / 5 (0.00%)	74 / 325 (22.77%)
occurrences (all)	157	0	97

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2008	Amendment 1: Updated background information for emerging data regarding hepatotoxicity seen with the use of lapatinib. To reflect changes due to updated lapatinib investigator's brochure. To clarify protocol regarding the study logistics, requirements for supporting documents, lapatinib tablet information and eligibility assessments.
07 January 2010	Amendment 2: To reflect changes in study logistics with regard to central disease assessment review and to add protocol clarifications throughout regarding assessments, CRFs and prohibited medications.
16 February 2010	Amendment 3: Safety amendment to require use of primary prophylactic treatment with G-CSF during combination therapy phase for subjects randomized to the lapatinib + docetaxel arm. Diarrhea management guidelines were also updated to reflect most current information for lapatinib.
22 April 2010	Amendment 4: To clarify eligibility criteria on cardiac illness and acceptance of slides of tumor tissue when blocks unavailable. Updated to describe the additional OS analysis that was conducted following completion of the final analysis for PFS. Updated to add protocol clarifications throughout regarding assessments, supporting documents and use of cimetidine per institutional practice.
15 June 2012	Amendment 5: To reflect changes in protocol conduct following disclosure of the results of the planned interim analysis of the study. Main changes included reduction of assessments and data collection and clarification on CRFs for submission.
08 April 2014	Amendment 6: To reflect changes in study conduct with removal of NCIC CTG from all aspects of ongoing study conduct. Further reduction in assessments as study is a long-term follow-up study. Updated to add prohibited medications list, updated diarrhea management guidelines.
23 March 2016	Amendment 7: Deleted or replaced references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship. Made administrative changes to align with Novartis processes and procedures.

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 for complete trial results.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25779558

http://www.ncbi.nlm.nih.gov/pubmed/28484925

http://www.ncbi.nlm.nih.gov/pubmed/28750133