Clinical trial results:
A Randomized, Double Blind, Placebo-Controlled, Multicenter, Phase III Study Comparing the Activity of Paclitaxel Plus Trastuzumab Plus Lapatinib to Paclitaxel Plus Trastuzumab Plus Placebo in Women with ErbB2 Overexpressing Metastatic Breast Cancer.

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

Summary

EudraCT number	2005-003432-22
Trial protocol	BE
Global end of trial date	21 October 2019

Results information

Result version number	v2 (current)
This version publication date	28 January 2022
First version publication date	06 November 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CLAP016A2301/EGF104383 (GSK)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00272987
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 October 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary objective for open label phase: To determine the safety and tolerability of lapatinib when administered in combination with both paclitaxel and trastuzumab

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	13 December 2005
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	United States: 61
Country: Number of subjects enrolled	Belgium: 2
Worldwide total number of subjects	63
EEA total number of subjects	2

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)	52
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Female participants (par.) with histologically confirmed invasive breast cancer (Stage IV disease) whose tumors overexpressed the ErbB2 protein, documented by either Immunohistochemistry (IHC) or fluorescence in situ hybridisation (FISH), were eligible for inclusion in this study.

Pre-assignment

Screening details:

Participants who met inclusion criteria were sequentially enrolled into three cohorts and received the open-label triple combination of paclitaxel, trastuzumab and lapatinib. The planned randomized phase of the study was terminated following the poor recruitment rate in the Open-label Phase.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg

Arm description:

Participants received an intravenous (IV) infusion of paclitaxel 80 milligrams per meter squared (mg/m^2) over 60 minutes weekly for 3 weeks of a 4-week cycle plus an IV infusion of trastuzumab 4 mg per kilogram (mg/kg) loading dose and 2 mg/kg weekly plus a daily dose of 4 tablets of lapatinib (1000 mg) at approximately the same time every day, either 1 hour (or more) before a meal or 1 hour (or more) after a meal.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

4 mg/kg IV loading dose and 2 mg/kg IV weekly

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

Dosage and administration details:

80mg/m2 IV weekly for 3 weeks of a 4 week cycle

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

Dosage and administration details:

1000 mg PO daily

Arm title	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg

Arm description:

Participants received an IV infusion of paclitaxel 70 mg/m^2 over 60 minutes weekly for 3 weeks of a 4-week cycle plus an IV infusion of trastuzumab 4 mg/kg loading dose and 2 mg/kg weekly plus a daily dose of 4 tablets of lapatinib (1000 mg) at approximately the same time every day, either 1 hour (or more) before a meal or 1 hour (or more) after a meal. The paclitaxel dose was systematically increased to 80 mg/m^2 after 2 cycles if 70 mg/m^2 was tolerated.

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

Dosage and administration details:

70mg/m2 IV weekly for 3 weeks of a 4 week cycle; Paclitaxel dose was to be systematically increased to 80 mg/m2 after 2 cycles if 70 mg/m2 was tolerated.

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

Dosage and administration details:

4 mg/kg IV loading dose and 2 mg/kg IV weekly

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

Dosage and administration details:

1000 mg PO daily

Arm title	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg

Arm description:

Participants received an IV infusion of paclitaxel 80 mg/m^2 over 60 minutes weekly for 3 weeks of a 4-week cycle plus an IV infusion of trastuzumab 4 mg/kg loading dose and 2 mg/kg weekly plus a daily dose of 3 tablets of lapatinib (750 mg) at approximately the same time every day, either 1 hour (or more) before a meal or 1 hour (or more) after a meal. The lapatinib dose was systematically increased to 1000 mg after 2 cycles if the 750 mg dose was tolerated.

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

Dosage and administration details:

80mg/m2 IV weekly for 3 weeks of a 4 week cycle

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

Dosage and administration details:

750 mg PO daily; Lapatinib dose was to be systematically increased to 1000 mg after 2 cycles if 750 mg was tolerated.

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

Dosage and administration details:

4 mg/kg IV loading dose and 2 mg/kg IV weekly

Number of subjects in period 1	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg
Started	29	14	20
Completed	20	10	9
Not completed	9	4	11
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	1	-	3
Disease progression	1	1	2
Adverse event, non-fatal	1	-	-
Sponsor Terminated study	-	1	1
Lost to follow-up	3	1	1
Lack of efficacy	2	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg

Reporting group description:

Participants received an intravenous (IV) infusion of paclitaxel 80 milligrams per meter squared (mg/m^2) over 60 minutes weekly for 3 weeks of a 4-week cycle plus an IV infusion of trastuzumab 4 mg per kilogram (mg/kg) loading dose and 2 mg/kg weekly plus a daily dose of 4 tablets of lapatinib (1000 mg) at approximately the same time every day, either 1 hour (or more) before a meal or 1 hour (or more) after a meal.

Reporting group title	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg

Reporting group description:

Participants received an IV infusion of paclitaxel 70 mg/m^2 over 60 minutes weekly for 3 weeks of a 4-week cycle plus an IV infusion of trastuzumab 4 mg/kg loading dose and 2 mg/kg weekly plus a daily dose of 4 tablets of lapatinib (1000 mg) at approximately the same time every day, either 1 hour (or more) before a meal or 1 hour (or more) after a meal. The paclitaxel dose was systematically increased to 80 mg/m^2 after 2 cycles if 70 mg/m^2 was tolerated.

Reporting group title	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg

Reporting group description:

Participants received an IV infusion of paclitaxel 80 mg/m^2 over 60 minutes weekly for 3 weeks of a 4-week cycle plus an IV infusion of trastuzumab 4 mg/kg loading dose and 2 mg/kg weekly plus a daily dose of 3 tablets of lapatinib (750 mg) at approximately the same time every day, either 1 hour (or more) before a meal or 1 hour (or more) after a meal. The lapatinib dose was systematically increased to 1000 mg after 2 cycles if the 750 mg dose was tolerated.

Reporting group values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg
Number of subjects	29	14	20
Age categorical Units: Subjects			
Adults (18-64 years)	25	11	16
From 65-84 years	4	3	4
Age continuous Units: years			
arithmetic mean	51.5	56.1	52.2
standard deviation	± 11.08	± 11.92	± 13.00
Gender categorical Units: Subjects			
Female	29	14	20
Male	0	0	0
GenderNIH Units: Subjects			
Female	29	14	20
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	7	2	4
Native Hawaiian or Other Pacific Islander	0	1	0

White - White/Caucasian/European Heritage	22	11	16

AgeContinuous			
Units: Years			
arithmetic mean	51.5	56.1	52.2
standard deviation	± 11.08	± 11.92	± 13.00

Reporting group values	Total		
Number of subjects	63		
Age categorical			
Units: Subjects			
Adults (18-64 years)	52		
From 65-84 years	11		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	63		
Male	0		
GenderNIH			
Units: Subjects			
Female	63		
Male	0		
Race/Ethnicity, Customized			
Units: Subjects			
African American/African Heritage	13		
Native Hawaiian or Other Pacific Islander	1		
White - White/Caucasian/European Heritage	49		
AgeContinuous			
Units: Years			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg

Reporting group description:

Participants received an intravenous (IV) infusion of paclitaxel 80 milligrams per meter squared (mg/m^2) over 60 minutes weekly for 3 weeks of a 4-week cycle plus an IV infusion of trastuzumab 4 mg per kilogram (mg/kg) loading dose and 2 mg/kg weekly plus a daily dose of 4 tablets of lapatinib (1000 mg) at approximately the same time every day, either 1 hour (or more) before a meal or 1 hour (or more) after a meal.

Reporting group title	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg

Reporting group description:

Participants received an IV infusion of paclitaxel 70 mg/m^2 over 60 minutes weekly for 3 weeks of a 4-week cycle plus an IV infusion of trastuzumab 4 mg/kg loading dose and 2 mg/kg weekly plus a daily dose of 4 tablets of lapatinib (1000 mg) at approximately the same time every day, either 1 hour (or more) before a meal or 1 hour (or more) after a meal. The paclitaxel dose was systematically increased to 80 mg/m^2 after 2 cycles if 70 mg/m^2 was tolerated.

Reporting group title	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg

Reporting group description:

Participants received an IV infusion of paclitaxel 80 mg/m^2 over 60 minutes weekly for 3 weeks of a 4-week cycle plus an IV infusion of trastuzumab 4 mg/kg loading dose and 2 mg/kg weekly plus a daily dose of 3 tablets of lapatinib (750 mg) at approximately the same time every day, either 1 hour (or more) before a meal or 1 hour (or more) after a meal. The lapatinib dose was systematically increased to 1000 mg after 2 cycles if the 750 mg dose was tolerated.

Primary: Extent of exposure to lapatinib, trastuzumab and paclitaxel by Mean/Standard Deviation

End point title	Extent of exposure to lapatinib, trastuzumab and paclitaxel by Mean/Standard Deviation[1]

End point description:

Extent of exposure is defined as the duration of the treatment administered during the study. The mean duration of exposure to lapatinib, trastuzumab and paclitaxel is calculated as the number of weeks between the start and end of treatment.

End point type	Primary

End point timeframe:

From the date of the first dose of the investigational product to end of study, up to approx. 14 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: no statistical analysis was planned for this endpoint

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	14	20	
Units: Weeks				
arithmetic mean (standard deviation)				
Lapatinib	70.9 (± 115.44)	93.1 (± 147.92)	82.5 (± 135.79)	

Trastuzumab	60.7 (± 72.07)	72.2 (± 88.66)	62.3 (± 75.52)	
Paclitaxel	26.9 (± 16.88)	29.4 (± 23.00)	23.8 (± 14.87)	

Statistical analyses

No statistical analyses for this end point

Primary: Extent of exposure to lapatinib, trastuzumab and paclitaxel by Median/Min-Max

End point title	Extent of exposure to lapatinib, trastuzumab and paclitaxel by Median/Min-Max[2]

End point description:

Extent of exposure is defined as the duration of the treatment administered during the study. The mean duration of exposure to lapatinib, trastuzumab and paclitaxel is calculated as the number of weeks between the start and end of treatment.

End point type	Primary

End point timeframe:

From the date of the first dose of the investigational product to end of study, up to approx. 14 years

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: no statistical analysis was planned for this endpoint

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	14	20	
Units: Weeks				
median (full range (min-max))				
Lapatinib	33.0 (3 to 615)	38.5 (2 to 547)	32.5 (1 to 574)	
Trastuzumab	33.0 (2 to 343)	37.0 (2 to 271)	31.5 (1 to 245)	
Paclitaxel	22.0 (2 to 86)	23.5 (2 to 94)	22.0 (1 to 63)	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with any adverse event (AE) or serious adverse event (SAE)

End point title	Number of participants with any adverse event (AE) or serious adverse event (SAE)[3]

End point description:

An AE is defined as any untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, or is a

congenital anomaly/birth defect. Medical or scientific judgment was exercised in deciding whether reporting was appropriate in other situations. Refer to the general AE/SAE module for a list of non-serious AEs and SAEs.

End point type	Primary

End point timeframe:

From the date of the first dose of investigational product until 30 days after the last dose of investigational product, up to approx. 14 years

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: no statistical analysis was planned for this endpoint

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	14	20	
Units: Participants				
Any AEs	29	14	20	
Any SAEs	14	6	5	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who died due to any cause

End point title	Number of participants who died due to any cause[4]

End point description:

Number of participants who died due to any cause throughout the study.

End point type	Primary

End point timeframe:

From the date of the first dose of investigational product until 30 days after the last dose of investigational product, up to approx. 14 years

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: no statistical analysis was planned for this endpoint

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	14	20	
Units: Participants	12	2	1	

Statistical analyses

No statistical analyses for this end point

Primary: Number of events of diarrhea with the indicated characteristics

End point title	Number of events of diarrhea with the indicated

End point description:

Events of diarrhea are characterized as serious, related to investigational product, leading to withdrawal from the study and fatal. Participants could have been counted in more than one category.

End point type	Primary

End point timeframe:

From the date of the first dose of investigational product until 30 days after the last dose of investigational product, up to approx. 3.5 years

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: no statistical analysis was planned for this endpoint

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	13	13	
Units: Events of diarrhea				
Any Event	358	90	37	
Serious	4	0	0	
Related to investigational product	347	75	26	
Leading to withdrawal from study	2	1	1	
Fatal	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of events of rash with the indicated characteristics

End point title	Number of events of rash with the indicated characteristics[6]

End point description:

Events of rash are characterized as serious, related to investigational product, leading to withdrawal from the study and fatal. Participants could have been counted in more than one category.

End point type	Primary

End point timeframe:

From the date of the first dose of investigational product until 30 days after the last dose of investigational product, up to approx. 3.5 years

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: no statistical analysis was planned for this endpoint

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	8	15	
Units: Events of rash				
Any Event	69	23	20	
Serious	2	0	0	
Related to investigational product	55	12	7	
Leading to withdrawal from study	3	0	0	
Fatal	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with the maximum toxicity grade for the indicated clinical hematology parameters

End point title	Number of participants with the maximum toxicity grade for the indicated clinical hematology parameters[7]

End point description:

Blood samples for clinical laboratory evaluation were taken at Baseline prior to the administration of investigational product and thereafter at each scheduled visit. Haematology parameters included haemoglobin, total white blood cell count (WBC), neutrophils, lymphocytes and platelets. Hematology data was summarized by the National Cancer Institute's Common toxicity criteria for adverse events (NCI CTCAE) toxicity grade (Version 3.0). Grade 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, life-threatening or disabling; Grade 5, death.

End point type	Primary

End point timeframe:

Baseline and every 4 weeks thereafter up to withdrawal/study completion and 30 day follow-up, up to approx. 3.5 years

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: no statistical analysis was planned for this endpoint

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	14	20	
Units: Participants				
Haemaglobin, Grade 1	19	11	11	
Haemaglobin, Grade 2	7	1	6	
Haemaglobin, Grade 3	2	0	1	
Haemaglobin, Grade 4	1	0	0	
Platelets, Grade 1	3	0	0	
Platelets, Grade 2	1	0	0	
Platelets, Grade 3	0	0	0	

Platelets, Grade 4	1	0	0	
Total WBC, Grade 1	10	6	7	
Total WBC, Grade 2	8	4	2	
Total WBC, Grade 3	3	1	4	
Total WBC, Grade 4	1	0	0	
Neutrophils, Grade 1	7	2	5	
Neutrophils, Grade 2	7	4	4	
Neutrophils, Grade 3	3	1	5	
Neutrophils, Grade 4	3	0	0	
Lymphocytes, Grade 1	5	3	7	
Lymphocytes, Grade 2	10	4	4	
Lymphocytes, Grade 3	5	3	1	
Lymphocytes, Grade 4	1	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with the maximum toxicity grade for the indicated clinical chemistry parameters

End point title	Number of participants with the maximum toxicity grade for the indicated clinical chemistry parameters[8]

End point description:

Blood samples for clinical laboratory evaluation were taken at Baseline prior to the administration of investigational product and thereafter at each scheduled visit. Clinical chemistry parameters included values > upper limit of normal (ULN)=Hyper; values < lower limit of normal (LLN)=Hypo of sodium (Hypernatraemia and Hyponatraemia), potassium (Hyperkalaemia and Hypokalaemia), calcium (Hypercalcaemia and Hypocalcaemia), glucose (Hyperglycaemia and Hyperglycaemia), creatinine (if >2 milligram per deciliter [mg/dL]), aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phophatase, total bilirubin (if available bilirubin fractionation is recommended if the total bilirubin is > twice of ULN), and albumin. Clinical chemistry data was summarized by National Cancer Institute's Common toxicity criteria for adverse events (NCI CTCAE) toxicity grade (Version 3.0). Grade 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, life-threatening or disabling; Grade 5, death.

End point type	Primary

End point timeframe:

Baseline and every 4 weeks thereafter up to withdrawal/study completion and 30 day follow-up, up to approx. 3.5 years

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: no statistical analysis was planned for this endpoint

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	14	20	
Units: Participants				
Hypernatraemia, Grade 1	0	1	1	
Hypernatraemia, Grade 2	1	0	0	
Hypernatraemia, Grade 3	0	0	0	

Hypernatraemia, Grade 4	0	0	0	
Hyponatraemia, Grade 1	8	1	1	
Hyponatraemia, Grade 2	0	0	0	
Hyponatraemia, Grade 3	0	1	0	
Hyponatraemia, Grade 4	0	0	0	
Hyperkalaemia, Grade 1	2	0	0	
Hyperkalaemia, Grade 2	2	1	1	
Hyperkalaemia, Grade 3	0	0	0	
Hyperkalaemia, Grade 4	1	0	1	
Hypokalaemia, Grade 1	11	6	6	
Hypokalaemia, Grade 2	0	0	0	
Hypokalaemia, Grade 3	6	2	0	
Hypokalaemia, Grade 4	0	0	0	
Hypercalcaemia, Grade 1, n=29, 14, 19	1	0	0	
Hypercalcaemia, Grade 2, n=29, 14, 19	0	0	0	
Hypercalcaemia, Grade 3, n=29, 14, 19	0	0	0	
Hypercalcaemia, Grade 4, n=29, 14, 19	0	0	0	
Hypocalcaemia, Grade 1, n=29, 14, 19	10	3	4	
Hypocalcaemia, Grade 2, n=29, 14, 19	7	2	3	
Hypocalcaemia, Grade 3, n=29, 14, 19	3	0	1	
Hypocalcaemia, Grade 4, n=29, 14, 19	0	0	0	
Hyperglycaemia, Grade 1, n=29, 14, 19	15	9	6	
Hyperglycaemia, Grade 2, n=29, 14, 19	3	3	2	
Hyperglycaemia, Grade 3, n=29, 14, 19	5	0	2	
Hyperglycaemia, Grade 4, n=29, 14, 19	0	0	0	
Hypoglycemia, Grade 1, n=29, 14, 19	5	2	2	
Hypoglycemia, Grade 2, n=29, 14, 19	0	1	1	
Hypoglycemia, Grade 3, n=29, 14, 19	0	0	0	
Hypoglycemia, Grade 4, n=29, 14, 19	0	0	0	
Albumin, Grade 1, n=29, 14, 18	5	3	1	
Albumin, Grade 2, n=29, 14, 18	3	0	0	
Albumin, Grade 3, n=29, 14, 18	1	0	0	
Albumin, Grade 4, n=29, 14, 18	0	0	0	
Total Bilirubin, Grade 1	2	1	3	
Total Bilirubin, Grade 2	2	2	1	
Total Bilirubin, Grade 3	1	1	0	
Total Bilirubin, Grade 4	0	0	0	
Creatinine, Grade 1	2	0	0	
Creatinine, Grade 2	2	0	0	
Creatinine, Grade 3	1	0	0	
Creatinine, Grade 4	0	0	0	
Alkaline Phophatase, Grade 1	14	3	5	
Alkaline Phophatase, Grade 2	2	0	0	
Alkaline Phophatase, Grade 3	2	0	0	
Alkaline Phophatase, Grade 4	0	0	0	
ALT, Grade 1	7	1	3	
ALT, Grade 2	3	3	2	
ALT, Grade 3	0	0	0	
ALT, Grade 4	0	0	0	
AST, Grade 1	6	3	6	
AST, Grade 2	1	1	0	
AST, Grade 3	1	1	0	

AST, Grade 4	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of events of hepatotoxicity with the indicated characteristics

End point title	Number of events of hepatotoxicity with the indicated characteristics[9]

End point description:

Events of hepatotoxicity are characterized as serious, related to investigational product, leading to withdrawal from the study and fatal. Participants could have been counted in more than one category.

End point type	Primary

End point timeframe:

From the date of the first dose of investigational product until 30 days after the last dose of investigational product, up to approx. 3.5 years

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: no statistical analysis was planned for this endpoint

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	0[10]	2	
Units: Events of hepatotoxicity				
Any Event	6		2	
Serious	0		0	
Related to investigational product	5		0	
Leading to withdrawal from study	0		0	
Fatal	0		0	

Notes:

[10] - no patients analyzed in this arm had a hepatotoxisity event

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in systolic blood pressure and diastolic blood pressure at the indicated time points

End point title	Change from Baseline in systolic blood pressure and diastolic blood pressure at the indicated time points[11]

End point description:

Blood pressure measurement included systolic blood pressure (SBP) and diastolic blood pressure (DBP) at Baseline and every 4 weeks thereafter up to withdrawal/study completion and at the 30 day follow-up visit. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Primary

End point timeframe:

Baseline and every 4 weeks thereafter up to withdrawal/study completion and 30 day follow-up, up to approx. 3.5 years

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: no statistical analysis was planned for this endpoint

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	14	20	
Units: Millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
SBP, Week 4, n=28, 12, 18	0.5 (± 16.29)	-7.2 (± 20.70)	-3.9 (± 22.76)	
SBP, Week 8, n=27, 13, 17	4.6 (± 12.35)	-8.6 (± 22.25)	-2.7 (± 24.73)	
SBP, Week 12, n=24, 12, 16	3.2 (± 18.46)	-6.9 (± 17.09)	-9.3 (± 23.54)	
SBP, Week 16, n= 23, 11, 15	0.8 (± 18.10)	-6.6 (± 15.26)	-7.9 (± 24.43)	
SBP, Week 20, n=23, 8, 12	1.7 (± 17.80)	-11.5 (± 14.69)	-13.8 (± 25.15)	
SBP, Week 24, n=21, 10, 6	2.9 (± 13.87)	-1.8 (± 11.81)	-7.8 (± 26.06)	
SBP, Week 28, n=17, 7, 5	2.3 (± 19.10)	-5.7 (± 20.38)	-5.2 (± 10.71)	
SBP, Week 32, n=16, 8, 3	3.2 (± 23.11)	-16.4 (± 10.03)	-6.3 (± 5.51)	
SBP, Week 36, n=13, 7, 3	1.6 (± 15.85)	-8.7 (± 12.19)	-26.7 (± 37.75)	
SBP, Week 40, n=12, 7, 2	-2.2 (± 24.44)	-3.4 (± 9.62)	-34.0 (± 38.18)	
SBP, Week 44, n=11, 6, 2	2.7 (± 14.47)	-3.8 (± 9.83)	-38.0 (± 32.53)	
SBP, Week 48, n=11, 6, 1	6.5 (± 18.76)	-6.7 (± 11.18)	-84.0 (± 999)	
SBP, Week 52, n=9, 5, 0	7.7 (± 14.47)	-3.8 (± 24.78)	999 (± 999)	
SBP, Week 56, n=9, 5, 0	8.4 (± 13.53)	-8.2 (± 18.74)	999 (± 999)	
SBP, Week 60, n=10, 4, 0	9.3 (± 22.07)	-17.0 (± 9.31)	999 (± 999)	
SBP, Week 64, n=10, 4, 0	3.5 (± 16.53)	-11.3 (± 11.24)	999 (± 999)	
SBP, Week 68, n=7, 2, 0	0.1 (± 10.71)	-6.5 (± 12.02)	999 (± 999)	
SBP, Week 72, n=7, 1, 0	7.1 (± 13.25)	-20.0 (± 999)	999 (± 999)	
SBP, Week 76, n=6, 0, 0	4.5 (± 12.96)	999 (± 999)	999 (± 999)	
SBP, Week 80, n=6, 0, 0	8.7 (± 6.92)	999 (± 999)	999 (± 999)	
SBP, Week 84, n=6, 0, 0	7.0 (± 20.20)	999 (± 999)	999 (± 999)	
SBP, Week 88, n=6, 0, 0	-2.7 (± 16.32)	999 (± 999)	999 (± 999)	
SBP, Week 92, n=5, 0, 0	10.4 (± 16.59)	999 (± 999)	999 (± 999)	
SBP, Week 96, n=4, 0, 0	-0.5 (± 4.12)	999 (± 999)	999 (± 999)	
SBP, Week 100, n=5, 0, 0	10.8 (± 7.53)	999 (± 999)	999 (± 999)	
SBP, Week 104, n=5, 0, 0	7.0 (± 16.00)	999 (± 999)	999 (± 999)	
SBP, Week 108, n=5, 0, 0	4.6 (± 7.89)	999 (± 999)	999 (± 999)	
SBP, Week 112, n=4, 0, 0	12.3 (± 10.72)	999 (± 999)	999 (± 999)	
SBP, Week 116, n=4, 0, 0	9.3 (± 15.22)	999 (± 999)	999 (± 999)	
SBP, Week 120, n=3, 0, 0	13.3 (± 19.86)	999 (± 999)	999 (± 999)	
SBP, Week 124, n=3, 0, 0	7.3 (± 8.50)	999 (± 999)	999 (± 999)	

SBP, Week 128, n=2, 0, 0	-11.0 (± 9.90)	999 (± 999)	999 (± 999)	
SBP, Week 132, n=2, 0, 0	-10.5 (± 10.61)	999 (± 999)	999 (± 999)	
SBP, Week 136, n=2, 0, 0	-4.0 (± 18.38)	999 (± 999)	999 (± 999)	
SBP, Week 140, n=2, 0, 0	4.5 (± 23.33)	999 (± 999)	999 (± 999)	
SBP, Week 144, n=1, 0, 0	10.0 (± 0)	999 (± 999)	999 (± 999)	
SBP, Week 148, n=1, 0, 0	25.0 (± 999)	999 (± 999)	999 (± 999)	
SBP, Withdrawal/Study Conclusion, n=23, 10, 8	0.5 (± 16.13)	-1.3 (± 15.64)	7.0 (± 20.28)	
SBP, 30 Day Follow-up, n=25, 9, 5	2.4 (± 19.18)	-3.9 (± 17.03)	13.8 (± 19.25)	
DBP, Week 4, n=28, 12, 18	-2.5 (± 10.36)	-3.9 (± 10.50)	-4.8 (± 11.10)	
DBP, Week 8, n=27, 13, 17	-0.6 (± 11.41)	-8.9 (± 11.54)	-1.2 (± 12.46)	
DBP, Week 12, n=24, 12, 16	-0.3 (± 10.19)	-6.2 (± 10.37)	-4.2 (± 12.87)	
DBP, Week 16, n= 23, 11, 15	-3.4 (± 12.98)	-3.2 (± 8.42)	-4.4 (± 15.18)	
DBP, Week 20, n=23, 8, 12	-3.0 (± 12.65)	-1.6 (± 9.53)	-9.1 (± 13.65)	
DBP, Week 24, n=21, 10, 6	-1.2 (± 11.30)	-1.8 (± 6.56)	-5.2 (± 13.08)	
DBP, Week 28, n=17, 7, 5	-1.8 (± 14.27)	-2.1 (± 8.15)	-2.0 (± 5.05)	
DBP, Week 32, n=16, 8, 3	-2.2 (± 13.70)	-6.3 (± 10.24)	-4.7 (± 6.51)	
DBP, Week 36, n=13, 7, 3	-7.2 (± 6.48)	-3.3 (± 6.40)	-10.7 (± 11.02)	
DBP, Week 40, n=12, 7, 2	-9.3 (± 11.36)	-0.7 (± 13.76)	-8.0 (± 19.80)	
DBP, Week 44, n=11, 6, 2	-9.0 (± 6.59)	-2.3 (± 10.33)	-19.5 (± 6.36)	
DBP, Week 48, n=11, 6, 1	-3.9 (± 7.57)	-0.2 (± 8.13)	-34.0 (± 999)	
DBP, Week 52, n=9, 5, 0	-7.4 (± 13.46)	-3.0 (± 12.33)	999 (± 999)	
DBP, Week 56, n=9, 5, 0	9 (± 8.62)	9 (± 7.99)	999 (± 999)	
DBP, Week 60, n=10, 4, 0	-3.6 (± 11.56)	-6.3 (± 6.24)	999 (± 999)	
DBP, Week 64, n=10, 4, 0	-7.7 (± 12.27)	-5.3 (± 8.54)	999 (± 999)	
DBP, Week 68, n=7, 2, 0	-11.0 (± 6.40)	-3.5 (± 7.78)	999 (± 999)	
DBP, Week 72, n=7, 1, 0	3.0 (± 9.26)	-16.0 (± 999)	999 (± 999)	
DBP, Week 76, n=6, 0, 0	-4.8 (± 5.00)	999 (± 999)	999 (± 999)	
DBP, Week 80, n=6, 0, 0	-3.5 (± 5.58)	999 (± 999)	999 (± 999)	
DBP, Week 84, n=6, 0, 0	-5.8 (± 9.50)	999 (± 999)	999 (± 999)	
DBP, Week 88, n=6, 0, 0	-9.3 (± 11.48)	999 (± 999)	999 (± 999)	
DBP, Week 92, n=5, 0, 0	-3.8 (± 5.26)	999 (± 999)	999 (± 999)	
DBP, Week 96, n=4, 0, 0	-7.3 (± 6.29)	999 (± 999)	999 (± 999)	
DBP, Week 100, n=5, 0, 0	-4.4 (± 6.50)	999 (± 999)	999 (± 999)	
DBP, Week 104, n=5, 0, 0	-4.6 (± 9.10)	999 (± 999)	999 (± 999)	
DBP, Week 108, n=5, 0, 0	-2.0 (± 5.89)	999 (± 999)	999 (± 999)	
DBP, Week 116, n=4, 0, 0	-8.5 (± 9.33)	999 (± 999)	999 (± 999)	
DBP, Week 120, n=3, 0, 0	-6.0 (± 7.94)	999 (± 999)	999 (± 999)	
DBP, Week 124, n=3, 0, 0	-6.0 (± 6.00)	999 (± 999)	999 (± 999)	
DBP, Week 128, n=2, 0, 0	-12.5 (± 0.71)	999 (± 999)	999 (± 999)	
DBP, Week 132, n=2, 0, 0	-14.5 (± 4.95)	999 (± 999)	999 (± 999)	
DBP, Week 136, n=2, 0, 0	-17.0 (± 4.24)	999 (± 999)	999 (± 999)	
DBP, Week 140, n=2, 0, 0	-7.5 (± 10.61)	999 (± 999)	999 (± 999)	
DBP, Week 144, n=1, 0, 0	0.0 (± 0)	999 (± 999)	999 (± 999)	
DBP, Week 148, n=1, 0, 0	1.0 (± 999)	999 (± 999)	999 (± 999)	
DBP, Withdrawal/Study Conclusion, n=23, 10, 8	-0.5 (± 11.39)	-0.4 (± 12.08)	2.1 (± 8.64)	
DBP, 30 Day Follow-up, n=25, 9, 5	-0.8 (± 11.96)	0.8 (± 11.62)	3.2 (± 9.98)	

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in heart rate at the indicated time points

End point title	Change from Baseline in heart rate at the indicated time

End point description:

Heart rate was measured at Baseline and every 4 weeks thereafter up to withdrawal/study completion and at the 30 day follow-up visit. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Primary

End point timeframe:

Baseline and every 4 weeks thereafter up to withdrawal/study completion and 30 day follow-up, up to approx. 3.5 years

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: no statistical analysis was planned for this endpoint

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	14	20	
Units: Beats per minute (BPM)				
arithmetic mean (standard deviation)				
Week 4, n=28, 12, 18	-1.714 (± 10.9099)	-3.417 (± 26.3593)	3.333 (± 12.1268)	
Week 8, n=27, 13, 17	-5.667 (± 14.7908)	-3.231 (± 16.8481)	5.353 (± 10.7642)	
Week 12, n=23, 12, 16	-0.217 (± 10.7109)	-0.417 (± 15.6812)	-2.875 (± 10.6074)	
Week 16, n= 22, 11, 14	-0.478 (± 13.4667)	2.625 (± 15.1369)	-1.917 (± 10.9084)	
Week 24, n=21, 10, 6	-0.476 (± 16.7768)	-5.300 (± 15.1808)	5.167 (± 10.2843)	
Week 28, n=16, 7, 5	-4.313 (± 16.0155)	-1.429 (± 17.7281)	3.600 (± 8.5615)	
Week 32, n=15, 8, 3	-4.933 (± 16.6496)	-0.500 (± 11.1098)	0.333 (± 10.5987)	
Week 36, n=13, 7, 3	-5.000 (± 13.0128)	4.857 (± 18.4791)	7.000 (± 11.5326)	
Week 40, n=12, 7, 2	-1.000 (± 14.1614)	-3.571 (± 17.6149)	-2.500 (± 9.1924)	
Week 44, n=11, 6, 2	-3.000 (± 11.1624)	-5.000 (± 17.9778)	-0.500 (± 10.6066)	
Week 48, n=10, 6, 1	-5.500 (± 8.1955)	-2.500 (± 12.9422)	-14.000 (± 999)	

Week 52, n=9, 5, 0	-1.889 (± 14.4866)	-2.000 (± 11.8533)	999 (± 999)	
Week 56, n=8, 5, 0	-2.000 (± 13.4907)	-2.000 (± 15.2151)	999 (± 999)	
Week 60, n=10, 4, 0	-2.600 (± 13.3766)	1.500 (± 15.0222)	999 (± 999)	
Week 64, n=9, 4, 0	-4.667 (± 16.1245)	0.000 (± 15.3840)	999 (± 999)	
Week 68, n=7, 2, 0	-8.286 (± 21.1638)	1.000 (± 25.4558)	999 (± 999)	
Week 72, n=7, 1, 0	-0.714 (± 21.0295)	19.000 (± 999)	999 (± 999)	
Week 76, n=6, 0, 0	-0.500 (± 16.6463)	999 (± 999)	999 (± 999)	
Week 80, n=5, 0, 0	0.800 (± 14.4810)	999 (± 999)	999 (± 999)	
Week 84, n=5, 0, 0	9.200 (± 21.1234)	999 (± 999)	999 (± 999)	
Week 88, n=5, 0, 0	2.200 (± 24.6110)	999 (± 999)	999 (± 999)	
Week 92, n=5, 0, 0	-2.400 (± 10.1390)	999 (± 999)	999 (± 999)	
Week 96, n=4, 0, 0	-8.250 (± 7.6322)	999 (± 999)	999 (± 999)	
Week 100, n=4, 0, 0	-6.750 (± 13.1751)	999 (± 999)	999 (± 999)	
Week 104, n=5, 0, 0	-6.800 (± 15.3525)	999 (± 999)	999 (± 999)	
Week 108, n=4, 0, 0	-8.750 (± 6.4485)	999 (± 999)	999 (± 999)	
Week 112, n=3, 0, 0	-0.667 (± 15.0444)	999 (± 999)	999 (± 999)	
Week 116, n=3, 0, 0	-4.667 (± 14.5717)	999 (± 999)	999 (± 999)	
Week 120, n=3, 0, 0	-7.667 (± 9.4516)	999 (± 999)	999 (± 999)	
Week 124, n=3, 0, 0	-5.333 (± 13.2035)	999 (± 999)	999 (± 999)	
Week 128, n=2, 0, 0	1.000 (± 21.2132)	999 (± 999)	999 (± 999)	
Week 132, n=2, 0, 0	-4.000 (± 14.1421)	999 (± 999)	999 (± 999)	
Week 136, n=2, 0, 0	-4.000 (± 15.5563)	999 (± 999)	999 (± 999)	
Week 140, n=2, 0, 0	-3.500 (± 16.2635)	999 (± 999)	999 (± 999)	
Week 144, n=1, 0, 0	3.000 (± 999)	999 (± 999)	999 (± 999)	
Week 148, n=1, 0, 0	6.000 (± 999)	999 (± 999)	999 (± 999)	
Withdrawal/Study Conclusion, n=23, 10, 8	-1.435 (± 19.3481)	-7.900 (± 19.3990)	7.750 (± 9.8814)	
30 Day Follow-up, n=25, 9, 5	0.560 (± 13.1564)	-7.889 (± 17.3526)	13.200 (± 11.6060)	

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in body temperature at the indicated time points

End point title	Change from Baseline in body temperature at the indicated time points[13]

End point description:

Body temperature was measured at Baseline and every 4 weeks thereafter up to withdrawal/study completion and at the 30 day follow-up visit. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Primary

End point timeframe:

Baseline and every 4 weeks thereafter up to withdrawal/study completion and 30 day follow-up, up to approx. 3.5 years

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: no statistical analysis was planned for this endpoint

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	14	20	
Units: Degree Celsius				
arithmetic mean (standard deviation)				
Week 4, n=28, 12, 18	-0.229 (± 0.5062)	-0.242 (± 0.3605)	0.078 (± 0.5976)	
Week 8, n=27, 13, 17	0.011 (± 0.5250)	-0.154 (± 0.4294)	0.247 (± 0.4652)	
Week 12, n=24, 12, 15	0.021 (± 0.4374)	-0.567 (± 0.4960)	0.173 (± 0.4636)	
Week 16, n= 23, 11, 14	-0.052 (± 0.5814)	-0.127 (± 0.4880)	0.121 (± 0.5494)	
Week 20, n=22, 8, 12	0.018 (± 0.5712)	-0.238 (± 0.4138)	0.300 (± 0.3536)	
Week 24, n=21, 9, 6	0.157 (± 0.5006)	-0.100 (± 0.4138)	0.017 (± 0.5193)	
Week 28, n=17, 7, 5	-0.094 (± 0.4956)	-0.529 (± 0.4751)	0.300 (± 0.3536)	
Week 32, n=16, 8, 3	-0.156 (± 0.6077)	-0.237 (± 0.2134)	0.000 (± 0.2000)	
Week 36, n=13, 7, 3	-0.215 (± 0.5728)	-0.129 (± 0.3946)	0.533 (± 0.3786)	
Week 40, n=11, 7, 2	0.045 (± 0.4634)	-0.314 (± 0.1952)	0.450 (± 0.9192)	
Week 44, n=11, 6, 2	-0.182 (± 0.4729)	-0.217 (± 0.3920)	0.250 (± 0.0707)	
Week 48, n=11, 6, 1	-0.109 (± 0.4571)	-0.200 (± 0.1414)	0.300 (± 999)	
Week 52, n=9, 5, 0	-0.222 (± 1.0616)	-0.340 (± 0.3286)	0 (± 0)	
Week 56, n=9, 5, 0	0.111 (± 0.6489)	-0.240 (± 0.6427)	999 (± 999)	
Week 60, n=10, 4, 0	-0.070 (± 0.5889)	-0.225 (± 0.2754)	999 (± 999)	
Week 64, n=10, 4, 0	-0.080 (± 0.4662)	-0.150 (± 0.1732)	999 (± 999)	
Week 68, n=7, 2, 0	0.286 (± 0.6744)	-0.550 (± 0.0707)	999 (± 999)	

Week 72, n=7, 1, 0	0.057 (± 0.7390)	-0.400 (± 999)	999 (± 999)	
Week 76, n=6, 0, 0	0.017 (± 0.4834)	999 (± 999)	999 (± 999)	
Week 80, n=6, 0, 0	-0.150 (± 0.6442)	999 (± 999)	999 (± 999)	
Week 84, n=6, 0, 0	0.067 (± 0.5610)	999 (± 999)	999 (± 999)	
Week 88, n=6, 0, 0	-0.267 (± 0.4131)	999 (± 999)	999 (± 999)	
Week 92, n=5, 0, 0	-0.200 (± 0.8155)	999 (± 999)	999 (± 999)	
Week 96, n=4, 0, 0	-0.125 (± 0.4573)	999 (± 999)	999 (± 999)	
Week 100, n=5, 0, 0	-0.100 (± 0.9083)	999 (± 999)	999 (± 999)	
Week 104, n=5, 0, 0	-0.160 (± 0.7436)	999 (± 999)	999 (± 999)	
Week 108, n=4, 0, 0	0.080 (± 0.6099)	999 (± 999)	999 (± 999)	
Week 112, n=4, 0, 0	0.050 (± 0.5000)	999 (± 999)	999 (± 999)	
Week 116, n=3, 0, 0	0.250 (± 0.6403)	999 (± 999)	999 (± 999)	
Week 120, n=3, 0, 0	0.200 (± 0.4359)	999 (± 999)	999 (± 999)	
Week 124, n=3, 0, 0	0.167 (± 0.8083)	999 (± 999)	999 (± 999)	
Week 128, n=2, 0, 0	0.200 (± 1.4142)	999 (± 999)	999 (± 999)	
Week 132, n=2, 0, 0	-0.150 (± 1.2021)	999 (± 999)	999 (± 999)	
Week 136, n=2, 0, 0	0.000 (± 1.2728)	999 (± 999)	999 (± 999)	
Week 140, n=2, 0, 0	0.450 (± 1.3435)	999 (± 999)	999 (± 999)	
Week 144, n=1, 0, 0	1.300 (± 999)	999 (± 999)	999 (± 999)	
Week 148, n=1, 0, 0	0.700 (± 999)	999 (± 999)	999 (± 999)	
Withdrawal/Study Conclusion, n=23, 10, 8	-0.083 (± 0.6833)	-0.020 (± 0.4367)	0.237 (± 0.5999)	
30 Day Follow-up, n=25, 9, 5	-0.092 (± 0.6238)	-0.400 (± 0.5074)	0.140 (± 0.5320)	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with at least 1 event of left ventricular ejection fraction decrease with the indicated characteristics

End point title	Number of participants with at least 1 event of left ventricular ejection fraction decrease with the indicated characteristics[14]

End point description:

Events of left ventricular ejection fraction (LVEF) decrease were characterized as serious, related to investigational product, leading to withdrawal from the study and fatal. A participant could have been counted in more than one category.

End point type	Primary

End point timeframe:

Baseline and every 8 weeks thereafter up to withdrawal/study completion and 30 day follow-up, up to approx. 3.5 years

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: no statistical analysis was planned for this endpoint

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	14	20[15]	
Units: Participants	8	2	0	

Notes:

[15] - no patients analyzed in this arm had an LVEF decrease event

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with the indicated eastern cooperative oncology group (ECOG) performance status value

End point title	Number of participants with the indicated eastern cooperative oncology group (ECOG) performance status value[16]

End point description:

The Eastern Cooperative Oncology Group (ECOG) performance status scales and grades/criteria are used to assess how a participant's disease is progressing, to assess how the disease affects the daily living abilities of the participant, and to determine appropriate treatment and prognosis. Grade 0, fully active, able to carry on all pre-disease performance without restriction. Grade 1, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. Grade 2, ambulatory and capable of all selfcare, but unable to carry out any work activities; up and about more than 50% of waking hours. Grade 3, capable of only limited selfcare; confined to bed or chair more than 50% of waking hours. Grade 4, completely disabled; cannot carry on any selfcare; totally confined to bed or chair. Grade 5, dead.

End point type	Primary

End point timeframe:

Baseline and every 4 weeks thereafter up to withdrawal/study completion and 30 day follow-up, up to approx. 3.5 years

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: no statistical analysis was planned for this endpoint

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	14	20	
Units: Participants				
Screening, Grade 3	0	0	0	
Screening, Grade 4	0	0	0	

Screening, Grade 5	0	0	0	
Day 1 pre-dose, Grade 3, n=29, 13, 20	0	0	0	
Day 1 pre-dose, Grade 4, n=29, 13, 20	0	0	0	
Day 1 pre-dose, Grade 5, n=29, 13, 20	0	0	0	
Week 4, Grade 3, n=28, 12, 18	0	0	0	
Week 4, Grade 4, n=28, 12, 18	0	0	0	
Week 4, Grade 5, n=28, 12, 18	0	0	0	
Week 8, Grade 3, n=27, 13, 16	0	0	0	
Week 8, Grade 4, n=27, 13, 16	0	0	0	
Week 8, Grade 5, n=27, 13, 16	0	0	0	
Week 12, Grade 3, n=24, 12, 16	0	0	0	
Week 12, Grade 4, n=24, 12, 16	0	0	0	
Week 12, Grade 5, n=24, 12, 16	0	0	0	
Week 16, Grade 3, n=22, 11, 15	0	0	0	
Week 16, Grade 4, n=22, 11, 15	0	0	0	
Week 16, Grade 5, n=22, 11, 15	0	0	0	
Week 20, Grade 3, n=24, 10, 11	0	0	0	
Week 20, Grade 4, n=24, 10, 11	0	0	0	
Week 20, Grade 5, n=24, 10, 11	0	0	0	
Week 24, Grade 3, n=21, 10, 6	0	0	0	
Week 24, Grade 4, n=21, 10, 6	0	0	0	
Week 24, Grade 5, n=21, 10, 6	0	0	0	
Week 28, Grade 3, n=17, 8, 4	0	0	0	
Week 28, Grade 4, n=17, 8, 4	0	0	0	
Week 28, Grade 5, n=17, 8, 4	0	0	0	
Week 32, Grade 3, n=16, 8, 3	0	0	0	
Week 32, Grade 4, n=16, 8, 3	0	0	0	
Week 32, Grade 5, n=16, 8, 3	0	0	0	
Week 36, Grade 3, n=12, 7, 3	0	0	0	
Week 36, Grade 4, n=12, 7, 3	0	0	0	
Week 36, Grade 5, n=12, 7, 3	0	0	0	
Week 40, Grade 3, n=12, 7, 2	0	0	0	
Week 40, Grade 4, n=12, 7, 2	0	0	0	
Week 40, Grade 5, n=12, 7, 2	0	0	0	
Week 44, Grade 3, n=11, 6, 2	0	0	0	
Week 44, Grade 4, n=11, 6, 2	0	0	0	
Week 44, Grade 5, n=11, 6, 2	0	0	0	
Week 48, Grade 3, n=10, 6, 1	0	0	0	
Week 48, Grade 4, n=10, 6, 1	0	0	0	
Week 48, Grade 5, n=10, 6, 1	0	0	0	
Week 52, Grade3 , n=9, 5, 0	0	0	0	
Week 52, Grade4 , n=9, 5, 0	0	0	0	
Week 52, Grade5 , n=9, 5, 0	0	0	0	
Week 56, Grade 3, n=8, 4, 0	0	0	0	
Week 56, Grade 4, n=8, 4, 0	0	0	0	
Week 56, Grade 5, n=8, 4, 0	0	0	0	
Week 60, Grade 3, n=10, 4, 0	0	0	0	
Week 60, Grade 4, n=10, 4, 0	0	0	0	
Week 60, Grade 5, n=10, 4, 0	0	0	0	
Week 64, Grade 3, n=9, 4, 0	0	0	0	
Week 64, Grade 4, n=9, 4, 0	0	0	0	
Week 64, Grade 5, n=9, 4, 0	0	0	0	

Week 68, Grade3 , n=8, 2, 0	0	0	0	
Week 68, Grade4 , n=8, 2, 0	0	0	0	
Week 68, Grade5 , n=8, 2, 0	0	0	0	
Week 72, Grade 3, n=7, 1, 0	0	0	0	
Week 72, Grade 4, n=7, 1, 0	0	0	0	
Week 72, Grade 5, n=7, 1, 0	0	0	0	
Week 76, Grade3 , n=6, 0, 0	0	0	0	
Week 76, Grade4 , n=6, 0, 0	0	0	0	
Week 76, Grade5 , n=6, 0, 0	0	0	0	
Week 80, Grade 3, n=6, 0, 0	0	0	0	
Week 80, Grade 4, n=6, 0, 0	0	0	0	
Week 80, Grade 5, n=6, 0, 0	0	0	0	
Week 84, Grade 3, n=6, 0, 0	0	0	0	
Week 84, Grade 4, n=6, 0, 0	0	0	0	
Week 84, Grade 5, n=6, 0, 0	0	0	0	
Week 88, Grade 3, n=6, 0, 0	0	0	0	
Week 88, Grade 4, n=6, 0, 0	0	0	0	
Week 88, Grade 5, n=6, 0, 0	0	0	0	
Week 92, Grade 3, n=5, 0, 0	0	0	0	
Week 92, Grade 4, n=5, 0, 0	0	0	0	
Week 92, Grade 5, n=5, 0, 0	0	0	0	
Week 96, Grade 3, n=4, 0, 0	0	0	0	
Week 96, Grade 4, n=4, 0, 0	0	0	0	
Week 96, Grade 5, n=4, 0, 0	0	0	0	
Week 100, Grade 3, n=5, 0, 0	0	0	0	
Week 100, Grade 4, n=5, 0, 0	0	0	0	
Week 100, Grade 5, n=5, 0, 0	0	0	0	
Week 104, Grade 3, n=5, 0, 0	0	0	0	
Week 104, Grade 4, n=5, 0, 0	0	0	0	
Week 104, Grade 5, n=5, 0, 0	0	0	0	
Week 108, Grade 3, n=5, 0, 0	0	0	0	
Week 108, Grade 4, n=5, 0, 0	0	0	0	
Week 108, Grade 5, n=5, 0, 0	0	0	0	
Week 112, Grade 3, n=4, 0, 0	0	0	0	
Week 112, Grade 4, n=4, 0, 0	0	0	0	
Week 112, Grade 5, n=4, 0, 0	0	0	0	
Week 116, Grade 3, n=4, 0, 0	0	0	0	
Week 116, Grade 4, n=4, 0, 0	0	0	0	
Week 116, Grade 5, n=4, 0, 0	0	0	0	
Week 120, Grade 3, n=3, 0, 0	0	0	0	
Week 120, Grade 4, n=3, 0, 0	0	0	0	
Week 120, Grade 5, n=3, 0, 0	0	0	0	
Week 124, Grade 3, n=3, 0, 0	0	0	0	
Week 124, Grade 4, n=3, 0, 0	0	0	0	
Week 124, Grade 5, n=3, 0, 0	0	0	0	
Week 128, Grade 3, n=2, 0, 0	0	0	0	
Week 128, Grade 4, n=2, 0, 0	0	0	0	
Week 128, Grade 5, n=2, 0, 0	0	0	0	
Week 132, Grade 3, n=2, 0, 0	0	0	0	
Week 132, Grade 4, n=2, 0, 0	0	0	0	
Week 132, Grade 5, n=2, 0, 0	0	0	0	
Week 136, Grade 3, n=2, 0, 0	0	0	0	

Week 136, Grade 4, n=2, 0, 0	0	0	0	
Week 136, Grade 5, n=2, 0, 0	0	0	0	
Week 140, Grade 3, n=2, 0, 0	2	0	0	
Week 140, Grade 4, n=2, 0, 0	0	0	0	
Week 140, Grade 5, n=2, 0, 0	0	0	0	
Week 144, Grade 3, n=1, 0, 0	0	0	0	
Week 144, Grade 4, n=1, 0, 0	0	0	0	
Week 144, Grade 5, n=1, 0, 0	0	0	0	
Week 148, Grade 3, n=1, 0, 0	0	0	0	
Week 148, Grade 4, n=1, 0, 0	0	0	0	
Week 148, Grade 5, n=1, 0, 0	0	0	0	
Withdrawal/Study conclusion, Grade 3, n=22, 10, 7	0	0	0	
Withdrawal/Study conclusion, Grade 4, n=22, 10, 7	0	0	0	
Withdrawal/Study conclusion, Grade 5, n=22, 10, 7	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who received any concomitant medications during the study period

End point title	Number of participants who received any concomitant medications during the study period[17]

End point description:

Number of participants who received any concomitant medication along with study drugs (lapatinib, trastuzumab and paclitaxel) were counted during the treatment period.

End point type	Primary

End point timeframe:

withdrawal/study completion, up to approx. 3.5 years

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: no statistical analysis was planned for this endpoint

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	14	20	
Units: Participants	29	14	20	

Statistical analyses

No statistical analyses for this end point

Primary: Overall Response (OR): Percentage of participants with a best overall response (OR) of confirmed complete response (CR) or confirmed partial response (PR) as assessed by the investigator

End point title	Overall Response (OR): Percentage of participants with a best overall response (OR) of confirmed complete response (CR) or confirmed partial response (PR) as assessed by the investigator[18]

End point description:

OR is defined as the number of participants achieving either a CR or PR, per Response Evaluation Criteria in Solid Tumors (RECIST). The best OR is defined as the best response recorded from the start of treatment until progressive disease (PD)/recurrence. CR is defined as the disappearance of all target lesions (TLs) and non-TLs. PR is defined as at least a 30% decrease in the sum of the longest diameters (LD) of TLs, taking as a reference the Baseline sum LD and no PD, or complete resolution of TLs and the persistence of one or more non-TL(s), as assessed by the IRC. PD is defined as at least a 20% increase in the sum of the LD of TLs, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions or unequivocal progression of existing non-TLs. Responses were confirmed at subsequent assessments made >=28 days after the original response. Participants with an unknown or missing response are treated as non-responders.

End point type	Primary

End point timeframe:

From the date of the first dose of investigational product to end of study, up to approx. 7 years

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: no statistical analysis was planned for this endpoint

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	14	20	
Units: Percentage of participants				
number (confidence interval 95%)	79.3 (64.6 to 94.1)	71.4 (47.8 to 95.1)	70.0 (49.9 to 90.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response as assessed by the investigator

End point title	Time to response as assessed by the investigator

End point description:

Time to response is defined as the time from randomization until the first documented evidence of a PR or CR (whichever status is recorded first). Analysis was based on responses confirmed at a repeat assessment made at least 4 weeks after the initial response, with the time to response taken as the first time the response was observed, not the confirmation assessment. Participants who withdraw with no tumor response were censored at the date of withdrawal from the study. CR is defined as the disappearance of all TLs and non-TLs. PR is defined as at least a 30% decrease in the sum of the LD of TLs, taking as a reference the Baseline sum LD and no PD, or complete resolution of TLs and the persistence of one or more non-TL(s). PD is defined as at least a 20% increase in the sum of the LD of TLs, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions or unequivocal progression of existing non-TLs.

End point type	Secondary

End point timeframe:

From the date of the first dose of investigational product until the first documented evidence of a PR or CR, up to approx. 7 years

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	10	14	
Units: Participants				
Week 8	15	8	8	
Week 12	5	1	1	
Week 16	2	1	3	
Week 20	0	0	1	
Week 24	1	0	0	
Week 28	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DoR), as assessed by the investigator

End point title	Duration of response (DoR), as assessed by the investigator

End point description:

DoR is defined for the subset of participants who had a confirmed CR (disappearance of all TLs and non-TLs) or PR (>=30% decrease in the sum of the LD of TLs, taking as a reference the Baseline sum LD and no PD, or complete resolution of TLs and the persistence of one or more non-TL[s]) as the time from the first documented evidence of a CR or PR until the first documentation of radiological PD or death due to breast cancer, if sooner. PD is defined as >=20% increase in the sum of the LD of TLs, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions or unequivocal progression of existing non-TLs. For participants who did not progress or die, DoR was censored on the date of the last radiological scan. If a participant had only a Baseline visit or did not have a date of a radiological scan that was later than the date of initiation of anti-cancer therapy, DoR was censored at the start date of treatment.

End point type	Secondary

End point timeframe:

From the first documented evidence of a PR or CR until the earlier of the date of disease progression or the date of death due to breast cancer, up to approx. 7 years

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	14	20	
Units: Weeks				
median (inter-quartile range (Q1-Q3))	56.6 (27.6 to 117.7)	59.0 (33.1 to 88.7)	70.6 (31.4 to 103.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with clinical benefit (complete response (CR), partial response (PR), and stable disease [SD] for at least 24 weeks) as assessed by investigator

End point title	Percentage of participants with clinical benefit (complete response (CR), partial response (PR), and stable disease [SD] for at least 24 weeks) as assessed by investigator

End point description:

Clinical benefit is defined as the percentage of participants achieving either a CR or PR or SD (neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (at least a 20% increase in the sum of the LD of target lesions, taking as a reference, the smallest sum LD recorded since the treatment started or the appearance of 1 or more new lesions), taking as reference, the smallest sum LD since the treatment started) for at least 24 weeks. This was based on confirmed responses from the investigator assessment of clinical benefit.

End point type	Secondary

End point timeframe:

From the date of the first dose of investigational product until the first documented evidence of a PR or CR or SD until the earlier of the date of disease progression or the date of death due to breast cancer, up to approx. 7 years

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	14	20	
Units: Percentage of Participants				
number (confidence interval 95%)	79.3 (64.6 to 94.1)	71.4 (47.8 to 95.1)	70.0 (49.9 to 90.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival as assessed by the investigator

End point title	Progression-free survival as assessed by the investigator

End point description:

Progression-free survival is defined as the time from randomization until the earliest date of disease progression or death due to any cause, if sooner. Disease progression was based on the investigator's assessments of the objective evidence (e.g., radiological scans and medical photographs). For participants who do not progress, or die, progression-free survival was censored at the time of the last investigator assessed radiological scan preceding the initiation of any alternative anti-cancer therapy. Progression-free survival was summarized using Kaplan-Meier curves.

End point type	Secondary

End point timeframe:

From the date of the first dose of investigational product until the earlier of the date of disease progression or death due to any cause, up to approx. 7 years

End point values	Cohort 1: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 2: Paclitaxel 70 mg/Trastuzumab 4 mg/Lapatinib 1000 mg	Cohort 3: Paclitaxel 80 mg/Trastuzumab 4 mg/Lapatinib 750 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	14	20	
Units: Weeks				
median (confidence interval 95%)	64.7 (33.1 to 117)	55.0 (20.4 to 96.1)	78.4 (31.9 to 111)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	1000 mg Lapatinib / 80 mg/m2 Paclitaxel/ 2 mg Trastuzumab
Reporting group description:	
1000 mg Lapatinib / 80 mg/m2 Paclitaxel/ 2 mg Trastuzumab	
Reporting group title	750 mg Lapatinib / 80 mg/m2 Paclitaxel 2 mg Trastuzumab
Reporting group description:	
750 mg Lapatinib / 80 mg/m2 Paclitaxel 2 mg Trastuzumab	
Reporting group title	1000 mg Lapatinib/ 70 mg/m2 Paclitaxel / 2 mg Trastuzumab
Reporting group description:	
1000 mg Lapatinib/ 70 mg/m2 Paclitaxel / 2 mg Trastuzumab	

Serious adverse events	1000 mg Lapatinib / 80 mg/m2 Paclitaxel/ 2 mg Trastuzumab	750 mg Lapatinib / 80 mg/m2 Paclitaxel 2 mg Trastuzumab	1000 mg Lapatinib/ 70 mg/m2 Paclitaxel / 2 mg Trastuzumab
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 29 (48.28%)	5 / 20 (25.00%)	6 / 14 (42.86%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (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
Mucosal inflammation			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (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
Pyrexia			

subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (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
Pelvic pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (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
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (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
Pleural effusion			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Ejection fraction decreased			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Compression fracture			

subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (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
Rib fracture			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (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
Spinal compression fracture			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (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
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Guillain-Barre syndrome			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (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
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 14 (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
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (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
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (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
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			

subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	2 / 14 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis streptococcal			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 14 (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
Clostridium difficile colitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (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
Infectious colitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (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	0 / 29 (0.00%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	5 / 29 (17.24%)	1 / 20 (5.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	4 / 5	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (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
Hypomagnesaemia			

subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (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
Hypokalaemia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	0 / 14 (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
Hypophosphataemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 14 (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

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

Non-serious adverse events	1000 mg Lapatinib / 80 mg/m2 Paclitaxel/ 2 mg Trastuzumab	750 mg Lapatinib / 80 mg/m2 Paclitaxel 2 mg Trastuzumab	1000 mg Lapatinib/ 70 mg/m2 Paclitaxel / 2 mg Trastuzumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 29 (100.00%)	20 / 20 (100.00%)	13 / 14 (92.86%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to bone			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	1
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Hot flush			
subjects affected / exposed	5 / 29 (17.24%)	3 / 20 (15.00%)	2 / 14 (14.29%)
occurrences (all)	5	4	4
Hypotension			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Lymphoedema			

subjects affected / exposed	4 / 29 (13.79%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences (all)	4	1	1
Surgical and medical procedures			
Prophylaxis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Mastectomy			
subjects affected / exposed	1 / 29 (3.45%)	2 / 20 (10.00%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences (all)	2	1	1
Chest pain			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	3	0	1
Chills			
subjects affected / exposed	4 / 29 (13.79%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	7	0	1
Fatigue			
subjects affected / exposed	21 / 29 (72.41%)	13 / 20 (65.00%)	12 / 14 (85.71%)
occurrences (all)	102	14	23
Mucosal inflammation			
subjects affected / exposed	8 / 29 (27.59%)	2 / 20 (10.00%)	6 / 14 (42.86%)
occurrences (all)	9	3	9
Non-cardiac chest pain			
subjects affected / exposed	0 / 29 (0.00%)	2 / 20 (10.00%)	4 / 14 (28.57%)
occurrences (all)	0	2	6
Oedema peripheral			
subjects affected / exposed	5 / 29 (17.24%)	0 / 20 (0.00%)	4 / 14 (28.57%)
occurrences (all)	13	0	5
Peripheral swelling			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Pain			

subjects affected / exposed	4 / 29 (13.79%)	4 / 20 (20.00%)	3 / 14 (21.43%)
occurrences (all)	4	4	5
Pyrexia			
subjects affected / exposed	6 / 29 (20.69%)	5 / 20 (25.00%)	5 / 14 (35.71%)
occurrences (all)	13	5	7
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 29 (0.00%)	2 / 20 (10.00%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Hypersensitivity			
subjects affected / exposed	3 / 29 (10.34%)	0 / 20 (0.00%)	2 / 14 (14.29%)
occurrences (all)	4	0	3
Seasonal allergy			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	5
Vaginal discharge			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	5 / 29 (17.24%)	4 / 20 (20.00%)	6 / 14 (42.86%)
occurrences (all)	7	4	11
Cough			
subjects affected / exposed	12 / 29 (41.38%)	4 / 20 (20.00%)	3 / 14 (21.43%)
occurrences (all)	27	5	8
Lower respiratory tract congestion			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Dyspnoea exertional			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Epistaxis			

subjects affected / exposed	10 / 29 (34.48%)	1 / 20 (5.00%)	2 / 14 (14.29%)
occurrences (all)	13	1	2
Oropharyngeal pain			
subjects affected / exposed	9 / 29 (31.03%)	5 / 20 (25.00%)	2 / 14 (14.29%)
occurrences (all)	11	9	2
Nasal congestion			
subjects affected / exposed	6 / 29 (20.69%)	1 / 20 (5.00%)	3 / 14 (21.43%)
occurrences (all)	8	1	6
Pleuritic pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	2 / 14 (14.29%)
occurrences (all)	1	2	3
Sinus congestion			
subjects affected / exposed	3 / 29 (10.34%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences (all)	5	1	1
Upper respiratory tract congestion			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Upper-airway cough syndrome			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 29 (6.90%)	2 / 20 (10.00%)	3 / 14 (21.43%)
occurrences (all)	2	2	4
Depression			
subjects affected / exposed	3 / 29 (10.34%)	1 / 20 (5.00%)	3 / 14 (21.43%)
occurrences (all)	3	1	4
Confusional state			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Insomnia			
subjects affected / exposed	6 / 29 (20.69%)	3 / 20 (15.00%)	7 / 14 (50.00%)
occurrences (all)	7	3	9

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 29 (10.34%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	7	0	3
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 29 (6.90%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences (all)	3	1	4
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 29 (13.79%)	1 / 20 (5.00%)	0 / 14 (0.00%)
occurrences (all)	6	1	0
Blood creatinine increased			
subjects affected / exposed	2 / 29 (6.90%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences (all)	7	1	1
Blood potassium decreased			
subjects affected / exposed	2 / 29 (6.90%)	1 / 20 (5.00%)	0 / 14 (0.00%)
occurrences (all)	2	1	0
Ejection fraction decreased			
subjects affected / exposed	6 / 29 (20.69%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences (all)	6	1	2
Blood pressure decreased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Haemoglobin decreased			
subjects affected / exposed	2 / 29 (6.90%)	2 / 20 (10.00%)	0 / 14 (0.00%)
occurrences (all)	6	2	0
Neutrophil count decreased			
subjects affected / exposed	2 / 29 (6.90%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences (all)	3	2	2
Lymphocyte count decreased			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Weight decreased			
subjects affected / exposed	7 / 29 (24.14%)	0 / 20 (0.00%)	3 / 14 (21.43%)
occurrences (all)	8	0	8
White blood cell count decreased			

subjects affected / exposed	3 / 29 (10.34%)	3 / 20 (15.00%)	1 / 14 (7.14%)
occurrences (all)	3	5	1
Weight increased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
White blood cell count increased			
subjects affected / exposed	2 / 29 (6.90%)	1 / 20 (5.00%)	0 / 14 (0.00%)
occurrences (all)	4	1	0
Injury, poisoning and procedural complications			
Postoperative wound complication			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Sunburn			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	5 / 29 (17.24%)	4 / 20 (20.00%)	3 / 14 (21.43%)
occurrences (all)	6	7	6
Dysgeusia			
subjects affected / exposed	3 / 29 (10.34%)	2 / 20 (10.00%)	1 / 14 (7.14%)
occurrences (all)	3	4	1
Headache			
subjects affected / exposed	8 / 29 (27.59%)	5 / 20 (25.00%)	5 / 14 (35.71%)
occurrences (all)	21	6	7
Hypoaesthesia			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences (all)	2	1	3
Neuropathy peripheral			

subjects affected / exposed	5 / 29 (17.24%)	4 / 20 (20.00%)	6 / 14 (42.86%)
occurrences (all)	6	6	14
Hyperaesthesia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	7 / 29 (24.14%)	5 / 20 (25.00%)	1 / 14 (7.14%)
occurrences (all)	23	8	8
Peripheral sensory neuropathy			
subjects affected / exposed	6 / 29 (20.69%)	3 / 20 (15.00%)	2 / 14 (14.29%)
occurrences (all)	6	4	2
Toxic neuropathy			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Eosinophilia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Anaemia			
subjects affected / exposed	11 / 29 (37.93%)	3 / 20 (15.00%)	2 / 14 (14.29%)
occurrences (all)	24	3	24
Leukopenia			
subjects affected / exposed	5 / 29 (17.24%)	1 / 20 (5.00%)	0 / 14 (0.00%)
occurrences (all)	17	2	0
Neutropenia			
subjects affected / exposed	4 / 29 (13.79%)	4 / 20 (20.00%)	1 / 14 (7.14%)
occurrences (all)	9	8	1
Ear and labyrinth disorders			
Ear pain			

subjects affected / exposed	1 / 29 (3.45%)	2 / 20 (10.00%)	0 / 14 (0.00%)
occurrences (all)	1	3	0
Vertigo			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Eye disorders			
Lacrimation increased			
subjects affected / exposed	3 / 29 (10.34%)	2 / 20 (10.00%)	0 / 14 (0.00%)
occurrences (all)	3	3	0
Eye irritation			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	0 / 14 (0.00%)
occurrences (all)	3	0	0
Ocular hyperaemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Vision blurred			
subjects affected / exposed	2 / 29 (6.90%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences (all)	5	1	1
Visual impairment			
subjects affected / exposed	3 / 29 (10.34%)	0 / 20 (0.00%)	0 / 14 (0.00%)
occurrences (all)	4	0	0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	5 / 29 (17.24%)	3 / 20 (15.00%)	1 / 14 (7.14%)
occurrences (all)	7	3	5
Abdominal pain upper			
subjects affected / exposed	4 / 29 (13.79%)	1 / 20 (5.00%)	3 / 14 (21.43%)
occurrences (all)	6	2	8
Constipation			
subjects affected / exposed	7 / 29 (24.14%)	5 / 20 (25.00%)	7 / 14 (50.00%)
occurrences (all)	11	5	9
Cheilitis			

subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	3
Dyspepsia			
subjects affected / exposed	7 / 29 (24.14%)	2 / 20 (10.00%)	3 / 14 (21.43%)
occurrences (all)	9	2	9
Diarrhoea			
subjects affected / exposed	28 / 29 (96.55%)	15 / 20 (75.00%)	13 / 14 (92.86%)
occurrences (all)	351	41	94
Dysphagia			
subjects affected / exposed	3 / 29 (10.34%)	0 / 20 (0.00%)	0 / 14 (0.00%)
occurrences (all)	3	0	0
Eructation			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	2 / 14 (14.29%)
occurrences (all)	2	0	2
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 29 (13.79%)	3 / 20 (15.00%)	1 / 14 (7.14%)
occurrences (all)	5	3	1
Gingival bleeding			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	16 / 29 (55.17%)	13 / 20 (65.00%)	11 / 14 (78.57%)
occurrences (all)	59	15	45
Oesophagitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Oral pain			
subjects affected / exposed	0 / 29 (0.00%)	2 / 20 (10.00%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Stomatitis			

subjects affected / exposed	8 / 29 (27.59%)	6 / 20 (30.00%)	3 / 14 (21.43%)
occurrences (all)	34	11	4
Rectal haemorrhage			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Toothache			
subjects affected / exposed	2 / 29 (6.90%)	1 / 20 (5.00%)	0 / 14 (0.00%)
occurrences (all)	4	1	0
Vomiting			
subjects affected / exposed	17 / 29 (58.62%)	4 / 20 (20.00%)	6 / 14 (42.86%)
occurrences (all)	31	7	11
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	22 / 29 (75.86%)	11 / 20 (55.00%)	8 / 14 (57.14%)
occurrences (all)	25	13	11
Dermatitis contact			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	2 / 14 (14.29%)
occurrences (all)	1	0	2
Dry skin			
subjects affected / exposed	5 / 29 (17.24%)	3 / 20 (15.00%)	3 / 14 (21.43%)
occurrences (all)	5	3	5
Nail disorder			
subjects affected / exposed	7 / 29 (24.14%)	3 / 20 (15.00%)	6 / 14 (42.86%)
occurrences (all)	9	3	10
Hyperhidrosis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Nail discolouration			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	2 / 14 (14.29%)
occurrences (all)	1	0	3
Nail ridging			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Pain of skin			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Rash			
subjects affected / exposed	25 / 29 (86.21%)	17 / 20 (85.00%)	9 / 14 (64.29%)
occurrences (all)	75	27	29
Photosensitivity reaction			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	6 / 29 (20.69%)	3 / 20 (15.00%)	5 / 14 (35.71%)
occurrences (all)	7	4	5
Skin discolouration			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	0 / 14 (0.00%)
occurrences (all)	4	0	0
Rash follicular			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Rash papular			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Telangiectasia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Skin fissures			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	3 / 29 (10.34%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	3	0	1

Ureteric stenosis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 29 (20.69%)	6 / 20 (30.00%)	1 / 14 (7.14%)
occurrences (all)	10	8	2
Back pain			
subjects affected / exposed	5 / 29 (17.24%)	3 / 20 (15.00%)	3 / 14 (21.43%)
occurrences (all)	7	3	8
Bone pain			
subjects affected / exposed	3 / 29 (10.34%)	1 / 20 (5.00%)	0 / 14 (0.00%)
occurrences (all)	5	1	0
Muscle twitching			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	2
Muscle spasms			
subjects affected / exposed	2 / 29 (6.90%)	1 / 20 (5.00%)	2 / 14 (14.29%)
occurrences (all)	2	1	4
Muscular weakness			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	4	0	1
Musculoskeletal chest pain			
subjects affected / exposed	3 / 29 (10.34%)	3 / 20 (15.00%)	0 / 14 (0.00%)
occurrences (all)	4	3	0
Musculoskeletal pain			
subjects affected / exposed	4 / 29 (13.79%)	1 / 20 (5.00%)	2 / 14 (14.29%)
occurrences (all)	27	1	2
Myalgia			
subjects affected / exposed	11 / 29 (37.93%)	4 / 20 (20.00%)	3 / 14 (21.43%)
occurrences (all)	26	5	6
Neck pain			
subjects affected / exposed	5 / 29 (17.24%)	1 / 20 (5.00%)	2 / 14 (14.29%)
occurrences (all)	5	2	2
Pain in extremity			

subjects affected / exposed	7 / 29 (24.14%)	5 / 20 (25.00%)	3 / 14 (21.43%)
occurrences (all)	9	7	6
Trismus			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Infections and infestations			
Angular cheilitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	2 / 29 (6.90%)	1 / 20 (5.00%)	0 / 14 (0.00%)
occurrences (all)	2	1	0
Candida infection			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Cellulitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	3
Conjunctivitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Ear infection			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	2 / 14 (14.29%)
occurrences (all)	2	0	2
Cystitis			
subjects affected / exposed	3 / 29 (10.34%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences (all)	3	1	1
Fungal skin infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 29 (0.00%)	2 / 20 (10.00%)	1 / 14 (7.14%)
occurrences (all)	0	3	1
Herpes zoster			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences (all)	0	2	1

Infection			
subjects affected / exposed	3 / 29 (10.34%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences (all)	3	1	1
Laryngitis			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Localised infection			
subjects affected / exposed	5 / 29 (17.24%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	9	0	1
Nail infection			
subjects affected / exposed	2 / 29 (6.90%)	1 / 20 (5.00%)	0 / 14 (0.00%)
occurrences (all)	2	2	0
Paronychia			
subjects affected / exposed	2 / 29 (6.90%)	1 / 20 (5.00%)	0 / 14 (0.00%)
occurrences (all)	6	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 29 (3.45%)	2 / 20 (10.00%)	0 / 14 (0.00%)
occurrences (all)	2	3	0
Sinusitis			
subjects affected / exposed	3 / 29 (10.34%)	1 / 20 (5.00%)	3 / 14 (21.43%)
occurrences (all)	5	1	3
Pneumonia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	2
Skin infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	8 / 29 (27.59%)	3 / 20 (15.00%)	6 / 14 (42.86%)
occurrences (all)	13	6	7
Urinary tract infection			
subjects affected / exposed	5 / 29 (17.24%)	2 / 20 (10.00%)	3 / 14 (21.43%)
occurrences (all)	12	3	9
Vulvovaginal mycotic infection			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	4	0	2

Vaginal infection			
subjects affected / exposed	3 / 29 (10.34%)	0 / 20 (0.00%)	0 / 14 (0.00%)
occurrences (all)	3	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 29 (27.59%)	3 / 20 (15.00%)	2 / 14 (14.29%)
occurrences (all)	11	6	11
Dehydration			
subjects affected / exposed	8 / 29 (27.59%)	1 / 20 (5.00%)	2 / 14 (14.29%)
occurrences (all)	10	1	2
Hyperglycaemia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	8	0	4
Hyperkalaemia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Hypoalbuminaemia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	0 / 14 (0.00%)
occurrences (all)	3	0	0
Hypocalcaemia			
subjects affected / exposed	5 / 29 (17.24%)	1 / 20 (5.00%)	0 / 14 (0.00%)
occurrences (all)	14	2	0
Hypomagnesaemia			
subjects affected / exposed	3 / 29 (10.34%)	0 / 20 (0.00%)	0 / 14 (0.00%)
occurrences (all)	8	0	0
Hypokalaemia			
subjects affected / exposed	12 / 29 (41.38%)	2 / 20 (10.00%)	3 / 14 (21.43%)
occurrences (all)	24	3	7
Hyponatraemia			
subjects affected / exposed	4 / 29 (13.79%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	6	0	1
Hypophosphataemia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	1 / 14 (7.14%)
occurrences (all)	6	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 August 2006	Applied to all centers. An IDMC was incorporated to monitor subject safety during the randomized phase of the study. Diarrhea management guidelines were added to the protocol to encourage proactive management of diarrhea during the study and thus avoid more serious complications. The efficacy data from the ongoing lapatinib clinical program showed clinical activity and benefit. Therefore, for the randomized phase, the primary efficacy analysis population was changed to the ITT population. Clinical disease assessment for palpable or visual lesions was preformed 4 weekly rather than 8 weekly and the list of prohibited medications was also updated.
22 February 2007	Applied to all centers. Due to a high rate of diarrhea observed in the initial open label safety cohort (cohort 1), the safety cohort was extended to investigate a lower dose of paclitaxel (70 mg/m2) when combined with 1000 mg once daily of lapatinib plus standard weekly dose of trastuzumab (cohort 2). Following a review of the data from cohort 2, the possibility of conducting an additional cohort in the open label phase to investigate a lower dose of lapatinib (750 mg once daily) plus 80 mg/m2 paclitaxel plus standard weekly dose of trastuzumab (cohort 3) was included. Primary prophylactic antidiarrheal treatment was also incorporated into the protocol. Pharmacokinetic sampling was introduced into the extended safety cohort and the open label secondary objectives were updated to explore any correlations between lapatinib and paclitaxel plasma concentrations and safety. The sample size was updated to reflect the extension of the safety cohort.
07 December 2007	This amendment was country specific for all centers in Belgium, and other future European countries included after the amendment, to allow the use of locally sourced Taxol or generic paclitaxel. The description of the vial size of tastuzumab was also updated to included 150 mg vials.
06 June 2008	Applied to all centers. Following a review of all hepatobiliary events reported across the lapatinib clinical program, a causal relationship between hepatobiliary disorders and lapatinib could not be excluded. Therefore, changes to the exclusion criteria, lapatinib stopping criteria and follow up criteria, and definition of an SAE due to potential liver toxicity, were made.
17 November 2008	Applied to all centers. The addition of PK sampling to the follow up assessment of subjects with a severe liver toxicity while on study medication was made to enable an accurate attribution of causality of the liver event to the study medication. To reduce the burden on the subject and center, the collection of serum samples for analysis of the extracellular domain of ErbB1 and ErbB2 was removed from the protocol. Similarly, the independent review of radiological scans was removed from the protocol. Only the investigator assessment of the subject’s radiological scans was to be used in the analysis.
22 June 2010	This amendment stopped the survival follow-up for subjects who had discontinued study treatment and stopped the follow-up for progression for subjects who had withdrawn from study treatment prematurely. Sites in North America were allowed to use local Laboratory results for hematology and chemistry assessments instead the central laboratory.

19 March 2013	Applied to all centers. Randomized Phase III part of the study was cancelled due to recruitment challenges. Long-term follow up phase of the study was added. Continued access to clinical trial material was allowed for subjects ongoing at the time of implementation of this amendment. Many study specific efficacy and safety assessments were discontinued. Information regarding use of proton pump inhibitors was updated. Subjects were allowed to switch to a 3-weekly trastuzumab (6 mg/kg trastuzumab) schedule in the maintenance phase of their treatment (i.e. lapatinib plus trastuzumab) based on investigator's clinical judgment. Information regarding diarrhea management for all grades was updated.
16 March 2016	Applied to all centers. References to GlaxoSmithKline or its staff were deleted or replaced with that of Novartis and its authorized agents to align with the change of sponsorship. Administrative changes were made to align with Novartis processes and procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: