Clinical trial results:
A randomized, multicenter open-label phase III study of neoadjuvant lapatinib, trastuzumab and their combination plus paclitaxel in women with HER2/ErbB2 positive primary breast cancer

Summary

EudraCT number	2006-000564-81
Trial protocol	FR DE BE GB LT GR HU ES IT SE
Global end of trial date	23 December 2019

Results information

Result version number	v3 (current)
This version publication date	09 September 2021
First version publication date	06 January 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	EGF106903

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00553358
WHO universal trial number (UTN)	-
Other trial identifiers	CLAP016B2302: CLAP016B2302

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	23 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate and compare the rate of pathological complete response (pCR) at the time of surgery in subjects with HER2 overexpressing or amplified operable breast cancer randomized to lapatinib followed by lapatinib plus paclitaxel versus trastuzumab followed by trastuzumab plus paclitaxel versus lapatinib in combination with trastuzumab followed by lapatinib, trastuzumab plus paclitaxel.

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 January 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: 17
Country: Number of subjects enrolled	Belgium: 33
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Czechia: 10
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 49
Country: Number of subjects enrolled	Hong Kong: 7
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	India: 12
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Korea, Republic of: 27
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Peru: 39
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Russian Federation: 25

Country: Number of subjects enrolled	South Africa: 26
Country: Number of subjects enrolled	Spain: 45
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Taiwan: 57
Country: Number of subjects enrolled	Ukraine: 23
Country: Number of subjects enrolled	United Kingdom: 12
Worldwide total number of subjects	455
EEA total number of subjects	201

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)	403
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This was a parallel group, three-arm, randomized, multicenter, open-label phase III study. The study compared the efficacy and tolerability of neoadjuvant lapatinib and paclitaxel, versus trastuzumab and paclitaxel, versus the combination of lapatinib with trastuzumab and paclitaxel.

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 1000/750 mg + Trastuzumab 2 mg/kg

Arm description:

Oral lapatinib 1000 mg daily plus trastuzumab 4 mg/kg IV load followed by 2 mg/kg IV weekly for 6 weeks, followed by lapatinib 750 mg daily plus trastuzumab (2 mg/kg IV weekly) plus weekly paclitaxel (80 mg/m^2 IV) for an additional 12 weeks

Arm type	Experimental
Investigational medicinal product name	Lapatinib
Investigational medicinal product code	LAP016
Other name	GW572016
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Oral lapatinib (1000 mg daily) plus trastuzumab (4 mg/kg iv load followed by 2 mg/kg iv weekly) for 6 weeks, followed by lapatinib (750 mg daily) plus trastuzumab (2 mg/kg iv weekly) plus weekly paclitaxel (80 mg/m2 iv) for an additional 12 weeks.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solvent for parenteral use
Routes of administration	Parenteral use

Dosage and administration details:

Oral lapatinib (1000 mg daily) plus trastuzumab (4 mg/kg iv load followed by 2 mg/kg iv weekly) for 6 weeks, followed by lapatinib (750 mg daily) plus trastuzumab (2 mg/kg iv weekly) plus weekly paclitaxel (80 mg/m2 iv) for an additional 12 weeks.

Arm title	Lapatinib 1500 mg

Arm description:

Oral lapatinib (1500 milligrams [mg] daily) for 6 weeks, followed by lapatinib plus weekly paclitaxel (80 mg per meters squared [mg/m^2]) intravenous (IV) for an additional 12 weeks

Arm type	Experimental
Investigational medicinal product name	Lapatinib
Investigational medicinal product code	LAP016
Other name	GW572016
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Oral lapatinib (1500 mg daily) for 6 weeks, followed by lapatinib plus weekly paclitaxel (80 mg/m2 iv) for an additional 12 weeks

Arm title	Trastuzumab 2 mg/kg

Arm description:

Trastuzumab (4 mg/kilograms [kg] IV load followed by 2 mg/kg IV weekly) for 6 weeks, followed by trastuzumab plus weekly paclitaxel (80 mg/m^2 IV) for an additional 12 weeks

Arm type	Active comparator
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solvent for parenteral use
Routes of administration	Parenteral use

Dosage and administration details:

Trastuzumab (4 mg/kg iv load followed by 2 mg/kg iv weekly) for 6 weeks, followed by trastuzumab plus weekly paclitaxel (80 mg/m2 iv) for an additional 12 weeks

Number of subjects in period 1	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg
Started	152	154	149
Completed	73	58	61
Not completed	79	96	88
Died during clinical follow-up	25	29	32
Randomized but did not receive treatment	3	3	1
Died after clinical follow-up ended	1	2	-
W/drew (survival only)–alive at end of f/up	1	1	1
Not dead but were last f/up prior to year 10	4	2	2
Lost to follow-up	22	26	18
Withdrew completely	23	33	34

Baseline characteristics

Reporting groups	
Reporting group title	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg
Reporting group description:	
Oral lapatinib 1000 mg daily plus trastuzumab 4 mg/kg IV load followed by 2 mg/kg IV weekly for 6 weeks, followed by lapatinib 750 mg daily plus trastuzumab (2 mg/kg IV weekly) plus weekly paclitaxel (80 mg/m^2 IV) for an additional 12 weeks	
Reporting group title	Lapatinib 1500 mg
Reporting group description:	
Oral lapatinib (1500 milligrams [mg] daily) for 6 weeks, followed by lapatinib plus weekly paclitaxel (80 mg per meters squared [mg/m^2]) intravenous (IV) for an additional 12 weeks	
Reporting group title	Trastuzumab 2 mg/kg
Reporting group description:	
Trastuzumab (4 mg/kilograms [kg] IV load followed by 2 mg/kg IV weekly) for 6 weeks, followed by trastuzumab plus weekly paclitaxel (80 mg/m^2 IV) for an additional 12 weeks	

Reporting group values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg
Number of subjects	152	154	149
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)	130	137	136
From 65-84 years	22	17	13
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	152	154	149
Male	0	0	0
GenderNIH Units: Subjects			
Female	152	154	149
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	15	13	14
Asian - Central/South	5	7	5
Asian - East	31	30	28
Asian - South East	2	0	0
Black or African American/African Heritage	4	0	4
White - Arabic/North African Heritage	3	6	5

White - Caucasian European Heritage	92	97	93
Missing	0	1	0
Number of participants with tumor cells of the indicated histologic grade			
Histologic grade, also called differentiation, refers to how much the tumor cells resemble normal cells of the same tissue type.			
Units: Subjects			
Well differentiated	5	2	5
Moderately differentiated	63	56	53
Poorly differentiated	64	73	68
Differentiation cannot be assessed	20	22	23
Missing	0	1	0
Number of participants with lymph nodes (LNs) of the indicated clinical N stage			
Clinical N stage is an evaluation/staging of LN status through physical examination. N0, no regional LN metastasis; N1, metastasis to movable ipsilateral axillary LNs (IALNs); N2a, metastasis in IALNs fixed to one another (matted) or the other structures; N2b, metastasis only in clinically apparent ipsilateral internal mammary nodes and in the absence of clinically evident axillary LN metastasis; N3a, metastasis in ipsilateral infraclavicular LNs; N3b, metastasis in ipsilateral internal mammary LNs fixed and axillary LN; N3c, metastasis in ipsilateral subclavicar LNs; Nx, not assessed.			
Units: Subjects			
N 0	48	34	41
N 1	80	95	85
N2 (including N2a and N2b)	15	19	13
N3 (including N3a, N3b, and N3c)	6	6	7
N x	3	0	3
Number of participants with the indicated IHC results			
An Immunohistochemistry (IHC) test gives a score of 0 to 3+, which indicates the amount of Human Epidermal Growth Factor (HER2) receptor proteins on the cancer cells in the sample tissue. A positive score (3+) indicates that HER2 receptor protein is present, a negative score (0-1+) indicates that no HER2 receptor protein is present, and an equivocal score (2+) indicates uncertainty and a result that is open for interpretation. Equivocal results require additional testing. “Not applicable” refers to the number of participants who did not have IHC testing done.			
Units: Subjects			
Not applicable	61	60	53
Equivocal: Score of 2+	8	9	5
Positive: Score of 3+	76	81	89
Negative: Score of 0-1+	3	0	1
Non interpretable	4	4	1
Number of participants with the indicated FISH results			
The Fluorescent In Situ Hybridization (FISH) assay was used to determine the overexpression and/or amplification of HER2 in the invasive component of the primary tumor. Amplified indicates that the cell is overexpressing copies of the HER2 gene. Not amplified indicates that there is no overexpression of copies of the HER2 gene. “Not applicable” refers to the number of participants who did not have the FISH assay performed.			
Units: Subjects			
Not applicable	41	38	42
Amplified	109	115	105
Not amplified	1	1	2
Not interpretable	1	0	0
AgeContinuous			
Units: Years			
median	50.0	50.0	49.0
full range (min-max)	25 to 80	28 to 79	23 to 77

Reporting group values	Total		
Number of subjects	455		
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)	403		
From 65-84 years	52		
85 years and over	0		
Gender categorical Units: Subjects			
Female	455		
Male	0		
GenderNIH Units: Subjects			
Female	455		
Male	0		
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	42		
Asian - Central/South	17		
Asian - East	89		
Asian - South East	2		
Black or African American/African Heritage	8		
White - Arabic/North African Heritage	14		
White - Caucasian European Heritage	282		
Missing	1		
Number of participants with tumor cells of the indicated histologic grade			
Histologic grade, also called differentiation, refers to how much the tumor cells resemble normal cells of the same tissue type.			
Units: Subjects			
Well differentiated	12		
Moderately differentiated	172		
Poorly differentiated	205		
Differentiation cannot be assessed	65		
Missing	1		
Number of participants with lymph nodes (LNs) of the indicated clinical N stage			
Clinical N stage is an evaluation/staging of LN status through physical examination. N0, no regional LN metastasis; N1, metastasis to movable ipsilateral axillary LNs (IALNs); N2a, metastasis in IALNs fixed to one another (matted) or the other structures; N2b, metastasis only in clinically apparent ipsilateral internal mammary nodes and in the absence of clinically evident axillary LN metastasis; N3a, metastasis in ipsilateral infraclavicular LNs; N3b, metastasis in ipsilateral internal mammary LNs fixed and axillary LN; N3c, metastasis in ipsilateral subclavicar LNs; Nx, not assessed.			

Units: Subjects			
N 0	123		
N 1	260		
N2 (including N2a and N2b)	47		
N3 (including N3a, N3b, and N3c)	19		
N x	6		
Number of participants with the indicated IHC results			
An Immunohistochemistry (IHC) test gives a score of 0 to 3+, which indicates the amount of Human Epidermal Growth Factor (HER2) receptor proteins on the cancer cells in the sample tissue. A positive score (3+) indicates that HER2 receptor protein is present, a negative score (0-1+) indicates that no HER2 receptor protein is present, and an equivocal score (2+) indicates uncertainty and a result that is open for interpretation. Equivocal results require additional testing. "Not applicable" refers to the number of participants who did not have IHC testing done.			
Units: Subjects			
Not applicable	174		
Equivocal: Score of 2+	22		
Positive: Score of 3+	246		
Negative: Score of 0-1+	4		
Non interpretable	9		
Number of participants with the indicated FISH results			
The Fluorescent In Situ Hybridization (FISH) assay was used to determine the overexpression and/or amplification of HER2 in the invasive component of the primary tumor. Amplified indicates that the cell is overexpressing copies of the HER2 gene. Not amplified indicates that there is no overexpression of copies of the HER2 gene. "Not applicable" refers to the number of participants who did not have the FISH assay performed.			
Units: Subjects			
Not applicable	121		
Amplified	329		
Not amplified	4		
Not interpretable	1		
AgeContinuous			
Units: Years			
median			
full range (min-max)	-		

Subject analysis sets

Subject analysis set title	Overall
Subject analysis set type	Intention-to-treat
Subject analysis set description: Overall - of the 3 arms	
Subject analysis set title	pathological Complete Response (pCR)
Subject analysis set type	Intention-to-treat
Subject analysis set description: locoregional pathological Complete Response (pCR)	
Subject analysis set title	No pathological Complete Response (pCR)
Subject analysis set type	Intention-to-treat
Subject analysis set description: no locoregional pathological Complete Response (pCR)	
Subject analysis set title	pathological Complete Response (pCR)
Subject analysis set type	Intention-to-treat
Subject analysis set description: locoregional pathological Complete Response (pCR)	

Subject analysis set title	No pathological Complete Response (pCR)
Subject analysis set type	Intention-to-treat
Subject analysis set description: no locoregional pathological Complete Response (pCR)	
Subject analysis set title	Overall
Subject analysis set type	Intention-to-treat
Subject analysis set description: Overall - of the 3 arms	

Reporting group values	Overall	pathological Complete Response (pCR)	No pathological Complete Response (pCR)
Number of subjects	410	136	274
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)	403		
From 65-84 years	52		
85 years and over	0		
Gender categorical Units: Subjects			
Female	455		
Male	0		
GenderNIH Units: Subjects			
Female			
Male			
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native			
Asian - Central/South			
Asian - East			
Asian - South East			
Black or African American/African Heritage			
White - Arabic/North African Heritage			
White - Caucasian European Heritage			
Missing			
Number of participants with tumor cells of the indicated histologic grade			
Histologic grade, also called differentiation, refers to how much the tumor cells resemble normal cells of the same tissue type.			
Units: Subjects			
Well differentiated			
Moderately differentiated			
Poorly differentiated			

Differentiation cannot be assessed Missing			
Number of participants with lymph nodes (LNs) of the indicated clinical N stage			
Clinical N stage is an evaluation/staging of LN status through physical examination. N0, no regional LN metastasis; N1, metastasis to movable ipsilateral axillary LNs (IALNs); N2a, metastasis in IALNs fixed to one another (matted) or the other structures; N2b, metastasis only in clinically apparent ipsilateral internal mammary nodes and in the absence of clinically evident axillary LN metastasis; N3a, metastasis in ipsilateral infraclavicular LNs; N3b, metastasis in ipsilateral internal mammary LNs fixed and axillary LN; N3c, metastasis in ipsilateral subclavicar LNs; Nx, not assessed.			
Units: Subjects			
N 0 N 1 N2 (including N2a and N2b) N3 (including N3a, N3b, and N3c) N x			
Number of participants with the indicated IHC results			
An Immunohistochemistry (IHC) test gives a score of 0 to 3+, which indicates the amount of Human Epidermal Growth Factor (HER2) receptor proteins on the cancer cells in the sample tissue. A positive score (3+) indicates that HER2 receptor protein is present, a negative score (0-1+) indicates that no HER2 receptor protein is present, and an equivocal score (2+) indicates uncertainty and a result that is open for interpretation. Equivocal results require additional testing. "Not applicable" refers to the number of participants who did not have IHC testing done.			
Units: Subjects			
Not applicable Equivocal: Score of 2+ Positive: Score of 3+ Negative: Score of 0-1+ Non interpretable			
Number of participants with the indicated FISH results			
The Fluorescent In Situ Hybridization (FISH) assay was used to determine the overexpression and/or amplification of HER2 in the invasive component of the primary tumor. Amplified indicates that the cell is overexpressing copies of the HER2 gene. Not amplified indicates that there is no overexpression of copies of the HER2 gene. "Not applicable" refers to the number of participants who did not have the FISH assay performed.			
Units: Subjects			
Not applicable Amplified Not amplified Not interpretable			
AgeContinuous Units: Years median full range (min-max)			

Reporting group values	pathological Complete Response (pCR)	No pathological Complete Response (pCR)	Overall
Number of subjects	137	283	420
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Gender categorical Units: Subjects			
Female Male			
GenderNIH Units: Subjects			
Female Male			
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native Asian - Central/South Asian - East Asian - South East Black or African American/African Heritage White - Arabic/North African Heritage White - Caucasian European Heritage Missing			
Number of participants with tumor cells of the indicated histologic grade			
Histologic grade, also called differentiation, refers to how much the tumor cells resemble normal cells of the same tissue type.			
Units: Subjects			
Well differentiated Moderately differentiated Poorly differentiated Differentiation cannot be assessed Missing			
Number of participants with lymph nodes (LNs) of the indicated clinical N stage			
Clinical N stage is an evaluation/staging of LN status through physical examination. N0, no regional LN metastasis; N1, metastasis to movable ipsilateral axillary LNs (IALNs); N2a, metastasis in IALNs fixed to one another (matted) or the other structures; N2b, metastasis only in clinically apparent ipsilateral internal mammary nodes and in the absence of clinically evident axillary LN metastasis; N3a, metastasis in ipsilateral infraclavicular LNs; N3b, metastasis in ipsilateral internal mammary LNs fixed and axillary LN; N3c, metastasis in ipsilateral subclavicar LNs; Nx, not assessed.			
Units: Subjects			
N 0 N 1 N2 (including N2a and N2b) N3 (including N3a, N3b, and N3c) N x			
Number of participants with the indicated IHC results			
An Immunohistochemistry (IHC) test gives a score of 0 to 3+, which indicates the amount of Human			

Epidermal Growth Factor (HER2) receptor proteins on the cancer cells in the sample tissue. A positive score (3+) indicates that HER2 receptor protein is present, a negative score (0-1+) indicates that no HER2 receptor protein is present, and an equivocal score (2+) indicates uncertainty and a result that is open for interpretation. Equivocal results require additional testing. “Not applicable” refers to the number of participants who did not have IHC testing done.			
Units: Subjects			
Not applicable Equivocal: Score of 2+ Positive: Score of 3+ Negative: Score of 0-1+ Non interpretable			
Number of participants with the indicated FISH results			
The Fluorescent In Situ Hybridization (FISH) assay was used to determine the overexpression and/or amplification of HER2 in the invasive component of the primary tumor. Amplified indicates that the cell is overexpressing copies of the HER2 gene. Not amplified indicates that there is no overexpression of copies of the HER2 gene. “Not applicable” refers to the number of participants who did not have the FISH assay performed.			
Units: Subjects			
Not applicable Amplified Not amplified Not interpretable			
AgeContinuous Units: Years median full range (min-max)			

End points

End points reporting groups

Reporting group title	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg
Reporting group description:	
Oral lapatinib 1000 mg daily plus trastuzumab 4 mg/kg IV load followed by 2 mg/kg IV weekly for 6 weeks, followed by lapatinib 750 mg daily plus trastuzumab (2 mg/kg IV weekly) plus weekly paclitaxel (80 mg/m^2 IV) for an additional 12 weeks	
Reporting group title	Lapatinib 1500 mg
Reporting group description:	
Oral lapatinib (1500 milligrams [mg] daily) for 6 weeks, followed by lapatinib plus weekly paclitaxel (80 mg per meters squared [mg/m^2]) intravenous (IV) for an additional 12 weeks	
Reporting group title	Trastuzumab 2 mg/kg
Reporting group description:	
Trastuzumab (4 mg/kilograms [kg] IV load followed by 2 mg/kg IV weekly) for 6 weeks, followed by trastuzumab plus weekly paclitaxel (80 mg/m^2 IV) for an additional 12 weeks	
Subject analysis set title	Overall
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Overall - of the 3 arms	
Subject analysis set title	pathological Complete Response (pCR)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
locoregional pathological Complete Response (pCR)	
Subject analysis set title	No pathological Complete Response (pCR)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
no locoregional pathological Complete Response (pCR)	
Subject analysis set title	pathological Complete Response (pCR)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
locoregional pathological Complete Response (pCR)	
Subject analysis set title	No pathological Complete Response (pCR)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
no locoregional pathological Complete Response (pCR)	
Subject analysis set title	Overall
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Overall - of the 3 arms	

Primary: Number of participants with pathological complete response (pCR) at the time of surgery

End point title	Number of participants with pathological complete response (pCR) at the time of surgery
End point description:	
Pathological complete response is defined as no invasive cancer in the breast or only non-invasive in situ cancer in the breast specimen. Surgical breast and axillary node resection specimens were evaluated for pathologic tumor response according to National Surgical Adjuvant Breast and Bowel Project (NSABP) guidelines, which do not take into account the histological nodal status.	
End point type	Primary
End point timeframe:	
Weeks 20 to 22	

End point values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	154	149	
Units: participants	78	38	44	

Statistical analyses

Statistical analysis title	Participants with pCR at the time of surgery
Comparison groups	Lapatinib 1500 mg v Trastuzumab 2 mg/kg
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3416
Method	Binomial
Parameter estimate	Percentage of participants with pCR
Point estimate	-4.85
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-17.6
upper limit	8.16

Statistical analysis title	Participants with pCR at the time of surgery
Comparison groups	Trastuzumab 2 mg/kg v Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0001
Method	Binomial
Parameter estimate	Percentage of participants with pCR
Point estimate	21.79
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	9.08
upper limit	34.23

Secondary: Number of participants with overall response at Week 6

End point title	Number of participants with overall response at Week 6

End point description:

The number of participants with overall response (complete response and/or partial response) was evaluated using World Health Organization (WHO) criteria by clinical examination and by mammography and breast echography with bi-dimensional measurements at Week 6. As per WHO criteria: complete response is defined as the disappearance of all lesions; partial response is defined as a greater than 50% decrease in the sum of products of the greatest length and width of the largest lesion; progressive disease is defined as a greater than 25% increase in the sum of products of all measurable lesions.

End point type	Secondary

End point timeframe:

Week 6

End point values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	154	149	
Units: participants				
Overall Response	102	81	45	
No Change	33	57	81	
Progressive Disease	2	5	11	
Not Evaluated	12	7	9	
Missing Data	3	4	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response at the time of surgery

End point title	Overall response at the time of surgery

End point description:

The number of participants with overall response (complete response and/or partial response) was evaluated using WHO criteria by clinical examination and mammography and breast echography with bi-dimensional measurements at the time of surgery (Weeks 20 to 22). As per WHO criteria: complete response is defined as the disappearance of all lesions; partial response is defined as a greater than 50% decrease in the sum of products of the greatest length and width of the largest lesion; progressive disease is defined as a greater than 25% increase in the sum of products of all measurable lesions.

End point type	Secondary

End point timeframe:

Time of surgery (Weeks 20 to 22)

End point values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	154	149	
Units: participants				
Overall Response	122	114	105	
No Change	7	8	16	
Progressive Disease	1	0	2	
Not Evaluated	14	19	20	
Missing Data	8	13	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with negative lymph nodes at the time of surgery

End point title	Number of participants with negative lymph nodes at the time of surgery

End point description:

Participants were assessed for node-negative lymph nodes at the time of surgery. As per the pathological TNM (Tumor, Node, Metastases) classification (pTNM) of malignant tumors: pN, absence or presence and extent of regional lymph node metastasis. Node-negative (pN0) participants had no regional lymph node metastasis. Although not assessed in this measure, pT is the extent of primary tumor, and pM is the absence or presence of distant metastasis.

End point type	Secondary

End point timeframe:

Time of surgery (Weeks 20 to 22)

End point values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	139	140	
Units: participants	100	72	82	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with actual indicated surgery

End point title	Number of participants with actual indicated surgery

End point description:

Participants were assessed for the type of surgery they underwent for breast cancer. Non-conservative

surgery is defined as a radical or modified radical mastectomy. Conservative surgery is comprised of a lumpectomy, a quadrantectomy/segmentectomy, or a partial mastectomy. Participants who were not assessed as being candidates for non-conservative or conservative surgery were classified as non-operable.

End point type	Secondary

End point timeframe:

At surgery (Weeks 20 to 22)

End point values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	154	149	
Units: participants				
Conservative	63	66	58	
Non-conservative	80	77	85	
Non-operable	9	11	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in tumor size at Week 6 and at surgery

End point title	Mean change from baseline in tumor size at Week 6 and at surgery

End point description:

Mean change from baseline in tumor in tumor size. Change from baseline in tumor size was defined as tumor size at Week 6/ surgery (Weeks 20 to 22) minus tumor size at baseline. The difference in treatment arms was estimated for Lapatinib 1500 mg versus Trastuzumab 2 mg/kg and for Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg versus Trastuzumab 2 mg/kg.

End point type	Secondary

End point timeframe:

Week 6 and surgery (Weeks 20 to 22)

End point values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	154	149	
Units: millimeters				
arithmetic mean (standard deviation)				
Week 6	-25.77 (± 19.91)	-20.45 (± 18.43)	-13.42 (± 16.44)	
Surgery (Weeks 20 to 22)	-43.59 (± 26.88)	-41.01 (± 23.81)	-35.47 (± 22.95)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants starting paclitaxel before completing 6 weeks of treatment with either lapatinib or trastuzumab

End point title	Number of participants starting paclitaxel before completing 6 weeks of treatment with either lapatinib or trastuzumab

End point description:

Participants with progressive disease at 4 week assessment that were permitted to commence treatment with paclitaxel.

End point type	Secondary

End point timeframe:

Week 6

End point values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	149	149	146	
Units: participants	6	8	12	

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free Survival (EFS) - Median clinical follow-up

End point title	Event-free Survival (EFS) - Median clinical follow-up

End point description:

Event free survival (EFS) is defined as the time from randomization to first EFS event. For subjects who had breast cancer surgery, EFS events were post-surgery breast cancer relapse, second primary malignancy or death without recurrence. For subjects who did not have breast cancer surgery, EFS events were death during clinical follow-up or non-completion of any neoadjuvant investigational product due to disease progression.

End point type	Secondary

End point timeframe:

From randomization up to approximately year 10

End point values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	154	149	
Units: years				
median (confidence interval 95%)	9.69 (9.55 to 9.73)	9.60 (8.21 to 9.69)	9.66 (9.50 to 9.72)	

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free Survival (EFS) - Events and censoring

End point title	Event-free Survival (EFS) - Events and censoring

End point description:

Event free survival (EFS) is defined as the time from randomization to first EFS event. For subjects who had breast cancer surgery, EFS events were post-surgery breast cancer relapse, second primary malignancy or death without recurrence. For subjects who did not have breast cancer surgery, EFS events were death during clinical follow-up or non-completion of any neoadjuvant investigational product due to disease progression.

End point type	Secondary

End point timeframe:

From randomization up to approximately year 10

End point values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	154	149	
Units: Number of Participants				
Number of subjects with EFS events	43	47	47	
Number of subjects censored - total	109	107	102	
No. censored - follow-up ongoing	0	0	0	
No. censored -follow-up ended - total	103	105	99	
No. censored - f/up ended - compl. study f/up	61	49	58	
No. censored - f/up ended - Lost to follow-up	17	20	10	
No. cens. -f/up ended - W/d (but consent for f/u)	3	6	4	
No. censored - Clinical f/up ended - Withdrew	22	30	27	
Number of subjects censored - Other	6	2	3	

Statistical analyses

Statistical analysis title	Event-free Survival (EFS) - Events and censoring
Comparison groups	Lapatinib 1500 mg v Trastuzumab 2 mg/kg
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.981 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.52

Notes:

[1] - The two-sided stratified log-rank test was implemented as the score test from the Cox model.

Statistical analysis title	Event-free Survival (EFS) - Events and censoring
Comparison groups	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg v Trastuzumab 2 mg/kg
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.548 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.878
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.34

Notes:

[2] - The two-sided stratified log-rank test was implemented as the score test from the Cox model.

Secondary: Overall Survival (OS) - Median survival follow-up

End point title	Overall Survival (OS) - Median survival follow-up

End point description:

Overall survival is defined as the period from randomization until death (from any cause). OS was assessed annually for up to 10 years after the randomization of the last participant into the study.

End point type	Secondary

End point timeframe:

From randomization up to approximately year 10

End point values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	154	149	
Units: years				
median (confidence interval 95%)	9.70 (9.60 to 9.76)	9.62 (8.86 to 9.67)	9.64 (9.35 to 9.71)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Deaths and censoring

End point title	Overall Survival (OS) - Deaths and censoring

End point description:

Overall survival is defined as the period from randomization until death (from any cause). OS was assessed annually for up to 10 years after the randomization of the last participant into the study.

End point type	Secondary

End point timeframe:

From randomization up to approximately year 10

End point values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	154	149	
Units: Number of Participants				
Number of deaths due to any cause	26	31	32	
Number of subjects censored - total	126	123	117	
No. censored - Survival follow-up ongoing	0	0	0	
No. censored -Survival follow-up ended - total	120	121	114	
No. censored - f/up ended - Compl. f/up	74	59	62	
No. censored - Survival f/up ended - Lost to f/up	22	27	18	
No. censored - Survival f/up ended - Withdrew	24	35	34	
Number of subjects censored - Other	6	2	3	

Statistical analyses

Statistical analysis title	Overall Survival (OS) - Deaths and censoring
Comparison groups	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg v Trastuzumab 2 mg/kg

Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.379 [3]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.788
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.34

Notes:

[3] - The two-sided stratified log-rank test was implemented as the score test from the Cox model.

Statistical analysis title	Overall Survival (OS) - Deaths and censoring
Comparison groups	Lapatinib 1500 mg v Trastuzumab 2 mg/kg
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.88 [4]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.962
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.6

Notes:

[4] - The two-sided stratified log-rank test was implemented as the score test from the Cox model.

Secondary: Assess associations between locoregional pathological Complete Response (pCR) and Event-free Survival (EFS) - Median clinical follow-up (EFS landmark population)

End point title	Assess associations between locoregional pathological Complete Response (pCR) and Event-free Survival (EFS) - Median clinical follow-up (EFS landmark population)

End point description:

The landmark date is 30 weeks after a subject's randomization. Subjects with missing pCR status were not included in the landmark analysis.

Clinical follow-up is the period during which the patient is monitored such that all recurrence or second primary malignancy (SPM) or contralateral breast cancer (CBC) events would be reported. Patients are considered in clinical follow-up from randomisation until one of the following occurs: lost to follow-up, withdrawal of consent, end of follow-up due to completion of year 10 visit, termination of study follow-up, or death.

End point type	Secondary

End point timeframe:

up to year 10

End point values	Overall	pathological Complete Response (pCR)	No pathological Complete Response (pCR)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	410	136	274	
Units: years				
median (confidence interval 95%)				
Median - total in EFS landmark analysis	9.09 (9.03 to 9.13)	9.05 (8.86 to 9.14)	9.11 (9.05 to 9.14)	
Median - lapatinib + trastuzumab arm(n=67,71,138)	9.12 (8.97 to 9.15)	9.13 (8.97 to 9.23)	9.10 (7.24 to 9.15)	
Median - lapatinib arm (n=30,104,134)	9.05 (8.23 to 9.12)	8.08 (6.08 to 9.12)	9.09 (8.52 to 9.19)	
Median - trastuzumab arm (n=39,99,138)	9.11 (8.96 to 9.17)	8.98 (8.38 to 9.21)	9.12 (9.03 to 9.25)	

Statistical analyses

Statistical analysis title	pCR v EFS
Statistical analysis description:	
Overall - All subjects in the EFS landmark analysis	
Comparison groups	pathological Complete Response (pCR) v No pathological Complete Response (pCR)
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00079
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.481
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.73

Statistical analysis title	pCR v EFS
Statistical analysis description:	
Subjects in the EFS landmark analysis in the lapatinib + trastuzumab arm	
Comparison groups	pathological Complete Response (pCR) v No pathological Complete Response (pCR)

Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.004
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.71

Statistical analysis title	pCR v EFS
Statistical analysis description:	
Subjects in the EFS landmark analysis in the lapatinib arm	
Comparison groups	pathological Complete Response (pCR) v No pathological Complete Response (pCR)
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.134
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.532
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	1.16

Statistical analysis title	pCR v EFS
Statistical analysis description:	
Subjects in the EFS landmark analysis in the trastuzumab arm	
Comparison groups	pathological Complete Response (pCR) v No pathological Complete Response (pCR)
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.163
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.601

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	1.2

Secondary: Assess associations between locoregional pathological Complete Response (pCR) and Event-free Survival (EFS) - Number of participants with EFS events (EFS landmark population)

End point title	Assess associations between locoregional pathological Complete Response (pCR) and Event-free Survival (EFS) - Number of participants with EFS events (EFS landmark population)

End point description:

The landmark date is 30 weeks after a subject's randomization. Subjects with missing pCR status were not included in the landmark analysis.

For patients who had breast cancer surgery, EFS events are post-surgery breast cancer relapse, second primary malignancy or death without recurrence. For patients who do not undergo breast cancer surgery, EFS events are death during clinical follow-up or non-completion of any neo-adjuvant investigational product due to disease progression or second primary malignancy or contralateral breast cancer.

End point type	Secondary

End point timeframe:

up to year 10

End point values	Overall	pathological Complete Response (pCR)	No pathological Complete Response (pCR)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	410	136	274	
Units: Number of participants				
All subjects with EFS events	127	29	98	
lapatinib + trastuzumab-w/ EFS events(n=67,71,138)	39	11	28	
lapatinib-w/ EFS events (n=30,104,134)	43	7	36	
trastuzumab-w/ EFS events (n=39,99,138)	45	11	34	

Statistical analyses

No statistical analyses for this end point

Secondary: Assess associations between locoregional pathological Complete Response (pCR) and and Overall Survival (OS) - Median clinical follow-up (OS landmark population)

End point title	Assess associations between locoregional pathological Complete Response (pCR) and and Overall Survival (OS) -

	Median clinical follow-up (OS landmark population)

End point description:

The landmark date is 30 weeks after a subject's randomization. Subjects with missing pCR status were not included in the landmark analysis.

Patients are considered in survival follow-up from randomisation until one of the following occurs: lost to follow-up, withdrawal of consent, end of follow-up due to completion of year 10 visit, termination of study follow-up, or death. For subjects with no death recorded in the database, time to death is censored.

End point type	Secondary

End point timeframe:

up to year 10

End point values	pathological Complete Response (pCR)	No pathological Complete Response (pCR)	Overall	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	137	283	420	
Units: years				
median (confidence interval 95%)				
median - all subjects in the OS landmark analysis	9.10 (8.97 to 9.18)	9.09 (9.03 to 9.12)	9.09 (9.04 to 9.13)	
median - lapatinib + trastuzumab arm (n=67,72,139)	9.14 (9.05 to 9.24)	9.09 (7.95 to 9.15)	9.12 (9.05 to 9.16)	
median - lapatinib arm (n=30,109,139)	8.31 (7.24 to 9.15)	9.08 (8.95 to 9.14)	9.07 (8.50 to 9.12)	
median - trastuzumab arm (n=40,102,142)	8.98 (8.02 to 9.21)	9.09 (8.51 to 9.15)	9.07 (8.86 to 9.14)	

Statistical analyses

Statistical analysis title	pCR v OS

Statistical analysis description:

Overall - All subjects in the OS landmark analysis

Comparison groups	pathological Complete Response (pCR) v No pathological Complete Response (pCR)
Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00041
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.366
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.63

Statistical analysis title	pCR v OS
Statistical analysis description:	
Subjects in the OS landmark analysis in the lapatinib arm	
Comparison groups	pathological Complete Response (pCR) v No pathological Complete Response (pCR)
Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.125
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.433
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	1.17

Statistical analysis title	pCR v OS
Statistical analysis description:	
Subjects in the OS landmark analysis in the trastuzumab arm	
Comparison groups	pathological Complete Response (pCR) v No pathological Complete Response (pCR)
Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.058
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.414
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	1

Statistical analysis title	pCR v OS
Statistical analysis description:	
Subjects in the OS landmark analysis in the lapatinib + trastuzumab arm	
Comparison groups	pathological Complete Response (pCR) v No pathological Complete Response (pCR)

Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.002
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.223
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.58

Secondary: Assess associations between locoregional pathological Complete Response (pCR) and and Overall Survival (OS) - Number of participants who died (OS landmark population).

End point title	Assess associations between locoregional pathological Complete Response (pCR) and and Overall Survival (OS) - Number of participants who died (OS landmark population).

End point description:

The landmark date is 30 weeks after a subject's randomization. Subjects with missing pCR status were not included in the landmark analysis. Includes deaths due to any cause.

End point type	Secondary

End point timeframe:

up to year 10

End point values	pathological Complete Response (pCR)	No pathological Complete Response (pCR)	Overall	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	137	283	420	
Units: Number of Participants				
Total No. in the OS landmark analysis who died	15	70	85	
n died - lapatinib + trastuzumab arm(n=67,72,139)	5	19	24	
n died - lapatinib arm (n=30,109,139)	4	26	30	
n died - trastuzumab arm (n=40,102,142)	6	25	31	

Statistical analyses

No statistical analyses for this end point

Secondary: To assess safety via a comparison of the three treatment arms - to measure on-treatment primary cardiac endpoints

End point title	To assess safety via a comparison of the three treatment arms - to measure on-treatment primary cardiac endpoints

End point description:

End point type	Secondary

End point timeframe:

Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of 31 weeks.

End point values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	149	151	148	
Units: Participants	2	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Metabolic Response Rate determined by Positron Emission Tomography/Computed Tomography (PET/CT)

End point title	Metabolic Response Rate determined by Positron Emission Tomography/Computed Tomography (PET/CT)

End point description:

Metabolic Response Rate determined by Positron Emission Tomography/Computed Tomography (PET/CT)

End point type	Secondary

End point timeframe:

Week 2 and Week 6

End point values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	26	26	
Units: Percentage of participants				
number (not applicable)				
MRR (%) Determined by PET/CT at week 2	95.0	66.7	56.5	
MRR (%) Determined by PET/CT at week 6	78.9	60.9	43.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with the Indicated Biomarker Expression - PIK3CA.

End point title	Percentage of Participants with the Indicated Biomarker Expression - PIK3CA.

End point description:

Biomarker levels of phosphatidylinositol 3-kinase (PI3K) catalytic subunit (PIK3CA) were assessed in participants at baseline.

End point type	Secondary

End point timeframe:

Baseline

End point values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	124	112	
Units: Percentage of participants	25	23	19	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with the Indicated Biomarker Expression - PTEN.

End point title	Percentage of Participants with the Indicated Biomarker Expression - PTEN.

End point description:

Biomarker levels of phosphate and tensin homolog deleted from chromosome 10 (PTEN) were assessed in participants at baseline.

End point type	Secondary

End point timeframe:

Baseline

End point values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	123	114	
Units: Percentage of participants				
PTEN Normal (%)	75	74	70	
PTEN Loss (%)	25	26	30	

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio (95% CI) of geometric means in p95HER2 expression in HR positive patients with pCR vs no pCR

End point title	Ratio (95% CI) of geometric means in p95HER2 expression in HR positive patients with pCR vs no pCR

End point description:

Ratio (95% CI) of geometric means in p95 human epidermal growth factor receptor (p95HER2) expression in hormone-receptor (HR) positive patients with pathological complete response (pCR) vs no pCR

End point type	Secondary

End point timeframe:

Baseline

End point values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	91	97	93	
Units: Ratio				
geometric mean (confidence interval 95%)	2.1 (1.2 to 3.7)	1.0 (0.50 to 1.87)	1.6 (1.0 to 2.71)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Circulating Tumor Cells (CTC) in the Bloodstream

End point title	Percentage of Participants with Circulating Tumor Cells (CTC) in the Bloodstream

End point description:

Circulating tumor cells (CTCs) are cells that have detached from a primary tumor and circulate in the bloodstream. In the adjuvant phase, after surgery all participants received 3 courses of adjuvant 5-fluorouracil, epirubicin and cyclophosphamide, followed by lapatinib 1500 mg or trastuzumab 2 mg/kg or lapatinib 1000/750 mg plus trastuzumab 2 mg/kg given prior to surgery in the neoadjuvant setting for an additional 34 weeks.

End point type	Secondary

End point timeframe:

Measurement performed at one or more of the time points: baseline, week 2 or week 18

End point values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	12	
Units: Percentage of Participants	25	21	17	

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 FPFT up to 30 days after study drug discontinuation, which was approximately 31 weeks. Deaths post treatment survival follow up were collected after the on treatment period, up to 10 years.

End point type	Post-hoc

End point timeframe:

on-treatment: up to week 31; post-treatment: up to year 10

End point values	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Lapatinib 1500 mg	Trastuzumab 2 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	154	149	
Units: Participants				
Total Deaths	26	31	32	
On-Treatment Deaths (n=151,148,149)	1	2	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of 31 weeks.

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	23.0

Reporting groups

Reporting group title	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg

Reporting group description:

Oral lapatinib 1000 mg daily plus trastuzumab 4 mg/kg IV load followed by 2 mg/kg IV weekly for 6 weeks, followed by lapatinib 750 mg daily plus trastuzumab (2 mg/kg IV weekly) plus weekly paclitaxel (80 mg/m^2 IV) for an additional 12 weeks

Reporting group title	Trastuzumab 2 mg/kg

Reporting group description:

Trastuzumab (4 mg/kilograms [kg] IV load followed by 2 mg/kg IV weekly) for 6 weeks, followed by trastuzumab plus weekly paclitaxel (80 mg/m^2 IV) for an additional 12 weeks

Reporting group title	Lapatinib 1500 mg

Reporting group description:

Oral lapatinib (1500 milligrams [mg] daily) for 6 weeks, followed by lapatinib plus weekly paclitaxel (80 mg per meters squared [mg/m^2]) intravenous (IV) for an additional 12 weeks

Serious adverse events	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Trastuzumab 2 mg/kg	Lapatinib 1500 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	61 / 149 (40.94%)	36 / 148 (24.32%)	58 / 151 (38.41%)
number of deaths (all causes)	1	0	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
LOBULAR BREAST CARCINOMA IN SITU			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UTERINE LEIOMYOMA			

subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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			
JUGULAR VEIN THROMBOSIS			
subjects affected / exposed	0 / 149 (0.00%)	1 / 148 (0.68%)	0 / 151 (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
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
CHEST DISCOMFORT			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
CHEST PAIN			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	5 / 149 (3.36%)	2 / 148 (1.35%)	2 / 151 (1.32%)
occurrences causally related to treatment / all	2 / 5	1 / 2	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
METRORRHAGIA			

subjects affected / exposed	0 / 149 (0.00%)	1 / 148 (0.68%)	0 / 151 (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
VULVOVAGINAL PRURITUS			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ASTHMA			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	2 / 149 (1.34%)	0 / 148 (0.00%)	0 / 151 (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
ORGANISING PNEUMONIA			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
PNEUMONITIS			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
PNEUMOTHORAX			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
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 EMBOLISM			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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			

GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
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			
ACCIDENTAL OVERDOSE			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
INFUSION RELATED REACTION			
subjects affected / exposed	0 / 149 (0.00%)	1 / 148 (0.68%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUMBAR VERTEBRAL FRACTURE			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
POISONING			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEROMA			
subjects affected / exposed	1 / 149 (0.67%)	1 / 148 (0.68%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL FRACTURE			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
TOXICITY TO VARIOUS AGENTS			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

TRANSFUSION REACTION			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
Cardiac disorders			
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	3 / 149 (2.01%)	1 / 148 (0.68%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
Nervous system disorders			
HEADACHE			
subjects affected / exposed	0 / 149 (0.00%)	1 / 148 (0.68%)	0 / 151 (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
NEUROPATHY PERIPHERAL			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SCIATICA			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
AGRANULOCYTOSIS			

subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
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	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE NEUTROPENIA			
subjects affected / exposed	3 / 149 (2.01%)	8 / 148 (5.41%)	2 / 151 (1.32%)
occurrences causally related to treatment / all	0 / 3	0 / 9	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LEUKOPENIA			
subjects affected / exposed	2 / 149 (1.34%)	1 / 148 (0.68%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIA			
subjects affected / exposed	14 / 149 (9.40%)	16 / 148 (10.81%)	13 / 151 (8.61%)
occurrences causally related to treatment / all	5 / 20	2 / 19	2 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCYTOPENIA			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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			
DIARRHOEA			
subjects affected / exposed	9 / 149 (6.04%)	0 / 148 (0.00%)	9 / 151 (5.96%)
occurrences causally related to treatment / all	11 / 11	0 / 0	9 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DUODENITIS			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
ENTERITIS			

subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
GASTRITIS EROSIVE			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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 HAEMORRHAGE			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
INGUINAL HERNIA			
subjects affected / exposed	0 / 149 (0.00%)	1 / 148 (0.68%)	0 / 151 (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
NAUSEA			
subjects affected / exposed	2 / 149 (1.34%)	1 / 148 (0.68%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	3 / 149 (2.01%)	2 / 148 (1.35%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	3 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATITIS ACUTE			

subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERBILIRUBINAEMIA			
subjects affected / exposed	4 / 149 (2.68%)	0 / 148 (0.00%)	4 / 151 (2.65%)
occurrences causally related to treatment / all	4 / 4	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTRANSAMINASAEMIA			
subjects affected / exposed	15 / 149 (10.07%)	3 / 148 (2.03%)	23 / 151 (15.23%)
occurrences causally related to treatment / all	15 / 17	3 / 3	25 / 28
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
BLISTER			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	2 / 149 (1.34%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEPHRECTASIA			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEPHROLITHIASIS			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
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			
OSTEOPOROTIC FRACTURE			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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

ROTATOR CUFF SYNDROME			
subjects affected / exposed	0 / 149 (0.00%)	1 / 148 (0.68%)	0 / 151 (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 / 149 (0.00%)	1 / 148 (0.68%)	0 / 151 (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
BACTERIAL SEPSIS			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BREAST CELLULITIS			
subjects affected / exposed	1 / 149 (0.67%)	1 / 148 (0.68%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CELLULITIS			
subjects affected / exposed	2 / 149 (1.34%)	2 / 148 (1.35%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CELLULITIS STAPHYLOCOCCAL			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
DEVICE RELATED INFECTION			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
DEVICE RELATED SEPSIS			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ERYSIPELAS			

subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
HEPATITIS B			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES SIMPLEX			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES ZOSTER			
subjects affected / exposed	0 / 149 (0.00%)	1 / 148 (0.68%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MASTITIS			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	2 / 151 (1.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PHARYNGITIS			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
PNEUMONIA			
subjects affected / exposed	2 / 149 (1.34%)	2 / 148 (1.35%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SKIN INFECTION			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
URINARY TRACT INFECTION			

subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	3 / 151 (1.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VASCULAR DEVICE INFECTION			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
WOUND INFECTION			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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	0 / 149 (0.00%)	0 / 148 (0.00%)	2 / 151 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETES MELLITUS			
subjects affected / exposed	0 / 149 (0.00%)	1 / 148 (0.68%)	0 / 151 (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
HYPERPHOSPHATASAEMIA			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
HYPOGLYCAEMIA			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	0 / 151 (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
HYPOKALAEMIA			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg	Trastuzumab 2 mg/kg	Lapatinib 1500 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	147 / 149 (98.66%)	141 / 148 (95.27%)	148 / 151 (98.01%)
Vascular disorders			
FLUSHING			
subjects affected / exposed	1 / 149 (0.67%)	6 / 148 (4.05%)	3 / 151 (1.99%)
occurrences (all)	1	6	3
HAEMATOMA			
subjects affected / exposed	3 / 149 (2.01%)	1 / 148 (0.68%)	1 / 151 (0.66%)
occurrences (all)	3	1	1
HOT FLUSH			
subjects affected / exposed	22 / 149 (14.77%)	21 / 148 (14.19%)	15 / 151 (9.93%)
occurrences (all)	26	23	15
HYPERTENSION			
subjects affected / exposed	5 / 149 (3.36%)	8 / 148 (5.41%)	5 / 151 (3.31%)
occurrences (all)	5	11	5
HYPOTENSION			
subjects affected / exposed	8 / 149 (5.37%)	2 / 148 (1.35%)	5 / 151 (3.31%)
occurrences (all)	9	2	6
LYMPHOEDEMA			
subjects affected / exposed	3 / 149 (2.01%)	3 / 148 (2.03%)	5 / 151 (3.31%)
occurrences (all)	3	3	5
PHLEBITIS			
subjects affected / exposed	2 / 149 (1.34%)	5 / 148 (3.38%)	3 / 151 (1.99%)
occurrences (all)	2	5	3
General disorders and administration site conditions			
AXILLARY PAIN			
subjects affected / exposed	5 / 149 (3.36%)	3 / 148 (2.03%)	0 / 151 (0.00%)
occurrences (all)	6	4	0
ASTHENIA			
subjects affected / exposed	39 / 149 (26.17%)	35 / 148 (23.65%)	47 / 151 (31.13%)
occurrences (all)	55	53	71
CHEST DISCOMFORT			

subjects affected / exposed	0 / 149 (0.00%)	6 / 148 (4.05%)	3 / 151 (1.99%)
occurrences (all)	0	8	3
CHEST PAIN			
subjects affected / exposed	5 / 149 (3.36%)	6 / 148 (4.05%)	5 / 151 (3.31%)
occurrences (all)	5	6	6
FACE OEDEMA			
subjects affected / exposed	3 / 149 (2.01%)	4 / 148 (2.70%)	5 / 151 (3.31%)
occurrences (all)	3	4	5
CHILLS			
subjects affected / exposed	11 / 149 (7.38%)	6 / 148 (4.05%)	3 / 151 (1.99%)
occurrences (all)	13	6	3
FATIGUE			
subjects affected / exposed	52 / 149 (34.90%)	38 / 148 (25.68%)	45 / 151 (29.80%)
occurrences (all)	81	55	54
FEELING COLD			
subjects affected / exposed	0 / 149 (0.00%)	3 / 148 (2.03%)	1 / 151 (0.66%)
occurrences (all)	0	3	1
GENERALISED OEDEMA			
subjects affected / exposed	1 / 149 (0.67%)	3 / 148 (2.03%)	3 / 151 (1.99%)
occurrences (all)	3	3	7
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	3 / 149 (2.01%)	2 / 148 (1.35%)	2 / 151 (1.32%)
occurrences (all)	3	2	2
MUCOSAL DRYNESS			
subjects affected / exposed	3 / 149 (2.01%)	2 / 148 (1.35%)	2 / 151 (1.32%)
occurrences (all)	3	2	2
MUCOSAL INFLAMMATION			
subjects affected / exposed	36 / 149 (24.16%)	22 / 148 (14.86%)	34 / 151 (22.52%)
occurrences (all)	39	27	38
MUCOSAL EROSION			
subjects affected / exposed	3 / 149 (2.01%)	0 / 148 (0.00%)	0 / 151 (0.00%)
occurrences (all)	4	0	0
OEDEMA			
subjects affected / exposed	4 / 149 (2.68%)	11 / 148 (7.43%)	0 / 151 (0.00%)
occurrences (all)	5	13	0
OEDEMA PERIPHERAL			

subjects affected / exposed	8 / 149 (5.37%)	13 / 148 (8.78%)	9 / 151 (5.96%)
occurrences (all)	10	14	12
PAIN			
subjects affected / exposed	3 / 149 (2.01%)	2 / 148 (1.35%)	6 / 151 (3.97%)
occurrences (all)	3	2	7
PERIPHERAL SWELLING			
subjects affected / exposed	4 / 149 (2.68%)	3 / 148 (2.03%)	2 / 151 (1.32%)
occurrences (all)	5	3	2
PYREXIA			
subjects affected / exposed	34 / 149 (22.82%)	23 / 148 (15.54%)	23 / 151 (15.23%)
occurrences (all)	43	28	33
Immune system disorders			
HYPERSENSITIVITY			
subjects affected / exposed	6 / 149 (4.03%)	7 / 148 (4.73%)	6 / 151 (3.97%)
occurrences (all)	7	8	6
SEASONAL ALLERGY			
subjects affected / exposed	3 / 149 (2.01%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences (all)	3	0	1
Reproductive system and breast disorders			
AMENORRHOEA			
subjects affected / exposed	6 / 149 (4.03%)	1 / 148 (0.68%)	3 / 151 (1.99%)
occurrences (all)	7	1	3
BREAST PAIN			
subjects affected / exposed	6 / 149 (4.03%)	15 / 148 (10.14%)	5 / 151 (3.31%)
occurrences (all)	6	15	6
BREAST DISCHARGE			
subjects affected / exposed	3 / 149 (2.01%)	0 / 148 (0.00%)	0 / 151 (0.00%)
occurrences (all)	4	0	0
MENSTRUATION IRREGULAR			
subjects affected / exposed	1 / 149 (0.67%)	3 / 148 (2.03%)	2 / 151 (1.32%)
occurrences (all)	1	3	2
PELVIC PAIN			
subjects affected / exposed	0 / 149 (0.00%)	4 / 148 (2.70%)	0 / 151 (0.00%)
occurrences (all)	0	4	0
VULVOVAGINAL DRYNESS			

subjects affected / exposed	2 / 149 (1.34%)	3 / 148 (2.03%)	2 / 151 (1.32%)
occurrences (all)	2	3	2
VULVOVAGINAL INFLAMMATION			
subjects affected / exposed	0 / 149 (0.00%)	0 / 148 (0.00%)	4 / 151 (2.65%)
occurrences (all)	0	0	4
VULVOVAGINAL PRURITUS			
subjects affected / exposed	2 / 149 (1.34%)	4 / 148 (2.70%)	2 / 151 (1.32%)
occurrences (all)	2	5	2
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	25 / 149 (16.78%)	26 / 148 (17.57%)	17 / 151 (11.26%)
occurrences (all)	34	30	19
DYSPNOEA			
subjects affected / exposed	16 / 149 (10.74%)	13 / 148 (8.78%)	11 / 151 (7.28%)
occurrences (all)	19	13	13
DYSPHONIA			
subjects affected / exposed	1 / 149 (0.67%)	2 / 148 (1.35%)	5 / 151 (3.31%)
occurrences (all)	1	3	5
DYSPNOEA EXERTIONAL			
subjects affected / exposed	6 / 149 (4.03%)	6 / 148 (4.05%)	2 / 151 (1.32%)
occurrences (all)	6	7	4
EPISTAXIS			
subjects affected / exposed	37 / 149 (24.83%)	22 / 148 (14.86%)	30 / 151 (19.87%)
occurrences (all)	43	23	32
HAEMOPTYSIS			
subjects affected / exposed	0 / 149 (0.00%)	3 / 148 (2.03%)	0 / 151 (0.00%)
occurrences (all)	0	4	0
NASAL INFLAMMATION			
subjects affected / exposed	5 / 149 (3.36%)	1 / 148 (0.68%)	3 / 151 (1.99%)
occurrences (all)	5	1	3
NASAL DRYNESS			
subjects affected / exposed	6 / 149 (4.03%)	2 / 148 (1.35%)	6 / 151 (3.97%)
occurrences (all)	6	4	6
OROPHARYNGEAL PAIN			

subjects affected / exposed	16 / 149 (10.74%)	15 / 148 (10.14%)	20 / 151 (13.25%)
occurrences (all)	18	19	24
PRODUCTIVE COUGH			
subjects affected / exposed	3 / 149 (2.01%)	0 / 148 (0.00%)	0 / 151 (0.00%)
occurrences (all)	3	0	0
RHINORRHOEA			
subjects affected / exposed	13 / 149 (8.72%)	10 / 148 (6.76%)	6 / 151 (3.97%)
occurrences (all)	16	12	6
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	7 / 149 (4.70%)	9 / 148 (6.08%)	5 / 151 (3.31%)
occurrences (all)	7	9	5
ANXIETY			
subjects affected / exposed	7 / 149 (4.70%)	11 / 148 (7.43%)	9 / 151 (5.96%)
occurrences (all)	7	12	9
INSOMNIA			
subjects affected / exposed	34 / 149 (22.82%)	24 / 148 (16.22%)	23 / 151 (15.23%)
occurrences (all)	39	26	26
SLEEP DISORDER			
subjects affected / exposed	5 / 149 (3.36%)	2 / 148 (1.35%)	4 / 151 (2.65%)
occurrences (all)	8	3	4
Investigations			
EJECTION FRACTION DECREASED			
subjects affected / exposed	6 / 149 (4.03%)	4 / 148 (2.70%)	2 / 151 (1.32%)
occurrences (all)	9	4	2
GAMMA-GLUTAMYLTRANSFERASE			
subjects affected / exposed	3 / 149 (2.01%)	0 / 148 (0.00%)	2 / 151 (1.32%)
occurrences (all)	4	0	3
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	3 / 149 (2.01%)	1 / 148 (0.68%)	7 / 151 (4.64%)
occurrences (all)	3	1	9
NEUTROPHIL COUNT INCREASED			
subjects affected / exposed	3 / 149 (2.01%)	2 / 148 (1.35%)	1 / 151 (0.66%)
occurrences (all)	4	4	1
WEIGHT INCREASED			

subjects affected / exposed	2 / 149 (1.34%)	3 / 148 (2.03%)	2 / 151 (1.32%)
occurrences (all)	2	3	2
WEIGHT DECREASED			
subjects affected / exposed	8 / 149 (5.37%)	1 / 148 (0.68%)	10 / 151 (6.62%)
occurrences (all)	8	1	11
Injury, poisoning and procedural complications			
RADIATION SKIN INJURY			
subjects affected / exposed	16 / 149 (10.74%)	18 / 148 (12.16%)	11 / 151 (7.28%)
occurrences (all)	17	19	11
SEROMA			
subjects affected / exposed	2 / 149 (1.34%)	6 / 148 (4.05%)	0 / 151 (0.00%)
occurrences (all)	2	6	0
THERMAL BURN			
subjects affected / exposed	3 / 149 (2.01%)	1 / 148 (0.68%)	0 / 151 (0.00%)
occurrences (all)	3	1	0
WOUND COMPLICATION			
subjects affected / exposed	4 / 149 (2.68%)	6 / 148 (4.05%)	4 / 151 (2.65%)
occurrences (all)	5	6	4
Cardiac disorders			
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	3 / 149 (2.01%)	1 / 148 (0.68%)	0 / 151 (0.00%)
occurrences (all)	4	1	0
LEFT VENTRICULAR DYSFUNCTION			
subjects affected / exposed	4 / 149 (2.68%)	2 / 148 (1.35%)	0 / 151 (0.00%)
occurrences (all)	6	2	0
PALPITATIONS			
subjects affected / exposed	6 / 149 (4.03%)	3 / 148 (2.03%)	6 / 151 (3.97%)
occurrences (all)	8	3	6
TACHYCARDIA			
subjects affected / exposed	4 / 149 (2.68%)	4 / 148 (2.70%)	2 / 151 (1.32%)
occurrences (all)	4	4	2
Nervous system disorders			
AGEUSIA			
subjects affected / exposed	4 / 149 (2.68%)	0 / 148 (0.00%)	3 / 151 (1.99%)
occurrences (all)	7	0	5
DIZZINESS			

subjects affected / exposed	13 / 149 (8.72%)	15 / 148 (10.14%)	13 / 151 (8.61%)
occurrences (all)	13	19	17
DYSGEUSIA			
subjects affected / exposed	6 / 149 (4.03%)	1 / 148 (0.68%)	6 / 151 (3.97%)
occurrences (all)	10	1	6
HEADACHE			
subjects affected / exposed	31 / 149 (20.81%)	26 / 148 (17.57%)	27 / 151 (17.88%)
occurrences (all)	43	33	31
HYPOAESTHESIA			
subjects affected / exposed	9 / 149 (6.04%)	12 / 148 (8.11%)	7 / 151 (4.64%)
occurrences (all)	11	14	7
MEMORY IMPAIRMENT			
subjects affected / exposed	2 / 149 (1.34%)	2 / 148 (1.35%)	4 / 151 (2.65%)
occurrences (all)	2	4	4
NEUROPATHY PERIPHERAL			
subjects affected / exposed	19 / 149 (12.75%)	19 / 148 (12.84%)	21 / 151 (13.91%)
occurrences (all)	22	21	22
NEUROTOXICITY			
subjects affected / exposed	3 / 149 (2.01%)	3 / 148 (2.03%)	6 / 151 (3.97%)
occurrences (all)	5	3	6
PARAESTHESIA			
subjects affected / exposed	24 / 149 (16.11%)	22 / 148 (14.86%)	15 / 151 (9.93%)
occurrences (all)	25	26	16
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	13 / 149 (8.72%)	14 / 148 (9.46%)	19 / 151 (12.58%)
occurrences (all)	15	15	22
POLYNEUROPATHY			
subjects affected / exposed	5 / 149 (3.36%)	3 / 148 (2.03%)	1 / 151 (0.66%)
occurrences (all)	7	3	2
TASTE DISORDER			
subjects affected / exposed	9 / 149 (6.04%)	1 / 148 (0.68%)	6 / 151 (3.97%)
occurrences (all)	9	1	8
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	36 / 149 (24.16%)	27 / 148 (18.24%)	33 / 151 (21.85%)
occurrences (all)	44	35	47

LEUKOPENIA			
subjects affected / exposed	21 / 149 (14.09%)	10 / 148 (6.76%)	18 / 151 (11.92%)
occurrences (all)	32	15	28
FEBRILE NEUTROPENIA			
subjects affected / exposed	3 / 149 (2.01%)	1 / 148 (0.68%)	0 / 151 (0.00%)
occurrences (all)	3	1	0
NEUTROPENIA			
subjects affected / exposed	47 / 149 (31.54%)	37 / 148 (25.00%)	51 / 151 (33.77%)
occurrences (all)	66	48	91
LYMPHOPENIA			
subjects affected / exposed	5 / 149 (3.36%)	6 / 148 (4.05%)	2 / 151 (1.32%)
occurrences (all)	7	7	5
THROMBOCYTOPENIA			
subjects affected / exposed	4 / 149 (2.68%)	1 / 148 (0.68%)	2 / 151 (1.32%)
occurrences (all)	4	1	2
Ear and labyrinth disorders			
EAR PAIN			
subjects affected / exposed	3 / 149 (2.01%)	1 / 148 (0.68%)	1 / 151 (0.66%)
occurrences (all)	3	1	1
TINNITUS			
subjects affected / exposed	6 / 149 (4.03%)	3 / 148 (2.03%)	1 / 151 (0.66%)
occurrences (all)	6	3	1
VERTIGO			
subjects affected / exposed	11 / 149 (7.38%)	6 / 148 (4.05%)	7 / 151 (4.64%)
occurrences (all)	11	7	8
Eye disorders			
DRY EYE			
subjects affected / exposed	4 / 149 (2.68%)	2 / 148 (1.35%)	1 / 151 (0.66%)
occurrences (all)	5	2	1
LACRIMATION INCREASED			
subjects affected / exposed	3 / 149 (2.01%)	1 / 148 (0.68%)	3 / 151 (1.99%)
occurrences (all)	4	1	3
VISUAL IMPAIRMENT			
subjects affected / exposed	2 / 149 (1.34%)	3 / 148 (2.03%)	2 / 151 (1.32%)
occurrences (all)	2	4	2
Gastrointestinal disorders			

ABDOMINAL DISCOMFORT			
subjects affected / exposed	3 / 149 (2.01%)	4 / 148 (2.70%)	1 / 151 (0.66%)
occurrences (all)	3	4	1
ABDOMINAL DISTENSION			
subjects affected / exposed	10 / 149 (6.71%)	5 / 148 (3.38%)	8 / 151 (5.30%)
occurrences (all)	12	6	9
ABDOMINAL PAIN			
subjects affected / exposed	21 / 149 (14.09%)	13 / 148 (8.78%)	28 / 151 (18.54%)
occurrences (all)	28	16	36
ANAL INFLAMMATION			
subjects affected / exposed	4 / 149 (2.68%)	1 / 148 (0.68%)	2 / 151 (1.32%)
occurrences (all)	5	1	2
ABDOMINAL PAIN UPPER			
subjects affected / exposed	23 / 149 (15.44%)	16 / 148 (10.81%)	27 / 151 (17.88%)
occurrences (all)	32	18	31
CONSTIPATION			
subjects affected / exposed	18 / 149 (12.08%)	15 / 148 (10.14%)	15 / 151 (9.93%)
occurrences (all)	23	19	19
DRY MOUTH			
subjects affected / exposed	9 / 149 (6.04%)	3 / 148 (2.03%)	5 / 151 (3.31%)
occurrences (all)	10	3	5
DIARRHOEA			
subjects affected / exposed	128 / 149 (85.91%)	52 / 148 (35.14%)	123 / 151 (81.46%)
occurrences (all)	296	79	238
DYSPEPSIA			
subjects affected / exposed	17 / 149 (11.41%)	10 / 148 (6.76%)	26 / 151 (17.22%)
occurrences (all)	20	11	30
DYSPHAGIA			
subjects affected / exposed	3 / 149 (2.01%)	3 / 148 (2.03%)	0 / 151 (0.00%)
occurrences (all)	3	3	0
EPIGASTRIC DISCOMFORT			
subjects affected / exposed	3 / 149 (2.01%)	2 / 148 (1.35%)	2 / 151 (1.32%)
occurrences (all)	4	2	2
FLATULENCE			
subjects affected / exposed	3 / 149 (2.01%)	2 / 148 (1.35%)	5 / 151 (3.31%)
occurrences (all)	3	2	6

GASTRITIS			
subjects affected / exposed	2 / 149 (1.34%)	3 / 148 (2.03%)	8 / 151 (5.30%)
occurrences (all)	2	3	8
HAEMORRHOIDS			
subjects affected / exposed	13 / 149 (8.72%)	10 / 148 (6.76%)	10 / 151 (6.62%)
occurrences (all)	13	12	10
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	5 / 149 (3.36%)	0 / 148 (0.00%)	2 / 151 (1.32%)
occurrences (all)	5	0	2
MOUTH ULCERATION			
subjects affected / exposed	12 / 149 (8.05%)	1 / 148 (0.68%)	4 / 151 (2.65%)
occurrences (all)	16	1	6
NAUSEA			
subjects affected / exposed	75 / 149 (50.34%)	76 / 148 (51.35%)	81 / 151 (53.64%)
occurrences (all)	140	111	152
RECTAL HAEMORRHAGE			
subjects affected / exposed	4 / 149 (2.68%)	0 / 148 (0.00%)	2 / 151 (1.32%)
occurrences (all)	4	0	2
STOMATITIS			
subjects affected / exposed	27 / 149 (18.12%)	23 / 148 (15.54%)	18 / 151 (11.92%)
occurrences (all)	39	25	29
TOOTHACHE			
subjects affected / exposed	4 / 149 (2.68%)	2 / 148 (1.35%)	1 / 151 (0.66%)
occurrences (all)	4	2	1
VOMITING			
subjects affected / exposed	54 / 149 (36.24%)	38 / 148 (25.68%)	57 / 151 (37.75%)
occurrences (all)	96	57	93
Hepatobiliary disorders			
HYPERBILIRUBINAEMIA			
subjects affected / exposed	21 / 149 (14.09%)	7 / 148 (4.73%)	26 / 151 (17.22%)
occurrences (all)	24	8	33
HYPERTRANSAMINASAEMIA			
subjects affected / exposed	55 / 149 (36.91%)	39 / 148 (26.35%)	55 / 151 (36.42%)
occurrences (all)	113	106	112
Skin and subcutaneous tissue disorders			

ACNE			
subjects affected / exposed	22 / 149 (14.77%)	5 / 148 (3.38%)	20 / 151 (13.25%)
occurrences (all)	28	7	25
ALOPECIA			
subjects affected / exposed	95 / 149 (63.76%)	96 / 148 (64.86%)	90 / 151 (59.60%)
occurrences (all)	101	103	97
DERMATITIS			
subjects affected / exposed	13 / 149 (8.72%)	8 / 148 (5.41%)	13 / 151 (8.61%)
occurrences (all)	13	11	13
DERMATITIS ACNEIFORM			
subjects affected / exposed	14 / 149 (9.40%)	4 / 148 (2.70%)	12 / 151 (7.95%)
occurrences (all)	18	4	16
DRY SKIN			
subjects affected / exposed	28 / 149 (18.79%)	8 / 148 (5.41%)	29 / 151 (19.21%)
occurrences (all)	28	8	30
ECZEMA			
subjects affected / exposed	6 / 149 (4.03%)	2 / 148 (1.35%)	4 / 151 (2.65%)
occurrences (all)	6	2	4
ERYTHEMA			
subjects affected / exposed	14 / 149 (9.40%)	15 / 148 (10.14%)	14 / 151 (9.27%)
occurrences (all)	15	16	18
EXFOLIATIVE RASH			
subjects affected / exposed	8 / 149 (5.37%)	0 / 148 (0.00%)	4 / 151 (2.65%)
occurrences (all)	9	0	4
HYPERHIDROSIS			
subjects affected / exposed	2 / 149 (1.34%)	3 / 148 (2.03%)	1 / 151 (0.66%)
occurrences (all)	2	3	1
NAIL DISORDER			
subjects affected / exposed	36 / 149 (24.16%)	18 / 148 (12.16%)	26 / 151 (17.22%)
occurrences (all)	44	20	32
NAIL DYSTROPHY			
subjects affected / exposed	3 / 149 (2.01%)	1 / 148 (0.68%)	2 / 151 (1.32%)
occurrences (all)	3	1	2
ONYCHOLYSIS			
subjects affected / exposed	7 / 149 (4.70%)	2 / 148 (1.35%)	0 / 151 (0.00%)
occurrences (all)	7	2	0

ONYCHALGIA			
subjects affected / exposed	3 / 149 (2.01%)	1 / 148 (0.68%)	3 / 151 (1.99%)
occurrences (all)	3	1	3
PAIN OF SKIN			
subjects affected / exposed	1 / 149 (0.67%)	2 / 148 (1.35%)	4 / 151 (2.65%)
occurrences (all)	1	2	4
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	14 / 149 (9.40%)	3 / 148 (2.03%)	14 / 151 (9.27%)
occurrences (all)	16	3	15
PRURITUS			
subjects affected / exposed	24 / 149 (16.11%)	9 / 148 (6.08%)	29 / 151 (19.21%)
occurrences (all)	32	10	33
RASH			
subjects affected / exposed	67 / 149 (44.97%)	28 / 148 (18.92%)	68 / 151 (45.03%)
occurrences (all)	94	34	93
RASH PRURITIC			
subjects affected / exposed	4 / 149 (2.68%)	3 / 148 (2.03%)	3 / 151 (1.99%)
occurrences (all)	4	4	4
SCAR PAIN			
subjects affected / exposed	1 / 149 (0.67%)	4 / 148 (2.70%)	3 / 151 (1.99%)
occurrences (all)	1	4	3
SKIN EXFOLIATION			
subjects affected / exposed	4 / 149 (2.68%)	1 / 148 (0.68%)	0 / 151 (0.00%)
occurrences (all)	4	1	0
SKIN FISSURES			
subjects affected / exposed	13 / 149 (8.72%)	4 / 148 (2.70%)	4 / 151 (2.65%)
occurrences (all)	17	4	5
SKIN HYPERPIGMENTATION			
subjects affected / exposed	6 / 149 (4.03%)	2 / 148 (1.35%)	6 / 151 (3.97%)
occurrences (all)	7	2	6
SKIN IRRITATION			
subjects affected / exposed	3 / 149 (2.01%)	1 / 148 (0.68%)	1 / 151 (0.66%)
occurrences (all)	3	1	1
SKIN LESION			

subjects affected / exposed	5 / 149 (3.36%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences (all)	6	0	1
SKIN REACTION			
subjects affected / exposed	2 / 149 (1.34%)	0 / 148 (0.00%)	4 / 151 (2.65%)
occurrences (all)	3	0	4
Renal and urinary disorders			
DYSURIA			
subjects affected / exposed	11 / 149 (7.38%)	5 / 148 (3.38%)	6 / 151 (3.97%)
occurrences (all)	12	6	7
HAEMATURIA			
subjects affected / exposed	4 / 149 (2.68%)	0 / 148 (0.00%)	0 / 151 (0.00%)
occurrences (all)	4	0	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	27 / 149 (18.12%)	32 / 148 (21.62%)	26 / 151 (17.22%)
occurrences (all)	31	38	31
BACK PAIN			
subjects affected / exposed	22 / 149 (14.77%)	14 / 148 (9.46%)	10 / 151 (6.62%)
occurrences (all)	25	15	11
BONE PAIN			
subjects affected / exposed	10 / 149 (6.71%)	18 / 148 (12.16%)	12 / 151 (7.95%)
occurrences (all)	13	21	12
JOINT STIFFNESS			
subjects affected / exposed	2 / 149 (1.34%)	4 / 148 (2.70%)	1 / 151 (0.66%)
occurrences (all)	2	4	1
MUSCLE SPASMS			
subjects affected / exposed	6 / 149 (4.03%)	3 / 148 (2.03%)	4 / 151 (2.65%)
occurrences (all)	7	4	5
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	4 / 149 (2.68%)	1 / 148 (0.68%)	2 / 151 (1.32%)
occurrences (all)	4	1	2
MUSCULOSKELETAL PAIN			
subjects affected / exposed	8 / 149 (5.37%)	11 / 148 (7.43%)	16 / 151 (10.60%)
occurrences (all)	9	12	20
MUSCULOSKELETAL STIFFNESS			

subjects affected / exposed	1 / 149 (0.67%)	3 / 148 (2.03%)	1 / 151 (0.66%)
occurrences (all)	1	3	1
MYALGIA			
subjects affected / exposed	31 / 149 (20.81%)	34 / 148 (22.97%)	33 / 151 (21.85%)
occurrences (all)	52	50	50
NECK PAIN			
subjects affected / exposed	7 / 149 (4.70%)	5 / 148 (3.38%)	5 / 151 (3.31%)
occurrences (all)	7	5	7
OSTEOPOROSIS			
subjects affected / exposed	0 / 149 (0.00%)	3 / 148 (2.03%)	1 / 151 (0.66%)
occurrences (all)	0	3	1
PAIN IN EXTREMITY			
subjects affected / exposed	13 / 149 (8.72%)	13 / 148 (8.78%)	20 / 151 (13.25%)
occurrences (all)	18	16	25
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	2 / 149 (1.34%)	3 / 148 (2.03%)	5 / 151 (3.31%)
occurrences (all)	2	3	6
CONJUNCTIVITIS			
subjects affected / exposed	11 / 149 (7.38%)	5 / 148 (3.38%)	8 / 151 (5.30%)
occurrences (all)	13	5	8
HERPES SIMPLEX			
subjects affected / exposed	3 / 149 (2.01%)	2 / 148 (1.35%)	0 / 151 (0.00%)
occurrences (all)	3	2	0
CYSTITIS			
subjects affected / exposed	8 / 149 (5.37%)	3 / 148 (2.03%)	6 / 151 (3.97%)
occurrences (all)	8	3	6
INFLUENZA			
subjects affected / exposed	8 / 149 (5.37%)	9 / 148 (6.08%)	8 / 151 (5.30%)
occurrences (all)	9	10	8
LOCALISED INFECTION			
subjects affected / exposed	3 / 149 (2.01%)	0 / 148 (0.00%)	3 / 151 (1.99%)
occurrences (all)	3	0	4
LOWER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	3 / 149 (2.01%)	1 / 148 (0.68%)	1 / 151 (0.66%)
occurrences (all)	3	1	1
MASTITIS			
subjects affected / exposed	2 / 149 (1.34%)	3 / 148 (2.03%)	1 / 151 (0.66%)
occurrences (all)	2	3	1
NAIL INFECTION			
subjects affected / exposed	8 / 149 (5.37%)	0 / 148 (0.00%)	1 / 151 (0.66%)
occurrences (all)	9	0	2
NASOPHARYNGITIS			
subjects affected / exposed	11 / 149 (7.38%)	11 / 148 (7.43%)	12 / 151 (7.95%)
occurrences (all)	15	11	13
ORAL HERPES			
subjects affected / exposed	2 / 149 (1.34%)	3 / 148 (2.03%)	0 / 151 (0.00%)
occurrences (all)	2	3	0
PARONYCHIA			
subjects affected / exposed	17 / 149 (11.41%)	2 / 148 (1.35%)	14 / 151 (9.27%)
occurrences (all)	22	2	22
PHARYNGITIS			
subjects affected / exposed	4 / 149 (2.68%)	5 / 148 (3.38%)	7 / 151 (4.64%)
occurrences (all)	4	5	7
RHINITIS			
subjects affected / exposed	6 / 149 (4.03%)	5 / 148 (3.38%)	4 / 151 (2.65%)
occurrences (all)	6	5	4
PUSTULE			
subjects affected / exposed	3 / 149 (2.01%)	1 / 148 (0.68%)	1 / 151 (0.66%)
occurrences (all)	3	1	2
SKIN INFECTION			
subjects affected / exposed	4 / 149 (2.68%)	2 / 148 (1.35%)	1 / 151 (0.66%)
occurrences (all)	4	2	1
SINUSITIS			
subjects affected / exposed	3 / 149 (2.01%)	2 / 148 (1.35%)	5 / 151 (3.31%)
occurrences (all)	3	2	5
TONSILLITIS			
subjects affected / exposed	0 / 149 (0.00%)	4 / 148 (2.70%)	3 / 151 (1.99%)
occurrences (all)	0	4	4
UPPER RESPIRATORY TRACT			

INFECTION			
subjects affected / exposed	10 / 149 (6.71%)	14 / 148 (9.46%)	9 / 151 (5.96%)
occurrences (all)	12	16	10
URINARY TRACT INFECTION			
subjects affected / exposed	11 / 149 (7.38%)	6 / 148 (4.05%)	14 / 151 (9.27%)
occurrences (all)	11	6	16
VAGINAL INFECTION			
subjects affected / exposed	5 / 149 (3.36%)	2 / 148 (1.35%)	1 / 151 (0.66%)
occurrences (all)	5	2	1
VIRAL INFECTION			
subjects affected / exposed	0 / 149 (0.00%)	3 / 148 (2.03%)	0 / 151 (0.00%)
occurrences (all)	0	3	0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	35 / 149 (23.49%)	17 / 148 (11.49%)	39 / 151 (25.83%)
occurrences (all)	57	21	50
DEHYDRATION			
subjects affected / exposed	1 / 149 (0.67%)	0 / 148 (0.00%)	5 / 151 (3.31%)
occurrences (all)	2	0	6
HYPERGLYCAEMIA			
subjects affected / exposed	3 / 149 (2.01%)	4 / 148 (2.70%)	0 / 151 (0.00%)
occurrences (all)	3	4	0
HYPERCHOLESTEROLAEMIA			
subjects affected / exposed	0 / 149 (0.00%)	3 / 148 (2.03%)	1 / 151 (0.66%)
occurrences (all)	0	3	1
HYPERPHOSPHATASAEMIA			
subjects affected / exposed	22 / 149 (14.77%)	12 / 148 (8.11%)	22 / 151 (14.57%)
occurrences (all)	30	18	29
HYPOKALAEMIA			
subjects affected / exposed	4 / 149 (2.68%)	0 / 148 (0.00%)	3 / 151 (1.99%)
occurrences (all)	4	0	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 April 2008	Amendment No. 01
10 October 2008	Amendment No. 02
17 May 2013	Amendment No. 03
13 May 2016	Amendment No. 04
24 August 2016	Amendment No. 05

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported