Clinical trial results:
A Phase III trial to compare the safety and efficacy of lapatinib plus trastuzumab plus an aromatase inhibitor (AI) vs. trastuzumab plus an AI vs. lapatinib plus an AI as 1st- or 2nd- line therapy in postmenopausal subjects with hormone receptor+, HER2-positive metastatic breast cancer (MBC) who received prior trastuzumab and endocrine therapies

Summary

EudraCT number	2010-019577-16
Trial protocol	DE HU IE PL BE BG NO GB LT PT ES GR IT
Global end of trial date	06 June 2022

Results information

Result version number	v1
This version publication date	05 May 2023
First version publication date	05 May 2023

Trial information

Trial identification

Sponsor protocol code	114299

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01160211
WHO universal trial number (UTN)	-
Other trial identifiers	GlaxoSmithKline: EGF114299, Novartis: CLAP016A2307

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 42 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 42 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	06 June 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate superiority of Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) combination (treatment group A) vs. Trastuzumab + Aromatase Inhibitor (AI) combination (treatment group B) for Progression Free Survival (PFS).

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	05 May 2011
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: 27
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Brazil: 50
Country: Number of subjects enrolled	Bulgaria: 23
Country: Number of subjects enrolled	China: 13
Country: Number of subjects enrolled	Croatia: 2
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Hong Kong: 7
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	India: 2
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Japan: 21
Country: Number of subjects enrolled	Korea, Republic of: 40
Country: Number of subjects enrolled	Peru: 5

Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Russian Federation: 46
Country: Number of subjects enrolled	Serbia: 13
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Taiwan: 6
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Ukraine: 28
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	369
EEA total number of subjects	90

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)	284
From 65 to 84 years	85
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was conducted at 113 centers in 29 countries worldwide (Argentina, Australia, Belgium, Brazil, Bulgaria, China, Croatia, France, Germany, Greece, Hong Kong, Hungary, India, Israel, Italy, Japan, Peru, Poland, Portugal, Republic of Korea, Russia, Serbia, Singapore, Spain, Taiwan, Turkey, UK, Ukraine and USA)

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 + Trastuzumab + Aromatase Inhibitor (AI)

Arm description:

Lapatinib 1000 mg PO once daily + Trastuzumab (loading dose of 8 mg/kg) followed by the maintenance dose of 6 mg/kg IV every 3 weeks (q3weeks) + an Aromatase Inhibitor (AI) of Investigator’s choice PO once daily.

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

Dosage and administration details:

1000 mg by mouth once a day

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

Dosage and administration details:

Aromatase inhibitor (either letrozole, anastrozole, or exemestane) of investigator’s choice given by mouth once daily

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Loading dose of 8 mg/kg IV followed by the maintenance dose of 6 mg/kg IV every 3 weeks (q3weeks)

Arm title	Lapatinib + Aromatase Inhibitor (AI)

Arm description:

Lapatinib 1500 mg PO once daily + an Aromatase Inhibitor (AI) of Investigator’s choice PO once daily.

Arm type	Active comparator

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

Dosage and administration details:

Aromatase inhibitor (either letrozole, anastrozole, or exemestane) of investigator's choice given by mouth once daily

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

Dosage and administration details:

1500 mg by mouth once a day

Arm title	Trastuzumab + Aromatase Inhibitor (AI)

Arm description:

Trastuzumab (loading dose of 8 mg/kg) followed by maintenance dose of 6 mg/kg IV every 3 weeks (q3weeks) + an Aromatase Inhibitor (AI) of Investigator's choice PO once daily.

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

Dosage and administration details:

Aromatase inhibitor (either letrozole, anastrozole, or exemestane) of investigator's choice given by mouth once daily

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Loading dose of 8 mg/kg IV followed by the maintenance dose of 6 mg/kg IV every 3 weeks (q3weeks)

Number of subjects in period 1	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI)	Lapatinib + Aromatase Inhibitor (AI)	Trastuzumab + Aromatase Inhibitor (AI)
Started	124	123	122
Safety Set	123	123	121
Completed	64	64	55
Not completed	60	59	67
Physician decision	1	-	-
Consent withdrawn by subject	4	2	2
Data unavailable due to regulatory issues	2	-	2
Subject Reached Protocol-Defined Stopping Criteria	49	49	59

Lost to follow-up	4	8	4

Baseline characteristics

Reporting groups	
Reporting group title	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI)
Reporting group description:	
Lapatinib 1000 mg PO once daily + Trastuzumab (loading dose of 8 mg/kg) followed by the maintenance dose of 6 mg/kg IV every 3 weeks (q3weeks) + an Aromatase Inhibitor (AI) of Investigator's choice PO once daily.	
Reporting group title	Lapatinib + Aromatase Inhibitor (AI)
Reporting group description:	
Lapatinib 1500 mg PO once daily + an Aromatase Inhibitor (AI) of Investigator's choice PO once daily.	
Reporting group title	Trastuzumab + Aromatase Inhibitor (AI)
Reporting group description:	
Trastuzumab (loading dose of 8 mg/kg) followed by maintenance dose of 6 mg/kg IV every 3 weeks (q3weeks) + an Aromatase Inhibitor (AI) of Investigator's choice PO once daily.	

Reporting group values	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI)	Lapatinib + Aromatase Inhibitor (AI)	Trastuzumab + Aromatase Inhibitor (AI)
Number of subjects	124	123	122
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	92	92	100
From 65-84 years	32	31	22
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	56.9	57.1	54.9
standard deviation	± 11.15	± 9.98	± 10.10
Sex: Female, Male			
Units: Participants			
Female	124	123	122
Male	0	0	0
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	1	1	1
Asian	31	31	32
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	4	3
White	89	85	84
More than one race	0	2	2
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	369		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	284		
From 65-84 years	85		
85 years and over	0		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	369		
Male	0		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	3		
Asian	94		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	10		
White	258		
More than one race	4		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI)

Reporting group description:

Lapatinib 1000 mg PO once daily + Trastuzumab (loading dose of 8 mg/kg) followed by the maintenance dose of 6 mg/kg IV every 3 weeks (q3weeks) + an Aromatase Inhibitor (AI) of Investigator's choice PO once daily.

Reporting group title	Lapatinib + Aromatase Inhibitor (AI)

Reporting group description:

Lapatinib 1500 mg PO once daily + an Aromatase Inhibitor (AI) of Investigator's choice PO once daily.

Reporting group title	Trastuzumab + Aromatase Inhibitor (AI)

Reporting group description:

Trastuzumab (loading dose of 8 mg/kg) followed by maintenance dose of 6 mg/kg IV every 3 weeks (q3weeks) + an Aromatase Inhibitor (AI) of Investigator's choice PO once daily.

Primary: Median Kaplan Meier estimates for PFS in Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) vs. Trastuzumab + Aromatase Inhibitor (AI)

End point title	Median Kaplan Meier estimates for PFS in Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) vs. Trastuzumab + Aromatase Inhibitor (AI)[1][2]

End point description:

Progression free survival (PFS) was defined as the interval of time between the date of randomization and the earliest date 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 approximately 5 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis performed

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary endpoint evaluated PFS comparing treatment group A (lapatinib+trastuzumab+AI) vs. treatment group B (trastuzumab+AI)

End point values	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI)	Trastuzumab + Aromatase Inhibitor (AI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	117		
Units: Months				
median (confidence interval 95%)	11.0 (8.3 to 13.8)	5.6 (5.4 to 8.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Progression Free Survival (PFS) events in Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) vs. Trastuzumab + Aromatase Inhibitor (AI)

End point title	Progression Free Survival (PFS) events in Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) vs. Trastuzumab + Aromatase Inhibitor (AI)[3]

End point description:

The Number of Participants with Progression free survival (PFS) events in the Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) arm vs. Trastuzumab + Aromatase Inhibitor (AI) arm 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 approximately 5 years

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary endpoint evaluated PFS comparing treatment group A (lapatinib+trastuzumab+AI) vs. treatment group B (trastuzumab+AI)

End point values	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI)	Trastuzumab + Aromatase Inhibitor (AI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	117		
Units: Participants				
Disease progression or died (event)	62	75		
Censored, follow-up for disease progression ended	7	3		
Censored, f/p for disease progression ongoing	51	39		

Statistical analyses

Statistical analysis title	PFS of lap.+trast.+AI vs. trast.+AI

Statistical analysis description:

Null hypothesis H0: $\lambda \geq 1$ or to reject it in favor of the alternative hypothesis HA: $\lambda < 1$, where λ is the hazard ratio (HR) between Treatment Group A and Treatment Group B for progression-free survival.

Comparison groups	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0063 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.88

Notes:

[4] - Pike estimate of the treatment hazard ratio, <1 indicates a lower risk compared with trastuzumab + AI.

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)

End point description:

Progression free survival (PFS) was defined as the interval of time between the date of randomization and the earliest date 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	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 11 years

End point values	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI)	Lapatinib + Aromatase Inhibitor (AI)	Trastuzumab + Aromatase Inhibitor (AI)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124	123	122	
Units: Months				
median (confidence interval 95%)	11.1 (10.0 to 15.3)	8.3 (7.1 to 11.0)	5.7 (5.5 to 8.3)	

Statistical analyses

Statistical analysis title	PFS of lap.+trast.+AI vs. trast.+AI
Comparison groups	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.79

Statistical analysis title	PFS of lap.+trast.+AI vs. lap.+AI
Comparison groups	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Lapatinib + Aromatase Inhibitor (AI)

Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.92

Statistical analysis title	PFS of lap.+AI vs. trast.+AI
Comparison groups	Lapatinib + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.15

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

Overall Response Rate (ORR) was defined as the proportion of participants achieving either a 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. Subjects who do not have measurable disease contributed to the Response Rate based analyses, for the evaluation of CR, SD and PD.

End point type	Secondary

End point timeframe:

Up approximately 11 years

End point values	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI)	Lapatinib + Aromatase Inhibitor (AI)	Trastuzumab + Aromatase Inhibitor (AI)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124	123	122	
Units: Percentage of Participants				
number (confidence interval 95%)	32.3 (24.2 to	22.8 (15.7 to	17.2 (11.0 to	

41.2)	31.2)	25.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

The Number of Participants with Overall Survival (OS) events was based on assessments by the Investigator.

End point type	Secondary

End point timeframe:

From date of randomization until date of death from any cause, assessed up approximately 11 years

End point values	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI)	Lapatinib + Aromatase Inhibitor (AI)	Trastuzumab + Aromatase Inhibitor (AI)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124	123	122	
Units: Participants				
Death	38	45	39	
Censored, follow-up ended	86	78	83	
Censored, follow-up ongoing	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

Clinical Benefit Rate (CBR) was defined as the percentage of patients with evidence of Complete Response (CR), Partial Response (PR), or maintaining Stable Disease (SD) for at least 6 months while on study, according to the investigator assessment of response per RECIST 1.1 criteria.

End point type	Secondary

End point timeframe:

Up approximately 11 years

End point values	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI)	Lapatinib + Aromatase Inhibitor (AI)	Trastuzumab + Aromatase Inhibitor (AI)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124	123	122	
Units: Percentage of Participants				
number (confidence interval 95%)	51.6 (42.5 to 60.7)	43.1 (34.2 to 52.3)	34.4 (26.1 to 43.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to Response (TTR) was defined as the time from randomization to the earliest date of Complete Response (CR) or Partial Response (PR)

End point type	Secondary

End point timeframe:

From date of randomization until the earliest date of Complete Response (CR) or Partial Response (PR), assessed up approximately 11 years

End point values	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI)	Lapatinib + Aromatase Inhibitor (AI)	Trastuzumab + Aromatase Inhibitor (AI)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	28	21	
Units: Days				
median (full range (min-max))	85.0 (72 to 1031)	86.5 (65 to 1175)	86.0 (67 to 337)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)

End point description:

Duration of Response (DOR) was defined as the duration between the date of first documented Complete Response (CR) or Partial Response (PR) and the date of first documented sign of Progressive Disease or Death, or to the date of censor.

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

End point values	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI)	Lapatinib + Aromatase Inhibitor (AI)	Trastuzumab + Aromatase Inhibitor (AI)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	28	21	
Units: Months				
median (confidence interval 95%)	22.5 (11.1 to 33.1)	11.1 (5.6 to 999)	11.8 (5.4 to 28.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in the Quality of Life (QoL) Status Relative to Baseline FACT-B Overall and Subscale Scores at Last On treatment Assessment

End point title	Mean change in the Quality of Life (QoL) Status Relative to Baseline FACT-B Overall and Subscale Scores at Last On treatment Assessment

End point description:

Quality of life was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire. It is a 37-item (27 general questions and 10 breast cancer specific questions) self-reporting instrument consisting of 5 dimensions: physical well-being (PWB), social well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and a breast cancer subscale (BCS). The followings were the score ranges for each self-reporting subscale: • PWB : 0-28 • SWB : 0-28 • EWB : 0-24 • FWB : 0-28 • BCS : 0-40 FACT-B Total Outcome Index (TOI) = PWB + FWB + BCS (range:0 - 96) FACT-B Total Score = PWB + SWB + EWB + FWB + BCS (range:0-148) FACT-G Total Score = PWB + SWB + EWB + FWB (range:0-108). For all the FACIT scales and symptom indices, the higher the score the better QoL

End point type	Secondary

End point timeframe:

Day 1 (pre-dose), up approximately 11 years

End point values	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI)	Lapatinib + Aromatase Inhibitor (AI)	Trastuzumab + Aromatase Inhibitor (AI)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	113	110	
Units: score on a scale				
least squares mean (standard error)				
FACT-B total score	-4.2 (± 1.48)	-6.3 (± 1.51)	-2.4 (± 1.51)	
FACT-G total score	-4.3 (± 1.22)	-5.9 (± 1.24)	-2.8 (± 1.24)	
FACT-B trial outcome Index (TOI)	-3.3 (± 1.05)	-4.2 (± 1.07)	-0.6 (± 1.07)	
Physical well-being (PWB)	-2.0 (± 0.48)	-2.1 (± 0.49)	-0.5 (± 0.49)	
Social family wellbeing (SWB)	-0.5 (± 0.50)	-1.5 (± 0.50)	-0.9 (± 0.51)	
Emotional wellbeing (EWB)	-0.4 (± 0.40)	-0.6 (± 0.40)	-1.0 (± 0.41)	

Functional wellbeing (FWB) Breast cancer subscale (BCS)	-1.3 (± 0.45) 0.0 (± 0.47)	-1.7 (± 0.46) -0.5 (± 0.47)	-0.3 (± 0.46) 0.4 (± 0.48)	

Statistical analyses

Statistical analysis title	FACT-B total score
Comparison groups	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Least square difference
Point estimate	-1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.95
upper limit	2.36
Variability estimate	Standard error of the mean
Dispersion value	2.111

Statistical analysis title	FACT-B total score
Comparison groups	Lapatinib + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Least square difference
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.09
upper limit	0.29
Variability estimate	Standard error of the mean
Dispersion value	2.13

Statistical analysis title	Emotional wellbeing (EWB)
Comparison groups	Lapatinib + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)

Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Least square difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	1.53
Variability estimate	Standard error of the mean
Dispersion value	0.571

Statistical analysis title	Emotional wellbeing (EWB)
Comparison groups	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Least square difference
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	1.66
Variability estimate	Standard error of the mean
Dispersion value	0.568

Statistical analysis title	Social family wellbeing (SWB)
Comparison groups	Lapatinib + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Least square difference
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.96
upper limit	0.86
Variability estimate	Standard error of the mean
Dispersion value	0.715

Statistical analysis title	FACT-G total score
Comparison groups	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Least square difference
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.92
upper limit	1.92
Variability estimate	Standard error of the mean
Dispersion value	1.739

Statistical analysis title	FACT-G total score
Comparison groups	Lapatinib + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Least square difference
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.55
upper limit	0.34
Variability estimate	Standard error of the mean
Dispersion value	1.751

Statistical analysis title	FACT-B trial outcome index (TOI)
Comparison groups	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Least square difference
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.66
upper limit	0.25
Variability estimate	Standard error of the mean
Dispersion value	1.502

Statistical analysis title	FACT-B trial outcome index (TOI)
Comparison groups	Lapatinib + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Least square difference
Point estimate	-3.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.59
upper limit	-0.64
Variability estimate	Standard error of the mean
Dispersion value	1.512

Statistical analysis title	Physical well-being (PWB)
Comparison groups	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Least square difference
Point estimate	-1.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.82
upper limit	-0.11
Variability estimate	Standard error of the mean
Dispersion value	0.69

Statistical analysis title	Physical well-being (PWB)
Comparison groups	Lapatinib + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Least square difference
Point estimate	-1.54

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	-0.18
Variability estimate	Standard error of the mean
Dispersion value	0.693

Statistical analysis title	Social family wellbeing (SWB)
Comparison groups	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Least square difference
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	1.79
Variability estimate	Standard error of the mean
Dispersion value	0.711

Statistical analysis title	Functional wellbeing (FWB)
Comparison groups	Lapatinib + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Least square difference
Point estimate	-1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.649

Statistical analysis title	Functional wellbeing (FWB)
Comparison groups	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)

Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Least square difference
Point estimate	-0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.26
upper limit	0.28
Variability estimate	Standard error of the mean
Dispersion value	0.646

Statistical analysis title	Breast cancer subscale (BCS)
Comparison groups	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Least square difference
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.66
upper limit	0.95
Variability estimate	Standard error of the mean
Dispersion value	0.665

Statistical analysis title	Breast cancer subscale (BCS)
Comparison groups	Lapatinib + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI)
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Least square difference
Point estimate	-0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.14
upper limit	0.48
Variability estimate	Standard error of the mean
Dispersion value	0.668

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 30 days after the last dose of study medication, for a maximum duration of approximately 131 months. Post-treatment survival follow-up deaths were collected from day 31 after last dose of study medication to end of study, up to approximately 132 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 131 months. Post-treatment survival follow-up deaths: Up to approximately 132 months

End point values	Lapatinib + Trastuzumab + Aromatase Inhibitor (AI)	Lapatinib + Aromatase Inhibitor (AI)	Trastuzumab + Aromatase Inhibitor (AI)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	123	121	
Units: Participants				
On-treatment deaths	5	8	5	
Post-treatment survival follow-up deaths	33	37	34	
All deaths	38	45	39	

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 30 days, up to a maximum duration of approximately 131 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	25.0

Reporting groups

Reporting group title	Lapatinib (1000mg) + Trastuzumab (6 mg/kg) + AI

Reporting group description:

Lapatinib (1000mg) + Trastuzumab (6 mg/kg) + AI

Reporting group title	Trastuzumab (6 mg/kg) + AI

Reporting group description:

Trastuzumab (6 mg/kg) + AI

Reporting group title	Lapatinib (1500mg) + AI

Reporting group description:

Lapatinib (1500mg) + AI

Serious adverse events	Lapatinib (1000mg) + Trastuzumab (6 mg/kg) + AI	Trastuzumab (6 mg/kg) + AI	Lapatinib (1500mg) + AI
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 123 (21.95%)	14 / 121 (11.57%)	23 / 123 (18.70%)
number of deaths (all causes)	5	5	8
number of deaths resulting from adverse events	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Metastases to lung			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Ovarian epithelial cancer			

subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Organ failure			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Asthenia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Iodine allergy			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Drug hypersensitivity			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			

subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hydrothorax			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Respiratory failure			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
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			
Confusional state			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Ejection fraction decreased			
subjects affected / exposed	7 / 123 (5.69%)	2 / 121 (1.65%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	6 / 8	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Muscle strain			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Post procedural inflammation			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Spinal compression fracture			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 123 (0.81%)	1 / 121 (0.83%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Cardiogenic shock			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebrovascular accident			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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

Headache			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial aneurysm			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech disorder			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Gastrointestinal disorders			
Anal fissure			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ascites			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pancreatitis acute			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Diarrhoea			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Gastritis			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelocaliectasis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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 failure			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Rheumatoid arthritis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	3 / 123 (2.44%)	2 / 121 (1.65%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Osteomyelitis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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

Pneumonia			
subjects affected / exposed	0 / 123 (0.00%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyuria			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Sepsis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 123 (1.63%)	1 / 121 (0.83%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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			
Dehydration			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Diabetic ketoacidosis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Hypercalcaemia			

subjects affected / exposed	0 / 123 (0.00%)	1 / 121 (0.83%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Hypomagnesaemia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 121 (0.00%)	0 / 123 (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
Hypokalaemia			
subjects affected / exposed	2 / 123 (1.63%)	0 / 121 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	1 / 3	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	Lapatinib (1000mg) + Trastuzumab (6 mg/kg) + AI	Trastuzumab (6 mg/kg) + AI	Lapatinib (1500mg) + AI
Total subjects affected by non-serious adverse events			
subjects affected / exposed	113 / 123 (91.87%)	86 / 121 (71.07%)	107 / 123 (86.99%)
Investigations			
Ejection fraction decreased			
subjects affected / exposed	10 / 123 (8.13%)	3 / 121 (2.48%)	3 / 123 (2.44%)
occurrences (all)	10	4	3
Blood bilirubin increased			
subjects affected / exposed	3 / 123 (2.44%)	1 / 121 (0.83%)	8 / 123 (6.50%)
occurrences (all)	3	1	8
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 123 (4.07%)	9 / 121 (7.44%)	7 / 123 (5.69%)
occurrences (all)	5	9	8
Aspartate aminotransferase increased			

subjects affected / exposed	11 / 123 (8.94%)	11 / 121 (9.09%)	22 / 123 (17.89%)
occurrences (all)	12	12	28
Alanine aminotransferase increased			
subjects affected / exposed	11 / 123 (8.94%)	9 / 121 (7.44%)	20 / 123 (16.26%)
occurrences (all)	15	11	26
Weight decreased			
subjects affected / exposed	12 / 123 (9.76%)	3 / 121 (2.48%)	13 / 123 (10.57%)
occurrences (all)	13	3	14
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 123 (7.32%)	8 / 121 (6.61%)	4 / 123 (3.25%)
occurrences (all)	13	9	5
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 123 (7.32%)	15 / 121 (12.40%)	21 / 123 (17.07%)
occurrences (all)	13	22	25
Dizziness			
subjects affected / exposed	10 / 123 (8.13%)	9 / 121 (7.44%)	10 / 123 (8.13%)
occurrences (all)	11	9	14
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	6 / 123 (4.88%)	3 / 121 (2.48%)	7 / 123 (5.69%)
occurrences (all)	6	7	10
Anaemia			
subjects affected / exposed	8 / 123 (6.50%)	8 / 121 (6.61%)	7 / 123 (5.69%)
occurrences (all)	11	8	7
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	15 / 123 (12.20%)	6 / 121 (4.96%)	7 / 123 (5.69%)
occurrences (all)	16	36	8
Fatigue			
subjects affected / exposed	15 / 123 (12.20%)	12 / 121 (9.92%)	19 / 123 (15.45%)
occurrences (all)	17	16	20
Oedema peripheral			
subjects affected / exposed	8 / 123 (6.50%)	5 / 121 (4.13%)	5 / 123 (4.07%)
occurrences (all)	8	5	5

Pyrexia			
subjects affected / exposed	7 / 123 (5.69%)	6 / 121 (4.96%)	6 / 123 (4.88%)
occurrences (all)	11	8	6
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	87 / 123 (70.73%)	11 / 121 (9.09%)	64 / 123 (52.03%)
occurrences (all)	235	11	130
Abdominal pain upper			
subjects affected / exposed	9 / 123 (7.32%)	9 / 121 (7.44%)	7 / 123 (5.69%)
occurrences (all)	9	9	8
Dyspepsia			
subjects affected / exposed	8 / 123 (6.50%)	0 / 121 (0.00%)	4 / 123 (3.25%)
occurrences (all)	10	0	4
Nausea			
subjects affected / exposed	28 / 123 (22.76%)	13 / 121 (10.74%)	28 / 123 (22.76%)
occurrences (all)	32	17	46
Stomatitis			
subjects affected / exposed	23 / 123 (18.70%)	5 / 121 (4.13%)	16 / 123 (13.01%)
occurrences (all)	29	5	26
Vomiting			
subjects affected / exposed	16 / 123 (13.01%)	1 / 121 (0.83%)	19 / 123 (15.45%)
occurrences (all)	17	1	28
Cheilitis			
subjects affected / exposed	7 / 123 (5.69%)	0 / 121 (0.00%)	1 / 123 (0.81%)
occurrences (all)	8	0	1
Respiratory, thoracic and mediastinal disorders			
Nasal dryness			
subjects affected / exposed	7 / 123 (5.69%)	1 / 121 (0.83%)	3 / 123 (2.44%)
occurrences (all)	8	1	3
Epistaxis			
subjects affected / exposed	10 / 123 (8.13%)	0 / 121 (0.00%)	8 / 123 (6.50%)
occurrences (all)	11	0	10
Dyspnoea			
subjects affected / exposed	7 / 123 (5.69%)	8 / 121 (6.61%)	9 / 123 (7.32%)
occurrences (all)	7	8	10
Cough			

subjects affected / exposed	12 / 123 (9.76%)	17 / 121 (14.05%)	16 / 123 (13.01%)
occurrences (all)	14	20	18
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	14 / 123 (11.38%)	2 / 121 (1.65%)	8 / 123 (6.50%)
occurrences (all)	14	2	8
Rash maculo-papular			
subjects affected / exposed	7 / 123 (5.69%)	0 / 121 (0.00%)	7 / 123 (5.69%)
occurrences (all)	10	0	11
Rash			
subjects affected / exposed	43 / 123 (34.96%)	3 / 121 (2.48%)	36 / 123 (29.27%)
occurrences (all)	64	3	51
Pruritus			
subjects affected / exposed	11 / 123 (8.94%)	2 / 121 (1.65%)	11 / 123 (8.94%)
occurrences (all)	14	2	13
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	13 / 123 (10.57%)	1 / 121 (0.83%)	11 / 123 (8.94%)
occurrences (all)	13	1	11
Dry skin			
subjects affected / exposed	11 / 123 (8.94%)	0 / 121 (0.00%)	11 / 123 (8.94%)
occurrences (all)	12	0	11
Dermatitis acneiform			
subjects affected / exposed	16 / 123 (13.01%)	2 / 121 (1.65%)	11 / 123 (8.94%)
occurrences (all)	25	2	15
Skin fissures			
subjects affected / exposed	7 / 123 (5.69%)	2 / 121 (1.65%)	3 / 123 (2.44%)
occurrences (all)	8	2	3
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 123 (4.07%)	4 / 121 (3.31%)	12 / 123 (9.76%)
occurrences (all)	5	4	14
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	22 / 123 (17.89%)	15 / 121 (12.40%)	19 / 123 (15.45%)
occurrences (all)	29	20	23
Back pain			

subjects affected / exposed	9 / 123 (7.32%)	10 / 121 (8.26%)	12 / 123 (9.76%)
occurrences (all)	10	13	13
Bone pain			
subjects affected / exposed	7 / 123 (5.69%)	7 / 121 (5.79%)	4 / 123 (3.25%)
occurrences (all)	8	8	4
Myalgia			
subjects affected / exposed	7 / 123 (5.69%)	8 / 121 (6.61%)	6 / 123 (4.88%)
occurrences (all)	7	12	7
Pain in extremity			
subjects affected / exposed	11 / 123 (8.94%)	5 / 121 (4.13%)	12 / 123 (9.76%)
occurrences (all)	13	6	14
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	7 / 123 (5.69%)	5 / 121 (4.13%)	0 / 123 (0.00%)
occurrences (all)	8	5	0
Nasopharyngitis			
subjects affected / exposed	8 / 123 (6.50%)	10 / 121 (8.26%)	6 / 123 (4.88%)
occurrences (all)	10	13	7
Paronychia			
subjects affected / exposed	39 / 123 (31.71%)	0 / 121 (0.00%)	21 / 123 (17.07%)
occurrences (all)	73	0	35
Upper respiratory tract infection			
subjects affected / exposed	13 / 123 (10.57%)	7 / 121 (5.79%)	8 / 123 (6.50%)
occurrences (all)	22	8	15
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	22 / 123 (17.89%)	4 / 121 (3.31%)	18 / 123 (14.63%)
occurrences (all)	25	4	20
Hypokalaemia			
subjects affected / exposed	9 / 123 (7.32%)	0 / 121 (0.00%)	8 / 123 (6.50%)
occurrences (all)	16	0	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 February 2013	Amendment 1: Country specific amendment for France. Protocol appendices 3 and 4 were updated to include the Diarrhea Management Guidelines and Dermatological Assessment Guidelines
23 July 2013	Amendment 2: Global amendment allowed entry of subjects who were receiving later lines of therapies, including at least one prior trastuzumab and chemotherapy regimen. Updates were made to inclusion/exclusion criteria; changes were made to prohibited medications (removal of restrictions around bisphosphonate use, allowance of denosumab, clarification on permitted use of radiotherapy, additions to prohibited medications table).
29 January 2014	Amendment 3: Country-specific amendment for France. Updates to protocol was done to include management guidelines for treatment of prolonged QT/QTc and a reference to a list of known drugs that cause QT/QTc prolongations were provided. Updates made to Dermatological Assessment Guidelines.
10 December 2014	Amendment 4: Country-specific amendment for China. Updates were done to protocol to adjust the time period of SAE collection in accordance with China regulations
18 March 2016	Amendment 5: Global amendment: Since study EGF114299 is a post-approval commitment to both the CHMP and the FDA, these regulatory agencies were consulted in light of the study enrollment challenges in this subject population (CHMP in October 2015 and FDA in September 2015). The primary endpoint was changed from OS to PFS. In addition, the amendment introduced the following changes: Secondary endpoints were updated, and survival follow-up removed The revised sample size was changed to approximately 345 subjects Country-specific amendments No. 3 and 4 for France and China, respectively, were included in this global amendment for harmonization purposes as it also applies to all countries Protocol appendices 3 and 4 were updated to include Diarrhea Management Guidelines and Dermatological Assessment Guidelines Protocol Section 5.8.4 and Section 6.2 were updated to include management guidelines for prolonged QT/QTc and to provide a reference to a list of drugs known to cause QT/QTc prolongations Protocol Section 7.3.3.5.was updated to adjust the time period of SAE collection in accordance with China regulations
19 May 2016	Amendment 6: Deleted or replaced references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship; administrative changes to align with Novartis processes and procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported