



Clinical trial results:

A Randomized, Multicenter, Open-Label Phase III Study To Evaluate The Efficacy And Safety Of Trastuzumab Emtansine Versus Trastuzumab As Adjuvant Therapy For Patients With HER2-Positive Primary Breast Cancer Who Have Residual Tumor Present Pathologically In The Breast Or Axillary Lymph Nodes Following Preoperative Therapy.

Summary

EudraCT number	2012-002018-37
Trial protocol	BE SE AT CZ GB IT IE ES GR FR
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	23 August 2019
First version publication date	23 August 2019

Trial information

Trial identification

Sponsor protocol code	BO27938
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01772472
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH4070
Public contact	Medical Communications, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com
Scientific contact	Medical Communications, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.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	Interim
Date of interim/final analysis	25 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 July 2018
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

This 2-arm, randomized, open-label study will evaluate the efficacy and safety of trastuzumab emtansine versus trastuzumab as adjuvant therapy in patients with HER2-positive breast cancer who have residual tumor present in the breast or axillary lymph nodes following preoperative therapy. Eligible patients will be randomized to receive either trastuzumab emtansine 3.6 mg/kg or trastuzumab 6 mg/kg intravenously every 3 weeks for 14 cycles. Radiotherapy and/or hormone therapy will be given in addition if indicated.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 58
Country: Number of subjects enrolled	United States: 276
Country: Number of subjects enrolled	Argentina: 8
Country: Number of subjects enrolled	Brazil: 45
Country: Number of subjects enrolled	China: 26
Country: Number of subjects enrolled	Colombia: 18
Country: Number of subjects enrolled	Czech Republic: 23
Country: Number of subjects enrolled	Guatemala: 22
Country: Number of subjects enrolled	Hong Kong: 15
Country: Number of subjects enrolled	Israel: 23
Country: Number of subjects enrolled	Mexico: 25
Country: Number of subjects enrolled	Panama: 13
Country: Number of subjects enrolled	Peru: 8
Country: Number of subjects enrolled	Serbia: 23
Country: Number of subjects enrolled	South Africa: 20
Country: Number of subjects enrolled	Taiwan: 60
Country: Number of subjects enrolled	Turkey: 17
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	France: 139

Country: Number of subjects enrolled	Germany: 291
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Ireland: 34
Country: Number of subjects enrolled	Italy: 110
Country: Number of subjects enrolled	Spain: 92
Country: Number of subjects enrolled	Sweden: 25
Country: Number of subjects enrolled	Switzerland: 10
Country: Number of subjects enrolled	United Kingdom: 71
Worldwide total number of subjects	1486
EEA total number of subjects	819

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)	1360
From 65 to 84 years	126
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

1486 patients were randomized in 268 centers across 28 countries.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Trastuzumab

Arm description:

Participants received trastuzumab 6 milligrams/kilogram (mg/kg) intravenously (IV) every 3 weeks for 14 cycles.

Arm type	Active comparator
Investigational medicinal product name	trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

6 mg/kg intravenously every 3 weeks, 14 cycles

Arm title	Trastuzumab emtansine
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Arm description:

Participants received trastuzumab emtansine 3.6 mg/kg IV every 3 weeks for 14 cycles.

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

Dosage and administration details:

3.6 mg/kg intravenously every 3 weeks, 14 cycles

Number of subjects in period 1	Trastuzumab	Trastuzumab emtansine
Started	743	743
Completed	0	0
Not completed	743	743
Consent withdrawn by subject	72	50
Physician decision	1	3

Death	56	42
Not Specified	5	5
Ongoing	597	635
Lost to follow-up	12	8

Baseline characteristics

Reporting groups

Reporting group title	Trastuzumab
Reporting group description:	
Participants received trastuzumab 6 milligrams/kilogram (mg/kg) intravenously (IV) every 3 weeks for 14 cycles.	
Reporting group title	Trastuzumab emtansine
Reporting group description:	
Participants received trastuzumab emtansine 3.6 mg/kg IV every 3 weeks for 14 cycles.	

Reporting group values	Trastuzumab	Trastuzumab emtansine	Total
Number of subjects	743	743	1486
Age Categorical			
Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	675	685	1360
>=65 years	68	58	126
Age continuous			
Units: years			
arithmetic mean	49.2	49.0	
standard deviation	± 10.9	± 10.4	-
Sex: Female, Male			
Units: Subjects			
Female	740	741	1481
Male	3	2	5
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	50	36	86
Asian	64	65	129
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	19	21	40
White	531	551	1082
More than one race	1	1	2
Unknown or Not Reported	77	69	146

End points

End points reporting groups

Reporting group title	Trastuzumab
Reporting group description:	
Participants received trastuzumab 6 milligrams/kilogram (mg/kg) intravenously (IV) every 3 weeks for 14 cycles.	
Reporting group title	Trastuzumab emtansine
Reporting group description:	
Participants received trastuzumab emtansine 3.6 mg/kg IV every 3 weeks for 14 cycles.	

Primary: Invasive disease-free survival (IDFS)

End point title	Invasive disease-free survival (IDFS)
End point description:	
IDFS event was defined as the first occurrence of one of the following events: Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion); ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast); distant recurrence (i.e., evidence of breast cancer in any anatomic site - other than the two above mentioned sites); death attributable to any cause; contralateral invasive breast cancer. 3-year IDFS event-free rate per randomized treatment arms in the ITT population were estimated using the Kaplan-Meier method and estimated the probability of a patient being event-free after 3 years after randomization.	
End point type	Primary
End point timeframe:	
From randomization up to 10 years	

End point values	Trastuzumab	Trastuzumab emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: Probability				
number (confidence interval 95%)	77.02 (73.78 to 80.26)	88.27 (85.81 to 90.72)		

Statistical analyses

Statistical analysis title	IDFS
Statistical analysis description:	
Unstratified analysis	
Comparison groups	Trastuzumab v Trastuzumab emtansine

Number of subjects included in analysis	1486
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.64

Secondary: Invasive disease-free survival including second primary non-breast cancer

End point title	Invasive disease-free survival including second primary non-breast cancer
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End point description:

IDFS including second primary non-breast cancer was defined the same way as IDFS for the primary endpoint but including second primary non breast invasive cancer as an event (with the exception of non-melanoma skin cancers and carcinoma in situ (CIS) of any site). 3-year IDFS including second primary non-breast cancer event-free rates per treatment arm in the ITT population were estimated using the Kaplan-Meier method and estimated the probability of a patient being event-free after 3 years after randomization.

End point type	Secondary
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End point timeframe:

From baseline up to 10 years

End point values	Trastuzumab	Trastuzumab emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: Probability				
number (confidence interval 95%)	76.89 (73.65 to 80.14)	87.68 (85.18 to 90.18)		

Statistical analyses

Statistical analysis title	IDFS Including Second Primary Non-Breast Cancer
Statistical analysis description:	
Unstratified analysis	
Comparison groups	Trastuzumab v Trastuzumab emtansine

Number of subjects included in analysis	1486
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.66

Secondary: Disease-free survival

End point title	Disease-free survival
End point description:	
Disease-free survival was defined as the time between randomization and the date of the first occurrence of an invasive disease-free survival event including second primary non-breast cancer event or contralateral or ipsilateral DCIS. 3-year DFS event-free rates per randomized treatment arms in the ITT population were estimated using the Kaplan-Meier method and estimated the probability of a patient being event-free after 3 years after randomization.	
End point type	Secondary
End point timeframe:	
From baseline up to 10 years	

End point values	Trastuzumab	Trastuzumab emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: Probability				
number (confidence interval 95%)	76.89 (73.65 to 80.14)	87.41 (84.88 to 89.93)		

Statistical analyses

Statistical analysis title	DFS
Statistical analysis description:	
Unstratified analysis	
Comparison groups	Trastuzumab v Trastuzumab emtansine
Number of subjects included in analysis	1486
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.68

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
Overall survival in the overall study population was defined as the time from the date of randomization to the date of death from any cause. 5 years OS event-free rate per randomized treatment arms in the ITT population were estimated using the Kaplan-Meier method and estimated the probability of a patient being event-free after 5 years after randomization.	
End point type	Secondary
End point timeframe:	
Baseline up to 10 years	

End point values	Trastuzumab	Trastuzumab emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: Probability				
number (confidence interval 95%)	86.79 (80.95 to 92.63)	92.09 (89.44 to 94.74)		

Statistical analyses

Statistical analysis title	OS
Statistical analysis description:	
Unstratified analysis	
Comparison groups	Trastuzumab v Trastuzumab emtansine
Number of subjects included in analysis	1486
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0848
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.05

Secondary: Distant Recurrence-Free Interval (DRFI)

End point title	Distant Recurrence-Free Interval (DRFI)
End point description: DRFI was defined as the time between randomization and the date of distant breast cancer recurrence. 3 years DRFI event-free rate per randomized treatment arms in the ITT population were estimated using the Kaplan-Meier method and estimated the probability of a patient being event-free after 3 years after randomization.	
End point type	Secondary
End point timeframe: Baseline up to 10 years	

End point values	Trastuzumab	Trastuzumab emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: Probability				
number (confidence interval 95%)	83.01 (80.10 to 85.92)	89.69 (87.37 to 92.01)		

Statistical analyses

Statistical analysis title	DRFI
Statistical analysis description: Unstratified analysis	
Comparison groups	Trastuzumab v Trastuzumab emtansine
Number of subjects included in analysis	1486
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0003
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.79

Secondary: Percentage of Participants with Adverse Events

End point title	Percentage of Participants with Adverse Events
End point description: An adverse event is any untoward medical occurrence in a participant administered a pharmaceutical	

product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. AEs, including AEs of Special Interest and AEs of Particular Interest, were reported based on the national cancer institute common terminology criteria for AEs, Version 4.0 (NCI-CTCAE, v4.0). Reported are the number of subjects with AEs, Grade 3-5 AEs, and Serious Adverse Events (SAEs).

End point type	Secondary
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End point timeframe:

From Day 1 to 30 days after last dose of study drug, up to the clinical cutoff date (approximately 64 months)

End point values	Trastuzumab	Trastuzumab emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	720	740		
Units: Percentage of Participants				
number (not applicable)	93.3	98.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Cardiac Dysfunction

End point title	Percentage of Participants with Cardiac Dysfunction
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End point description:

Cardiac events were reported based on the NCI-CTCAE, v4.0.

End point type	Secondary
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End point timeframe:

From baseline up to 10 years

End point values	Trastuzumab	Trastuzumab emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	720	740		
Units: Percentage of Participants				
number (not applicable)	5.6	3.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of Functional Scales, Symptom Scales and Single

Items in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Core 30 (QLQ-C30)

End point title	Change from Baseline of Functional Scales, Symptom Scales and Single Items in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Core 30 (QLQ-C30)
End point description:	
<p>The EORTC QLQ-C30 included global health status, functional scales (physical, role, emotional, cognitive, and social), symptom scales (fatigue, nausea/vomiting, and pain) and single items (dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Most questions used a 4-point scale (1 'Not at all' to 4 'Very much'; 2 questions used 7-point scale [1 'very poor' to 7 'Excellent']). Scores were averaged and transformed to 0 - 100 scale, whereby higher scores indicate greater functioning, greater quality of life, or a greater degree of symptoms, with changes of 5 - 10 points considered to be a minimally important difference to participants. A positive value means an increase, while a negative value means a decrease, in score at the indicated time-point relative to the score at baseline (Cycle 1, Day 1).</p>	
End point type	Secondary
End point timeframe:	
Baseline, Cycle 5, 11, Follow-up (FU) Month 6, Follow-up Month 12	

End point values	Trastuzumab	Trastuzumab emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Baseline: Appetite Loss	7.9 (± 17.4)	7.1 (± 16.4)		
Change at Cycle 5: Appetite Loss	1.0 (± 18.7)	6.5 (± 23.7)		
Change at Cycle 11: Appetite Loss	-0.5 (± 17.2)	2.9 (± 20.2)		
Change at FU Month 6: Appetite Loss	-1.6 (± 18.3)	-1.7 (± 19.9)		
Change at FU Month 12: Appetite Loss	0.5 (± 20.3)	-1.9 (± 20.1)		
Baseline: Constipation	9.8 (± 20.2)	9.5 (± 19.0)		
Change at Cycle 5: Constipation	1.0 (± 22.4)	4.6 (± 22.6)		
Change at Cycle 11: Constipation	3.4 (± 23.6)	7.3 (± 23.1)		
Change at FU Month 6: Constipation	4.1 (± 23.7)	3.7 (± 23.3)		
Change at FU Month 12: Constipation	3.2 (± 23.2)	4.3 (± 24.6)		
Baseline: Diarrhea	8.8 (± 17.6)	6.4 (± 14.9)		
Change at Cycle 5: Diarrhea	-1.6 (± 19.3)	-1.5 (± 19.5)		
Change at Cycle 11: Diarrhea	-0.4 (± 21.4)	-2.4 (± 17.5)		
Change at FU Month 6: Diarrhea	-3.4 (± 18.5)	-1.9 (± 18.3)		
Change at FU Month 12: Diarrhea	-2.8 (± 18.9)	-1.6 (± 18.4)		
Baseline: Dyspnea	12.7 (± 20.7)	11.0 (± 18.8)		
Change at Cycle 5: Dyspnea	2.3 (± 21.9)	4.1 (± 22.4)		
Change at Cycle 11: Dyspnea	2.8 (± 21.2)	2.7 (± 20.4)		
Change at FU Month 6: Dyspnea	3.3 (± 22.8)	3.8 (± 22.7)		
Change at FU Month 12: Dyspnea	3.9 (± 24.9)	5.3 (± 22.4)		
Baseline: Fatigue	29.2 (± 21.1)	28.0 (± 20.0)		
Change at Cycle 5: Fatigue	1.1 (± 20.1)	5.5 (± 19.7)		
Change at Cycle 11: Fatigue	1.1 (± 20.5)	3.8 (± 21.3)		
Change at FU Month 6: Fatigue	-1.4 (± 21.9)	-0.1 (± 22.2)		
Change at FU Month 12: Fatigue	-0.1 (± 23.3)	-0.1 (± 22.1)		
Baseline: Financial Difficulties	28.6 (± 33.3)	27.6 (± 31.9)		

Change at Cycle 5: Financial Difficulties	-3.1 (± 26.5)	-3.0 (± 28.0)		
Change at Cycle 11: Financial Difficulties	-5.1 (± 27.6)	-1.7 (± 28.7)		
Change at FU Month 6: Financial Difficulties	-8.4 (± 28.3)	-6.5 (± 30.6)		
Change at FU Month 12: Financial Difficulties	-10.9 (± 30.5)	-7.3 (± 31.0)		
Baseline: Insomnia	30.6 (± 30.8)	30.6 (± 29.2)		
Change at Cycle 5: Insomnia	1.9 (± 28.4)	1.3 (± 29.7)		
Change at Cycle 11: Insomnia	2.4 (± 29.9)	1.5 (± 30.3)		
Change at FU Month 6: Insomnia	1.8 (± 31.3)	-0.9 (± 32.1)		
Change at FU Month 12: Insomnia	0.3 (± 30.4)	0.7 (± 31.7)		
Baseline: Nausea/Vomiting	3.3 (± 9.0)	2.8 (± 8.0)		
Change at Cycle 5: Nausea/Vomiting	1.5 (± 11.2)	3.2 (± 12.5)		
Change at Cycle 11: Nausea/Vomiting	1.3 (± 12.8)	3.0 (± 11.8)		
Change at FU Month 6: Nausea/Vomiting	0.8 (± 10.4)	0.2 (± 11.1)		
Change at FU Month 12: Nausea/Vomiting	0.4 (± 10.5)	1.2 (± 10.9)		
Baseline: Pain	22.2 (± 22.2)	22.6 (± 22.8)		
Change at Cycle 5: Pain	0.0 (± 23.2)	1.8 (± 23.9)		
Change at Cycle 11: Pain	0.1 (± 23.1)	2.1 (± 24.4)		
Change at FU Month 6: Pain	-0.3 (± 24.6)	-0.5 (± 24.3)		
Change at FU Month 12: Pain	-1.2 (± 25.6)	-0.8 (± 25.4)		
Baseline: Cognitive Functioning	83.3 (± 20.2)	84.4 (± 19.0)		
Change at Cycle 5: Cognitive Functioning	-3.8 (± 18.4)	-4.5 (± 18.7)		
Change at Cycle 11: Cognitive Functioning	-5.4 (± 21.3)	-5.3 (± 19.6)		
Change at FU Month 6: Cognitive Functioning	-4.1 (± 22.0)	-6.1 (± 21.6)		
Change at FU Month 12: Cognitive Functioning	-4.9 (± 22.2)	-6.9 (± 21.7)		
Baseline: Emotional Functioning	75.0 (± 22.0)	75.2 (± 21.2)		
Change at Cycle 5: Emotional Functioning	-0.4 (± 20.0)	-1.3 (± 21.3)		
Change at Cycle 11: Emotional Functioning	-1.0 (± 21.3)	0.1 (± 22.0)		
Change at FU Month 6: Emotional Functioning	-2.9 (± 22.0)	-0.8 (± 23.3)		
Change at FU Month 12: Emotional Functioning	-2.0 (± 22.7)	-1.6 (± 23.5)		
Baseline: Physical Functioning	84.5 (± 15.3)	85.8 (± 14.1)		
Change at Cycle 5: Physical Functioning	0.3 (± 12.9)	-1.6 (± 12.7)		
Change at Cycle 11: Physical Functioning	1.9 (± 14.2)	-0.6 (± 14.6)		
Change at FU Month 6: Physical Functioning	2.8 (± 15.4)	0.7 (± 15.1)		
Change at FU Month 12: Physical Functioning	2.7 (± 14.5)	0.8 (± 14.5)		
Baseline: Role Functioning	77.5 (± 25.0)	78.6 (± 23.3)		
Change at Cycle 5: Role Functioning	2.0 (± 24.3)	-0.2 (± 24.1)		
Change at Cycle 11: Role Functioning	4.0 (± 24.3)	0.6 (± 24.5)		
Change at FU Month 6: Role Functioning	7.4 (± 25.8)	3.6 (± 26.7)		
Change at FU Month 12: Role Functioning	8.0 (± 27.5)	4.6 (± 25.5)		
Baseline: Social Functioning	77.1 (± 24.1)	76.8 (± 23.2)		

Change at Cycle 5: Social Functioning	4.0 (± 22.5)	1.6 (± 23.8)		
Change at Cycle 11: Social Functioning	5.8 (± 24.0)	2.5 (± 23.6)		
Change at FU Month 6: Social Functioning	8.5 (± 23.7)	6.5 (± 26.1)		
Change at FU Month 12: Social Functioning	9.5 (± 25.1)	7.4 (± 26.4)		
Baseline: Global Health Status	71.2 (± 19.3)	71.4 (± 18.0)		
Change at Cycle 5: Global Health Status	0.6 (± 18.9)	-1.9 (± 19.6)		
Change at Cycle 11: Global Health Status	1.7 (± 17.8)	-0.5 (± 19.9)		
Change at FU Month 6: Global Health Status	2.5 (± 19.3)	2.0 (± 19.2)		
Change at FU Month 12: Global Health Status	3.2 (± 19.5)	2.8 (± 20.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of Four Functioning Scales and Four Symptom Scales in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Breast Cancer (QLQ-BR23)

End point title	Change from Baseline of Four Functioning Scales and Four Symptom Scales in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Breast Cancer (QLQ-BR23)
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End point description:

EORTC-QLQ-BR23 is a 23-item breast cancer-specific companion module to the EORTC-QLQ-C30 and consists of four functional scales (body image, sexual enjoyment, sexual functioning, future perspective [FP]) and four symptom scales (systemic side effects [SE], upset by hair loss, arm symptoms, breast symptoms). Questions used 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Scores averaged and transformed to 0-100 scale. High score for functional scale indicated high/better level of functioning/healthy functioning. Higher scores for symptom scales represent higher levels of symptoms/problems. For functional scales, positive change from baseline indicated improvement in quality of life (QOL) and negative change from baseline indicated a deterioration in QOL. For symptom scales, positive change from baseline indicated a deterioration in quality of life (QOL) and negative change from baseline indicated an improvement in QOL.

End point type	Secondary
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End point timeframe:

Baseline, Cycle 5, 11, Follow-up Month 6, Follow-up Month 12

End point values	Trastuzumab	Trastuzumab emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Baseline: Body Image	69.8 (± 28.5)	67.5 (± 28.5)		
Change at Cycle 5: Body Image	1.5 (± 20.5)	4.6 (± 22.7)		
Change at Cycle 11: Body Image	3.4 (± 24.4)	5.7 (± 23.9)		
Change at FU Month 6: Body Image	3.6 (± 25.1)	7.8 (± 25.8)		
Change at FU Month 12: Body Image	6.2 (± 27.1)	6.1 (± 27.2)		

Baseline: FP	51.3 (± 31.2)	50.1 (± 31.7)		
Change at Cycle 5: FP	2.6 (± 28.3)	6.5 (± 29.9)		
Change at Cycle 11: FP	6.3 (± 30.0)	6.1 (± 31.4)		
Change at FU Month 6: FP	7.7 (± 33.5)	8.1 (± 34.6)		
Change at FU Month 12: FP	8.1 (± 31.1)	8.2 (± 33.0)		
Baseline: Sexual Enjoyment	50.9 (± 28.8)	52.3 (± 28.5)		
Change at Cycle 5: Sexual Enjoyment	2.3 (± 26.4)	-1.9 (± 24.6)		
Change at Cycle 11: Sexual Enjoyment	4.4 (± 27.5)	4.4 (± 24.5)		
Change at FU Month 6: Sexual Enjoyment	3.2 (± 28.1)	0.3 (± 27.5)		
Change at FU Month 12: Sexual Enjoyment	5.6 (± 26.0)	1.8 (± 26.2)		
Baseline: Sexual Function	20.2 (± 23.6)	22.0 (± 23.4)		
Change at Cycle 5: Sexual Function	3.3 (± 20.0)	2.3 (± 20.0)		
Change at Cycle 11: Sexual Function	3.1 (± 20.8)	1.9 (± 20.3)		
Change at FU Month 6: Sexual Function	5.1 (± 23.9)	4.3 (± 23.1)		
Change at FU Month 12: Sexual Function	5.9 (± 23.7)	5.2 (± 22.7)		
Baseline: Arm Symptoms	24.6 (± 21.1)	24.5 (± 21.0)		
Change at Cycle 5: Arm Symptoms	-2.8 (± 20.9)	-2.6 (± 23.0)		
Change at Cycle 11: Arm Symptoms	-2.6 (± 21.2)	0.2 (± 24.2)		
Change at FU Month 6: Arm Symptoms	-3.0 (± 23.5)	-1.3 (± 24.2)		
Change at FU Month 12: Arm Symptoms	-5.7 (± 22.8)	-1.5 (± 22.6)		
Baseline: Breast Symptoms	22.7 (± 19.1)	21.4 (± 17.9)		
Change at Cycle 5: Breast Symptoms	-1.1 (± 20.3)	-1.1 (± 19.1)		
Change at Cycle 11: Breast Symptoms	-3.7 (± 19.8)	-0.6 (± 19.5)		
Change at FU Month 6: Breast Function	-6.5 (± 20.0)	-2.2 (± 19.7)		
Change at Follow-up Month 12: Breast Function	-8.3 (± 19.9)	-3.8 (± 19.2)		
Baseline: Systemic Therapy Side Effects (SE)	16.7 (± 13.7)	16.9 (± 14.1)		
Change at Cycle 5: Systemic Therapy SE	0.7 (± 13.0)	5.5 (± 15.3)		
Change at Cycle 11: Systemic Therapy SE	1.2 (± 12.2)	4.2 (± 15.4)		
Change at FU Month 6: Systemic Therapy SE	1.9 (± 13.9)	1.1 (± 15.3)		
Change at FU Month 12: Systemic Therapy SE	1.3 (± 13.9)	1.4 (± 16.3)		
Baseline: Upset by Hair Loss Item	40.3 (± 35.6)	50.7 (± 38.4)		
Change at Cycle 5: Upset by Hair Loss Item	-5.1 (± 38.1)	-17.6 (± 39.3)		
Change at Cycle 11: Upset by Hair Loss Item	-28.6 (± 45.0)	-14.3 (± 33.9)		
Change at FU Month 6: Upset by Hair Loss Item	-12.0 (± 47.0)	-15.2 (± 42.1)		
Change at FU Month 12: Upset by Hair Loss Item	-2.9 (± 37.5)	-14.3 (± 41.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentrations (Area Under the Concentration-time Curve [AUC]) of Trastuzumab Emtansine (including Total Trastuzumab and DM1)

End point title	Serum Concentrations (Area Under the Concentration-time Curve [AUC]) of Trastuzumab Emtansine (including Total Trastuzumab and DM1)
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End point description:

Blood and serum samples for measurement of trastuzumab emtansine, total trastuzumab, and DM1 will be obtained from patients randomized to the trastuzumab emtansine arm.

End point type	Secondary
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End point timeframe:

Cycle (C) 1, Day (D) 1 and C4D1 of pre-infusion, C1D1 and C4D1 post-infusion, C2D1 and C5D1 pre-infusion and study treatment termination

End point values	Trastuzumab	Trastuzumab emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[1]	0 ^[2]		
Units: ug/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[1] - As the data is not mature yet, this endpoint will be presented at final analysis stage.

[2] - As the data is not mature yet, this endpoint will be presented at final analysis stage.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentrations (AUC) of Trastuzumab

End point title	Serum Concentrations (AUC) of Trastuzumab
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End point description:

Serum blood samples were collected for trastuzumab measurement prior to dosing and 15-30 minutes post infusion for Cycle 1 and Cycle 4. Additional serum samples were collected at study treatment termination.

End point type	Secondary
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End point timeframe:

C1D1 and C4D1 of post-infusion and study treatment termination

End point values	Trastuzumab	Trastuzumab emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[3]	0 ^[4]		
Units: ug/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[3] - As the data is not mature yet, this endpoint will be presented at final analysis stage.

[4] - As the data is not mature yet, this endpoint will be presented at final analysis stage.

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to primary clinical cutoff date of approximately 64 months

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Trastuzumab emtansine
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Reporting group description:

Participants received trastuzumab emtansine 3.6 mg/kg IV every 3 weeks for 14 cycles.

Reporting group title	Trastuzumab
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Reporting group description:

Participants received trastuzumab 6 milligrams/kilogram (mg/kg) intravenously (IV) every 3 weeks for 14 cycles.

Serious adverse events	Trastuzumab emtansine	Trastuzumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	94 / 740 (12.70%)	58 / 720 (8.06%)	
number of deaths (all causes)	42	56	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon Cancer Stage 1			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial Adenocarcinoma			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal Proliferative Breast Lesion			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary Tumour Benign			

subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 740 (0.14%)	3 / 720 (0.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 740 (0.14%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-Cardiac Chest pain			
subjects affected / exposed	3 / 740 (0.41%)	2 / 720 (0.28%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza Like Illness			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic Inflammatory Response Syndrome			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune system disorders			
Hypersensitivity			
subjects affected / exposed	4 / 740 (0.54%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian Cyst			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Haemorrhage			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Obstruction			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Prolapse			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 740 (0.27%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	2 / 740 (0.27%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Obstructive Pulmonary			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal Ideation			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Platelet Count Decreased			
subjects affected / exposed	10 / 740 (1.35%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	9 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection Fraction Decreased			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin T Increased			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Wound Dehiscence			
subjects affected / exposed	3 / 740 (0.41%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural haemorrhage			
subjects affected / exposed	1 / 740 (0.14%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation Pneumonitis			
subjects affected / exposed	2 / 740 (0.27%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia Fracture			
subjects affected / exposed	2 / 740 (0.27%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ankle Fracture			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb Fracture			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Complication			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist Fracture			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac Failure			
subjects affected / exposed	2 / 740 (0.27%)	2 / 720 (0.28%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			

subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Peripheral Sensory Neuropathy			
subjects affected / exposed	3 / 740 (0.41%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Motor Neuropathy			
subjects affected / exposed	2 / 740 (0.27%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 740 (0.27%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Vision Blurred			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 740 (0.41%)	2 / 720 (0.28%)	
occurrences causally related to treatment / all	4 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain			
subjects affected / exposed	3 / 740 (0.41%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 740 (0.14%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 740 (0.14%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal Perforation			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric Emptying			

subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestinal Obstruction			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 740 (0.14%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodular Regenerative Hyperplasia			
subjects affected / exposed	2 / 740 (0.27%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder Polyp			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Cyst			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Photosensitivity reaction			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Telangiectasia			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder Pain			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular Weakness			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Mastitis			
subjects affected / exposed	8 / 740 (1.08%)	6 / 720 (0.83%)	
occurrences causally related to treatment / all	2 / 8	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Related Infection			

subjects affected / exposed	6 / 740 (0.81%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	3 / 740 (0.41%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 740 (0.41%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Infection			
subjects affected / exposed	2 / 740 (0.27%)	2 / 720 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection			
subjects affected / exposed	2 / 740 (0.27%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	1 / 740 (0.14%)	2 / 720 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Infection			
subjects affected / exposed	1 / 740 (0.14%)	2 / 720 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 740 (0.27%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	1 / 740 (0.14%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 740 (0.27%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess Intestinal			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis Infections			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant Site Cellulitis			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected Seroma			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal Abscess			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Bacteraemia			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular Neuronitis			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvitis			
subjects affected / exposed	1 / 740 (0.14%)	0 / 720 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 740 (0.00%)	1 / 720 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Trastuzumab emtansine	Trastuzumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	719 / 740 (97.16%)	634 / 720 (88.06%)	
Vascular disorders			
Hot Flush			
subjects affected / exposed	95 / 740 (12.84%)	146 / 720 (20.28%)	
occurrences (all)	99	154	
Lymphoedema			
subjects affected / exposed	37 / 740 (5.00%)	48 / 720 (6.67%)	
occurrences (all)	37	51	
Hypertension			
subjects affected / exposed	41 / 740 (5.54%)	34 / 720 (4.72%)	
occurrences (all)	58	38	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	366 / 740 (49.46%)	243 / 720 (33.75%)	
occurrences (all)	456	276	
Influenza like Illness			
subjects affected / exposed	100 / 740 (13.51%)	86 / 720 (11.94%)	
occurrences (all)	138	96	
Pain			
subjects affected / exposed	93 / 740 (12.57%)	92 / 720 (12.78%)	
occurrences (all)	114	113	
Pyrexia			
subjects affected / exposed	76 / 740 (10.27%)	29 / 720 (4.03%)	
occurrences (all)	98	32	
Oedema Peripheral			
subjects affected / exposed	29 / 740 (3.92%)	52 / 720 (7.22%)	
occurrences (all)	33	56	
Chills			
subjects affected / exposed	39 / 740 (5.27%)	14 / 720 (1.94%)	
occurrences (all)	57	16	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	53 / 740 (7.16%)	42 / 720 (5.83%)	
occurrences (all)	56	50	

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	100 / 740 (13.51%)	86 / 720 (11.94%)	
occurrences (all)	112	93	
Epistaxis			
subjects affected / exposed	158 / 740 (21.35%)	25 / 720 (3.47%)	
occurrences (all)	220	30	
Dyspnoea			
subjects affected / exposed	62 / 740 (8.38%)	52 / 720 (7.22%)	
occurrences (all)	69	56	
Oropharyngeal Pain			
subjects affected / exposed	37 / 740 (5.00%)	33 / 720 (4.58%)	
occurrences (all)	39	36	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	101 / 740 (13.65%)	86 / 720 (11.94%)	
occurrences (all)	110	95	
Depression			
subjects affected / exposed	41 / 740 (5.54%)	44 / 720 (6.11%)	
occurrences (all)	44	47	
Anxiety			
subjects affected / exposed	27 / 740 (3.65%)	42 / 720 (5.83%)	
occurrences (all)	29	44	
Investigations			
Aspartate Aminotransferase Increased			
subjects affected / exposed	209 / 740 (28.24%)	40 / 720 (5.56%)	
occurrences (all)	253	44	
Platelet Count Decreased			
subjects affected / exposed	205 / 740 (27.70%)	17 / 720 (2.36%)	
occurrences (all)	256	21	
Alanine Aminotransferase Increased			
subjects affected / exposed	171 / 740 (23.11%)	41 / 720 (5.69%)	
occurrences (all)	208	51	
White Blood Cell Count Decreased			
subjects affected / exposed	61 / 740 (8.24%)	42 / 720 (5.83%)	
occurrences (all)	81	62	

Neutrophil Count Decreased subjects affected / exposed occurrences (all)	61 / 740 (8.24%) 78	36 / 720 (5.00%) 46	
Blood Alkaline Phosphatase Increased subjects affected / exposed occurrences (all)	61 / 740 (8.24%) 68	13 / 720 (1.81%) 14	
Blood Bilirubin Increased subjects affected / exposed occurrences (all)	49 / 740 (6.62%) 74	2 / 720 (0.28%) 2	
Injury, poisoning and procedural complications Radiation Skin Injury subjects affected / exposed occurrences (all)	188 / 740 (25.41%) 198	199 / 720 (27.64%) 208	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	210 / 740 (28.38%) 287	122 / 720 (16.94%) 146	
Peripheral Sensory Neuropathy subjects affected / exposed occurrences (all)	135 / 740 (18.24%) 146	50 / 720 (6.94%) 51	
Dizziness subjects affected / exposed occurrences (all)	69 / 740 (9.32%) 76	57 / 720 (7.92%) 61	
Paraesthesia subjects affected / exposed occurrences (all)	60 / 740 (8.11%) 72	40 / 720 (5.56%) 43	
Dysgeusia subjects affected / exposed occurrences (all)	60 / 740 (8.11%) 61	11 / 720 (1.53%) 12	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	74 / 740 (10.00%) 89	60 / 720 (8.33%) 79	
Eye disorders Lacrimation Increased			

subjects affected / exposed occurrences (all)	41 / 740 (5.54%) 44	13 / 720 (1.81%) 13	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	308 / 740 (41.62%)	93 / 720 (12.92%)	
occurrences (all)	438	111	
Constipation			
subjects affected / exposed	126 / 740 (17.03%)	59 / 720 (8.19%)	
occurrences (all)	152	66	
Diarrhoea			
subjects affected / exposed	91 / 740 (12.30%)	89 / 720 (12.36%)	
occurrences (all)	117	116	
Vomiting			
subjects affected / exposed	106 / 740 (14.32%)	37 / 720 (5.14%)	
occurrences (all)	139	45	
Dry Mouth			
subjects affected / exposed	100 / 740 (13.51%)	9 / 720 (1.25%)	
occurrences (all)	109	9	
Stomatitis			
subjects affected / exposed	80 / 740 (10.81%)	27 / 720 (3.75%)	
occurrences (all)	96	29	
Abdominal Pain			
subjects affected / exposed	55 / 740 (7.43%)	42 / 720 (5.83%)	
occurrences (all)	66	48	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	51 / 740 (6.89%)	42 / 720 (5.83%)	
occurrences (all)	57	44	
Dry Skin			
subjects affected / exposed	48 / 740 (6.49%)	36 / 720 (5.00%)	
occurrences (all)	52	41	
Rash Maculo-Papular			
subjects affected / exposed	42 / 740 (5.68%)	26 / 720 (3.61%)	
occurrences (all)	49	27	
Dermatitis Acneiform			

subjects affected / exposed occurrences (all)	39 / 740 (5.27%) 44	21 / 720 (2.92%) 23	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	192 / 740 (25.95%)	148 / 720 (20.56%)	
occurrences (all)	221	162	
Myalgia			
subjects affected / exposed	114 / 740 (15.41%)	80 / 720 (11.11%)	
occurrences (all)	125	87	
Pain In Extremity			
subjects affected / exposed	86 / 740 (11.62%)	70 / 720 (9.72%)	
occurrences (all)	97	81	
Back Pain			
subjects affected / exposed	53 / 740 (7.16%)	66 / 720 (9.17%)	
occurrences (all)	56	73	
Bone Pain			
subjects affected / exposed	52 / 740 (7.03%)	35 / 720 (4.86%)	
occurrences (all)	55	38	
Muscle Spasms			
subjects affected / exposed	33 / 740 (4.46%)	45 / 720 (6.25%)	
occurrences (all)	36	45	
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	58 / 740 (7.84%)	53 / 720 (7.36%)	
occurrences (all)	69	65	
Urinary Tract Infection			
subjects affected / exposed	64 / 740 (8.65%)	37 / 720 (5.14%)	
occurrences (all)	79	39	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	62 / 740 (8.38%)	16 / 720 (2.22%)	
occurrences (all)	70	19	
Hypokalaemia			
subjects affected / exposed	48 / 740 (6.49%)	14 / 720 (1.94%)	
occurrences (all)	58	20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2013	Clarification and details of IHC and ISH assays used for determining HER2 status were made. Inclusion of patients who had received dose-dense chemotherapy regimens, provided at least 8 weeks of taxane-based therapy and at least 8 weeks of trastuzumab had been given. Revision of language to differentiate radiotherapy for T3 disease with and without lymph node involvement. Recommendations for hormonal therapy were revised to allow 5 to 10 years, rather than only 5 years, of tamoxifen therapy as a result of changing practice guidelines. Guidelines for managing the specific adverse events of nodular regenerative hyperplasia and interstitial lung disease were added. For nodular regenerative hyperplasia, a new appendix for guidelines for liver biopsy was added. Radiotherapy-related toxicity was split into interstitial lung disease and skin toxicity, in order to differentiate between radiation-induced and drug-induced toxicities. Text on use of strong/potent CYP3A4/5 inhibitors was revised to provide further instruction to investigators, and remove erythromycin from the list of examples as it is only a moderate CYP3A4/5 inhibitor, not a potent inhibitor. Suspected transmission of an infection agent by the study drug was added as an adverse event of special interest.
06 September 2013	The duration of patient monitoring following first dose of trastuzumab emtansine was changed from 60 minutes to 90 minutes. Assessment of total protein at baseline was added to the list of assessments because it was inadvertently omitted. Requirements for long-term reporting of concomitant medication, adverse events and serious adverse events were clarified. Detail on severe/fatal hemorrhage was added under the identified risk of hematologic toxicity.
28 March 2014	Addition of language to allow shorter duration of an escalated dose-dense administration of paclitaxel. Inclusion criteria were revised to clarify that if pre-chemotherapy LVEF assessments were not conducted, the screening LVEF assessment must be at least 55% in order for the patient to be eligible. Dose modifications related to increases in AST and for thrombocytopenia were revised. Guidelines for Grade 1-2 pneumonitis were updated such that to require diagnosis of drug-related ILD/pneumonitis should lead to permanent discontinuation of trastuzumab emtansine treatment.
13 October 2015	The reporting of LVSD events as SAEs was clarified. Pregnancy reporting requirements were updated, in line with the Global Enhancement Pharmacovigilance Pregnancy Program.
09 July 2019	Updated to correct a small but significant error in language in the general inclusion criteria, and indicate that left ventricular ejection fraction (LVEF) should be $\geq 50\%$ prior to receiving neoadjuvant chemotherapy instead of after receiving neoadjuvant chemotherapy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported