



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 DE GB IT IE ES GR FR
Global end of trial date	23 May 2024

Results information

Result version number	v3 (current)
This version publication date	27 July 2025
First version publication date	23 August 2019
Version creation reason	

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	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4058
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +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	Final
Date of interim/final analysis	23 May 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 May 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to evaluate the efficacy of trastuzumab emtansine versus trastuzumab as adjuvant therapy in participants with human epidermal growth factor receptor 2 (HER2)-positive breast cancer who had residual tumors present in the breast or axillary lymph nodes following preoperative therapy. This study also evaluated the safety and pharmacokinetics (PK) of trastuzumab emtansine and trastuzumab.

Protection of trial subjects:

All study participants 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	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	11 Years
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	Czechia: 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	Türkiye: 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	748

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:

A total of 1486 participants with HER2-positive primary breast cancer who had residual invasive disease in either the breast or axillary lymph nodes took part in the study at 268 investigative sites across 28 countries from April 03, 2013 to May 23, 2024. Participants were randomized to receive either trastuzumab or trastuzumab emtansine (T-DM1).

Pre-assignment

Screening details:

1 participant randomized to trastuzumab arm was later re-randomized to T-DM1 arm & received T-DM1. Another participant received 13 cycles of trastuzumab & 1 of T-DM1. Both these participants were included in the trastuzumab ITT & T-DM1 safety analysis. 1 participant in T-DM1 received 9 cycles of trastuzumab & included in trastuzumab safety.

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 milligram per kilograms (mg/kg), intravenously (IV), every 3 weeks (Q3W), as a maintenance dose for 14 cycles (1 cycle = 21 days) or until disease recurrence or unacceptable toxicity which ever occurs first

Arm type	Active comparator
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	HERCEPTIN®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab, 6 mg/kg, IV was administered Q3W for 14 cycles (1 cycle = 21 days).

Arm title	Trastuzumab Emtansine
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Arm description:

Participants received trastuzumab emtansine, 3.6 mg/kg, IV, Q3W for 14 cycles (1 cycle = 21 days) or until disease recurrence or unacceptable toxicity which ever occurs first.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab Emtansine
Investigational medicinal product code	RO5304020
Other name	Kadcyla®, Ado-trastuzumab emtansine
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab emtansine, 3.6 mg/kg, IV was administered Q3W for 14 cycles (1 cycle = 21 days).

Number of subjects in period 1	Trastuzumab	Trastuzumab Emtansine
Started	743	743
Safety-evaluable (SE) Population	720	740
Completed	0	0
Not completed	743	743
Physician decision	1	7
Consent withdrawn by subject	115	90
Follow-up Terminated by Sponsor	441	495
Death	126	94
Not Specified	9	7
Lost to follow-up	51	50

Baseline characteristics

Reporting groups

Reporting group title	Trastuzumab
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Reporting group description:

Participants received trastuzumab, 6 milligram per kilograms (mg/kg), intravenously (IV), every 3 weeks (Q3W), as a maintenance dose for 14 cycles (1 cycle = 21 days) or until disease recurrence or unacceptable toxicity which ever occurs first

Reporting group title	Trastuzumab Emtansine
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Reporting group description:

Participants received trastuzumab emtansine, 3.6 mg/kg, IV, Q3W for 14 cycles (1 cycle = 21 days) or until disease recurrence or unacceptable toxicity which ever occurs first.

Reporting group values	Trastuzumab	Trastuzumab Emtansine	Total
Number of subjects	743	743	1486
Age Categorical Units: participants			
<=18 years	0	0	0
Between 18 and 65 years	675	685	1360
>=65 years	68	58	126
Sex: Female, Male Units: participants			
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	530	551	1081
More than one race	2	1	3
Unknown or Not Reported	77	69	146
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	107	91	198
Not Hispanic or Latino	543	579	1122
Unknown or Not Reported	93	73	166

End points

End points reporting groups

Reporting group title	Trastuzumab
Reporting group description: Participants received trastuzumab, 6 milligram per kilograms (mg/kg), intravenously (IV), every 3 weeks (Q3W), as a maintenance dose for 14 cycles (1 cycle = 21 days) or until disease recurrence or unacceptable toxicity which ever occurs first	
Reporting group title	Trastuzumab Emtansine
Reporting group description: Participants received trastuzumab emtansine, 3.6 mg/kg, IV, Q3W for 14 cycles (1 cycle = 21 days) or until disease recurrence or unacceptable toxicity which ever occurs first.	

Primary: Invasive Disease-free Survival (IDFS) Rate at 3 Years

End point title	Invasive Disease-free Survival (IDFS) Rate at 3 Years
End point description: IDFS event =the first occurrence of any 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 &/or skin of the ipsilateral breast); distant recurrence (i.e., evidence of breast cancer in any anatomic site-other than the 2 above-mentioned sites - that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer); contralateral invasive breast cancer; death attributable to any cause including breast cancer, non-breast cancer or unknown cause . 3-year IDFS rate in ITT population was estimated using Kaplan Meier (KM) method & the percentage of participants who were event-free 3 years after randomization was estimated. ITT population.	
End point type	Primary
End point timeframe: At Year 3	

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: percentage of participants				
number (confidence interval 95%)	77.12 (73.96 to 80.28)	88.44 (86.07 to 90.81)		

Statistical analyses

Statistical analysis title	Trastuzumab vs Trastuzumab Emtansine
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	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.66

Secondary: IDFS Including Second Primary Non-breast Cancer (SPNBC) Rate at 3 Years

End point title	IDFS Including Second Primary Non-breast Cancer (SPNBC) Rate at 3 Years
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End point description:

IDFS including SPNBC was defined the same way as IDFS 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). IDFS event was defined as outlined in the description for IDFS rate outcome measure (OM) number 1. 3-year IDFS including SPNBC rate in the ITT population was estimated using KM method, and the percentage of participants who were event-free 3 years after randomization was estimated. ITT population included all participants who were randomized to the study regardless of whether they received any study treatment.

End point type	Secondary
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End point timeframe:

At Year 3

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: percentage of participants				
number (confidence interval 95%)	76.98 (73.82 to 80.15)	87.87 (85.45 to 90.29)		

Statistical analyses

Statistical analysis title	Trastuzumab vs Trastuzumab Emtansine
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	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.69

Secondary: IDFS Including SPNBC Rate at 7 Years

End point title	IDFS Including SPNBC Rate at 7 Years
End point description:	
IDFS including SPNBC was defined the same way as IDFS but including second primary non breast invasive cancer as an event (with the exception of non-melanoma skin cancers and CIS of any site). IDFS event was defined as outlined in the description for IDFS rate OM number 1. 7-year IDFS including SPNBC rate in the ITT population was estimated using KM method, and the percentage of participants who were event-free 7 years after randomization was estimated. ITT population included all participants who were randomized to the study regardless of whether they received any study treatment.	
End point type	Secondary
End point timeframe:	
At Year 7	

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: percentage of participants				
number (confidence interval 95%)	66.19 (62.59 to 69.80)	79.81 (76.79 to 82.82)		

Statistical analyses

Statistical analysis title	Trastuzumab vs Trastuzumab Emtansine
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	0.57

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.69

Secondary: IDFS Including SPNBC Rate at 8 Years

End point title	IDFS Including SPNBC Rate at 8 Years
End point description:	
IDFS including SPNBC was defined the same way as IDFS but including second primary non breast invasive cancer as an event (with the exception of non-melanoma skin cancers and CIS of any site). IDFS event was defined as outlined in the description for IDFS rate OM number 1. 8-year IDFS including SPNBC rate in the ITT population was estimated using KM method, and the percentage of participants who were event-free 8 years after randomization was estimated. ITT population included all participants who were randomized to the study regardless of whether they received any study treatment.	
End point type	Secondary
End point timeframe:	
At Year 8	

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: percentage of participants				
number (confidence interval 95%)	63.65 (59.96 to 67.34)	77.76 (74.60 to 80.92)		

Statistical analyses

Statistical analysis title	Trastuzumab vs Trastuzumab Emtansine
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	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.69

Secondary: Disease-free Survival (DFS) Rate at 3 Years

End point title	Disease-free Survival (DFS) Rate at 3 Years
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End point description:

DFS was defined as the time between randomization and the date of the first occurrence of an IDFS event including SPNBC event or contralateral or ipsilateral ductal carcinoma in situ (DCIS). IDFS event was defined as outlined in the description for IDFS rate OM number 1. 3-year DFS rate in the ITT population was estimated using KM method, and the percentage of participants who were event-free 3 years after randomization was estimated. ITT population included all participants who were randomized to the study regardless of whether they received any study treatment.

End point type	Secondary
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End point timeframe:

At Year 3

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: percentage of participants				
number (confidence interval 95%)	76.98 (73.82 to 80.15)	87.59 (85.15 to 90.03)		

Statistical analyses

Statistical analysis title	Trastuzumab vs Trastuzumab Emtansine
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	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.7

Secondary: DFS Rate at 7 Years

End point title	DFS Rate at 7 Years
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End point description:

DFS was defined as the time between randomization and the date of the first occurrence of an IDFS event including SPNBC event or contralateral or ipsilateral DCIS. IDFS event was defined as outlined in the description for IDFS rate OM number 1. 7-year DFS rate in the ITT population was estimated using KM method, and the percentage of participants who were event-free 7 years after randomization was estimated. ITT population included all participants who were randomized to the study regardless of whether they received any study treatment.

End point type	Secondary
End point timeframe:	
At Year 7	

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: percentage of participants				
number (confidence interval 95%)	66.03 (62.42 to 69.64)	79.37 (76.33 to 82.42)		

Statistical analyses

Statistical analysis title	Trastuzumab vs Trastuzumab Emtansine
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	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.7

Secondary: DFS Rate at 8 Years

End point title	DFS Rate at 8 Years
End point description:	
DFS was defined as the time between randomization and the date of the first occurrence of an IDFS event including SPNBC event or contralateral or ipsilateral DCIS. IDFS event was defined as outlined in the description for IDFS rate OM number 1. 8-year DFS rate in the ITT population was estimated using KM method, and the percentage of participants who were event-free 8 years after randomization was estimated. ITT population included all participants who were randomized to the study regardless of whether they received any study treatment.	
End point type	Secondary
End point timeframe:	
At Year 8	

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: percentage of participants				
number (confidence interval 95%)	63.49 (59.80 to 67.18)	77.14 (73.95 to 80.33)		

Statistical analyses

Statistical analysis title	Trastuzumab vs Trastuzumab Emtansine
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	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.7

Secondary: Overall Survival (OS) Rate at 5 Years

End point title	Overall Survival (OS) Rate at 5 Years
End point description:	OS was defined as the time from randomization to death due to any cause. 5-year OS event-free rate in the ITT population was estimated using KM method, and the percentage of participants who were event-free 5 years after randomization was estimated. ITT population included all participants who were randomized to the study regardless of whether they received any study treatment.
End point type	Secondary
End point timeframe:	
At Year 5	

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: percentage of participants				
number (confidence interval 95%)	87.71 (85.20 to 90.22)	91.40 (89.30 to 93.50)		

Statistical analyses

Statistical analysis title	Trastuzumab vs Trastuzumab Emtansine
Comparison groups	Trastuzumab v Trastuzumab Emtansine
Number of subjects included in analysis	1486
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0082
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.91

Secondary: OS Rate at 7 Years

End point title	OS Rate at 7 Years
End point description:	
OS was defined as the time from randomization to death due to any cause. 7-year OS event-free rate in the ITT population was estimated using KM method, and the percentage of participants who were event-free 7 years after randomization was estimated. ITT population included all participants who were randomized to the study regardless of whether they received any study treatment.	
End point type	Secondary
End point timeframe:	
At Year 7	

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: percentage of participants				
number (confidence interval 95%)	84.38 (81.59 to 87.17)	89.07 (86.72 to 91.43)		

Statistical analyses

Statistical analysis title	Trastuzumab vs Trastuzumab Emtansine
Comparison groups	Trastuzumab v Trastuzumab Emtansine
Number of subjects included in analysis	1486
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0082
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.91

Secondary: OS Rate at 8 Years

End point title	OS Rate at 8 Years
End point description:	OS was defined as the time from randomization to death due to any cause. 8-year OS event-free rate in the ITT population was estimated using KM method, and the percentage of participants who were event-free 8 years after randomization was estimated. ITT population included all participants who were randomized to the study regardless of whether they received any study treatment.
End point type	Secondary
End point timeframe:	
At Year 8	

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: percentage of participants				
number (confidence interval 95%)	81.91 (78.94 to 84.89)	87.16 (84.62 to 89.70)		

Statistical analyses

Statistical analysis title	Trastuzumab vs Trastuzumab Emtansine
Comparison groups	Trastuzumab v Trastuzumab Emtansine
Number of subjects included in analysis	1486
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0082
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.91

Secondary: Distant Recurrence-free Interval (DRFI) Rate at 3 Years

End point title	Distant Recurrence-free Interval (DRFI) Rate at 3 Years
End point description:	
DRFI was defined as the time between randomization and the date of distant breast cancer recurrence. 3-year DRFI event-free rate in the ITT population was estimated using KM method, and the percentage of participants who were event-free 3 years after randomization was estimated. ITT population included all participants who were randomized to the study regardless of whether they received any study treatment.	
End point type	Secondary
End point timeframe:	
At Year 3	

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: percentage of participants				
number (confidence interval 95%)	83.26 (80.43 to 86.08)	89.95 (87.72 to 92.19)		

Statistical analyses

Statistical analysis title	Trastuzumab vs Trastuzumab Emtansine
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	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.76

Secondary: DRFI Rate at 7 Years

End point title	DRFI Rate at 7 Years
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End point description:

DRFI was defined as the time between randomization and the date of distant breast cancer recurrence. 7-year DRFI event-free rate in the ITT population was estimated using KM method, and the percentage of participants who were event-free 7 years after randomization was estimated. ITT population included all participants who were randomized to the study regardless of whether they received any study treatment.

End point type	Secondary
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End point timeframe:

At Year 7

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: percentage of participants				
number (confidence interval 95%)	76.22 (72.95 to 79.48)	84.55 (81.82 to 87.27)		

Statistical analyses

Statistical analysis title	Trastuzumab vs Trastuzumab Emtansine
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	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.76

Secondary: Percentage of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)
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End point description:

AE=any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, regardless of causal attribution. AE can therefore be any unfavorable & unintended sign (including abnormal laboratory finding), symptom/disease temporally associated with use of a medicinal product, whether or not considered related to medicinal product. SAE=any AE that met any given criteria: fatal (i.e. AE causes/leads to death); life-threatening (i.e. AE, in view of

investigator, placed the participant at immediate risk of death); required/prolonged inpatient hospitalization; resulted in persistent or significant disability/incapacity (i.e. AE results in substantial disruption of participant's ability to conduct normal life functions); congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug; significant medical event in investigator's judgment. SE population=all randomized participants who received any amount of study treatment.

End point type	Secondary
End point timeframe:	
From signing of informed consent till end of follow up (up to approximately 131 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)				
AEs	93.3	98.8		
SAEs	8.1	12.7		

Statistical analyses

No statistical analyses for this end point

Secondary: DRFI Rate at 8 Years

End point title	DRFI Rate at 8 Years
End point description:	
DRFI was defined as the time between randomization and the date of distant breast cancer recurrence. 8-year DRFI event-free rate in the ITT population was estimated using KM method, and the percentage of participants who were event-free 8 years after randomization was estimated. ITT population included all participants who were randomized to the study regardless of whether they received any study treatment.	
End point type	Secondary
End point timeframe:	
At Year 8	

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: percentage of participants				
number (confidence interval 95%)	74.28 (70.90 to 77.65)	83.82 (81.03 to 86.62)		

Statistical analyses

Statistical analysis title	Trastuzumab vs Trastuzumab Emtansine
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	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.76

Secondary: Percentage of Participants With Hepatotoxicity Events as Adjudicated by the Hepatic Review Committee

End point title	Percentage of Participants With Hepatotoxicity Events as Adjudicated by the Hepatic Review Committee
End point description: Hepatotoxicity events were summarized by treatment arm. Hepatotoxicity events were assessed using liver function laboratory test (LFT) results which included the analysis of baseline and post-baseline levels of alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin (TBILI), and alkaline phosphatase (ALK). Hepatic events, as adjudicated by the Hepatic Review Committee, are summarized. SE population included all randomized participants who received any amount of study treatment. Percentages have been rounded off.	
End point type	Secondary
End point timeframe: Up to 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)	0.1	0.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Cardiac Events as Adjudicated by the Cardiac Review Committee

End point title	Percentage of Participants With Cardiac Events as Adjudicated by the Cardiac Review Committee
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End point description:

Cardiac events were defined as death from cardiac cause or severe congestive heart failure (New York Heart Association [NYHA] Class III or IV) with a decrease in left ventricular ejection fraction (LVEF) of 10 percentage points or more from baseline to an LVEF of < 50%. Other cardiac-related events (e.g., any symptomatic congestive heart failure [CHF] associated with a 10% drop in LVEF to < 50%; asymptomatic declines in LVEF requiring dose delay) were summarized as adjudicated by the Cardiac Review Committee. SE population included all randomized participants who received any amount of study treatment. Percentages have been rounded off.

End point type	Secondary
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End point timeframe:

Up to approximately 126 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)	4.2	3.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Treatment Due to AEs

End point title	Number of Participants Who Discontinued Treatment Due to AEs
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End point description:

An AE was any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Participants were treated for up to 14 cycles (1 cycle = 21 days). SE population included all randomized participants who received any amount of study treatment.

End point type	Secondary
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End point timeframe:

Up to approximately 9.6 months

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	720	740		
Units: participants	15	134		

Statistical analyses

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Core 30 (QLQ-C30)

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Core 30 (QLQ-C30)
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End point description:

EORTC QLQ-C30 consists of 30 questions which assess 5 functional domains (physical, role, cognitive, emotional & social), a global health status/quality of life (GHS/QoL) scale, 3 symptom scales (fatigue, pain, nausea & vomiting), 5 single items (dyspnea, appetite loss, sleep disturbance, constipation & diarrhea), & a perceived financial impact of the disease item. Most questions used a 4-point scale (1=Not at all - 4=Very much; 2 questions used a 7-point scale [1=very poor - 7=Excellent]). Obtained scores are linearly transformed to a score range of 0-100, where higher scores=greater functioning, greater QoL, or a greater degree of symptoms. A positive change from baseline indicates improvement. ITT population. Number analyzed=number of participants with data available for analysis. n=unique number of participants out of all the assessed participants with data available for analysis at the specified timepoint. Different participants may have contributed data for each timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Cycles 5 & 11, Follow-up (FU) Month 6, FU Month 12 (1 cycle = 21 days)

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline: Appetite Loss (n=624, 645)	7.9 (± 17.4)	7.1 (± 16.4)		
Cycle 5: Appetite Loss (n=558, 571)	1.0 (± 18.7)	6.5 (± 23.7)		
Cycle 11: Appetite Loss (n=496, 496)	-0.5 (± 17.2)	2.9 (± 20.2)		
FU Month 6: Appetite Loss (n=410, 462)	-1.6 (± 18.3)	-1.7 (± 19.9)		
FU Month 12: Appetite Loss (n=384, 430)	0.5 (± 20.3)	-1.9 (± 20.1)		
Constipation (n=624, 645)	9.8 (± 20.2)	9.5 (± 19.0)		
Cycle 5: Constipation (n=558, 571)	1.0 (± 22.4)	4.6 (± 22.6)		
Cycle 11: Constipation (n=496, 496)	3.4 (± 23.6)	7.3 (± 23.1)		
FU Month 6: Constipation (n=410, 462)	4.1 (± 23.7)	3.7 (± 23.3)		
FU Month 12: Constipation (n=384, 430)	3.2 (± 23.2)	4.3 (± 24.6)		
Baseline: Diarrhea (n=624, 645)	8.8 (± 17.6)	6.4 (± 14.9)		
Cycle 5: Diarrhea (n=558, 571)	-1.6 (± 19.3)	-1.5 (± 19.5)		
Cycle 11: Diarrhea (n=496, 496)	-0.4 (± 21.4)	-2.4 (± 17.5)		
FU Month 6: Diarrhea (n=410, 462)	-3.4 (± 18.5)	-1.9 (± 18.3)		
FU Month 12: Diarrhea (n=384, 430)	-2.8 (± 18.9)	-1.6 (± 18.4)		
Baseline: Dyspnea (n=624, 645)	12.7 (± 20.7)	11.0 (± 18.8)		
Cycle 5: Dyspnea (n=558, 571)	2.3 (± 21.9)	4.1 (± 22.4)		
Cycle 11: Dyspnea (n=496, 496)	2.8 (± 21.2)	2.7 (± 20.4)		
FU Month 6: Dyspnea (n=410, 462)	3.3 (± 22.8)	3.8 (± 22.7)		
FU Month 12: Dyspnea (n=384, 430)	3.9 (± 24.9)	5.3 (± 22.4)		
Baseline: Fatigue (n=624, 645)	29.2 (± 21.1)	28.0 (± 20.0)		
Cycle 5: Fatigue (n=558, 571)	1.1 (± 20.1)	5.5 (± 19.7)		
Cycle 11: Fatigue (n=496, 496)	1.1 (± 20.5)	3.8 (± 21.3)		

FU Month 6: Fatigue (n=410, 462)	-1.4 (± 21.9)	-0.1 (± 22.2)		
FU Month 12: Fatigue (n=384, 430)	-0.1 (± 23.3)	-0.1 (± 22.1)		
Baseline: Financial Difficulties (n=604, 635)	28.6 (± 33.3)	27.6 (± 31.9)		
Cycle 5: Financial Difficulties (n=530, 548)	-3.1 (± 26.5)	-3.0 (± 28.0)		
Cycle 11: Financial Difficulties (n=472, 480)	-5.1 (± 27.6)	-1.7 (± 28.7)		
FU Month 6: Financial Difficulties (n=393, 444)	-8.4 (± 28.3)	-6.5 (± 30.6)		
FU Month 12: Financial Difficulties (n=367, 413)	-10.9 (± 30.5)	-7.3 (± 31.0)		
Baseline: Insomnia (n=624, 645)	30.6 (± 30.8)	30.6 (± 29.2)		
Cycle 5: Insomnia (n=558, 571)	1.9 (± 28.4)	1.3 (± 29.7)		
Cycle 11: Insomnia (n=494, 494)	2.4 (± 29.9)	1.5 (± 30.3)		
FU Month 6: Insomnia (n=410, 462)	1.8 (± 31.3)	-0.9 (± 32.1)		
FU Month 12: Insomnia (n=384, 430)	0.3 (± 30.4)	0.7 (± 31.7)		
Baseline: Nausea/Vomiting (n=624, 645)	3.3 (± 9.0)	2.8 (± 8.0)		
Cycle 5: Nausea/Vomiting (n=558, 571)	1.5 (± 11.2)	3.2 (± 12.5)		
Cycle 11: Nausea/Vomiting (n=496, 496)	1.3 (± 12.8)	3.0 (± 11.8)		
FU Month 6: Nausea/Vomiting (n=410, 462)	0.8 (± 10.4)	0.2 (± 11.1)		
FU Month 12: Nausea/Vomiting (n=384, 430)	0.4 (± 10.5)	1.2 (± 10.9)		
Baseline: Pain (n=624, 645)	22.2 (± 22.2)	22.6 (± 22.8)		
Cycle 5: Pain (n=558, 571)	0.0 (± 23.2)	1.8 (± 23.9)		
Cycle 11: Pain (n=496, 496)	0.1 (± 23.1)	2.1 (± 24.4)		
FU Month 6: Pain (n=410, 462)	-0.3 (± 24.6)	-0.5 (± 24.3)		
FU Month 12: Pain (n=384, 430)	-1.2 (± 25.6)	-0.8 (± 25.4)		
Baseline: Cognitive Functioning (n=624, 645)	83.3 (± 20.2)	84.4 (± 19.0)		
Cycle 5: Cognitive Functioning (n=558, 571)	-3.8 (± 18.4)	-4.5 (± 18.7)		
Cycle 11: Cognitive Functioning (n=496, 496)	-5.4 (± 21.3)	-5.3 (± 19.6)		
FU Month 6: Cognitive Functioning (n=410, 462)	-4.1 (± 22.0)	-6.1 (± 21.6)		
FU Month 12: Cognitive Functioning (n=384, 430)	-4.9 (± 22.2)	-6.9 (± 21.7)		
Baseline: Emotional Functioning (n=624, 645)	75.0 (± 22.0)	75.2 (± 21.2)		
Cycle 5: Emotional Functioning (n=558, 571)	-0.4 (± 20.0)	-1.3 (± 21.3)		
Cycle 11: Emotional Functioning (n=496, 496)	-1.0 (± 21.3)	0.1 (± 22.0)		
FU Month 6: Emotional Functioning (n=410, 462)	-2.9 (± 22.0)	-0.8 (± 23.3)		
FU Month 12: Emotional Functioning (n=384, 430)	-2.0 (± 22.7)	-1.6 (± 23.5)		
Baseline: Physical Functioning (n=624, 645)	84.5 (± 15.3)	85.8 (± 14.1)		
Cycle 5: Physical Functioning (n=558, 571)	0.3 (± 12.9)	-1.6 (± 12.7)		
Cycle 11: Physical Functioning (n=496, 496)	1.9 (± 14.2)	-0.6 (± 14.6)		
FU Month 6: Physical Functioning (n=410, 462)	2.8 (± 15.4)	0.7 (± 15.1)		

FU Month 12: Physical Functioning (n=384, 430)	2.7 (± 14.5)	0.8 (± 14.5)		
Baseline: Role Functioning (n=624, 645)	77.5 (± 25.0)	78.6 (± 23.3)		
Cycle 5: Role Functioning (n=558, 571)	2.0 (± 24.3)	-0.2 (± 24.1)		
Cycle 11: Role Functioning (n=496, 496)	4.0 (± 24.3)	0.6 (± 24.5)		
FU Month 6: Role Functioning (n=410, 462)	7.4 (± 25.8)	3.6 (± 26.7)		
FU Month 12: Role Functioning (n=384, 430)	8.0 (± 27.5)	4.6 (± 25.5)		
Baseline: Social Functioning (n=624, 645)	77.1 (± 24.1)	76.8 (± 23.2)		
Cycle 5: Social Functioning (n=558, 571)	4.0 (± 22.5)	1.6 (± 23.8)		
Cycle 11: Social Functioning (n=496, 496)	5.8 (± 24.0)	2.5 (± 23.6)		
FU Month 6: Social Functioning (410, 462)	8.5 (± 23.7)	6.5 (± 26.1)		
FU Month 12: Social Functioning (n=384, 430)	9.5 (± 25.1)	7.4 (± 26.4)		
Baseline: Global Health Status (n=624, 645)	71.2 (± 19.3)	71.4 (± 18.0)		
Cycle 5: Global Health Status (n=558, 571)	0.6 (± 18.9)	-1.9 (± 19.6)		
Cycle 11: Global Health Status (n=496, 496)	1.7 (± 17.8)	-0.5 (± 19.9)		
FU Month 6: Global Health Status (n=410, 462)	2.5 (± 19.3)	2.0 (± 19.2)		
FU Month 12: Global Health Status (n=384, 430)	3.2 (± 19.5)	2.8 (± 20.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With AEs and SAEs Leading to Death

End point title	Number of Participants With AEs and SAEs Leading to Death
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End point description:

AE=any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, regardless of causal attribution. AE can therefore be any unfavorable & unintended sign (including abnormal laboratory finding), symptom/disease temporally associated with use of a medicinal product, whether or not considered related to medicinal product. SAE=any AE that met any given criteria: fatal (i.e. AE causes/leads to death); life-threatening (i.e. AE, in view of investigator, placed the participant at immediate risk of death); required/prolonged inpatient hospitalization; resulted in persistent or significant disability/incapacity (i.e. AE results in substantial disruption of participant's ability to conduct normal life functions); congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug; significant medical event in investigator's judgment. SE population=all randomized participants who received any amount of study treatment.

End point type	Secondary
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End point timeframe:

From signing of informed consent till end of follow up (up to approximately 131 months)

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	720	740		
Units: participants	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EORTC Quality of Life Questionnaire – Breast Cancer (QLQ-BR23)

End point title	Change From Baseline in EORTC Quality of Life Questionnaire – Breast Cancer (QLQ-BR23)
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End point description:

EORTC-QLQ-BR23= 23-item breast cancer-specific module that consists of 4 functional scales (body image, sexual enjoyment, sexual functioning, future perspective) & 4 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). Obtained scores are linearly transformed to a score range of 0-100. High score for functional scale=high/better level of functioning/healthy functioning. Higher scores for symptom scales=higher levels of symptoms/problems. For functional scales, positive change from baseline=deterioration in QOL & negative change from baseline=improvement in QOL. For symptom scales, positive change from baseline=improvement in QOL & negative change from baseline=deterioration in QOL. ITT population. Number analyzed=number of participants with data available for analysis. n=unique number of participants with data available for analysis at the specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline, Cycles 5 & 11, Follow-up (FU) Month 6, FU Month 12 (1 cycle = 21 days)

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline: Body Image (n=622, 645)	69.8 (± 28.5)	67.5 (± 28.5)		
Cycle 5: Body Image (n=555, 571)	1.5 (± 20.5)	4.6 (± 22.7)		
Cycle 11: Body Image (n=493, 495)	3.4 (± 24.4)	5.7 (± 23.9)		
FU Month 6: Body Image (n=409, 462)	3.6 (± 25.1)	7.8 (± 25.8)		
FU Month 12: Body Image (n=383, 428)	6.2 (± 27.1)	6.1 (± 27.2)		
Baseline: Future Perspective (FP) (n=622, 645)	51.3 (± 31.2)	50.1 (± 31.7)		
Cycle 5: FP (n=551, 571)	2.6 (± 28.3)	6.5 (± 29.9)		
Cycle 11: FP (n=493, 495)	6.3 (± 30.0)	6.1 (± 31.4)		
FU Month 6: FP (n=409, 462)	7.7 (± 33.5)	8.1 (± 34.6)		
Change at FU Month 12: FP (n=383, 428)	8.1 (± 31.1)	8.2 (± 33.0)		
Baseline: Sexual Enjoyment (n=218, 241)	50.9 (± 28.8)	52.3 (± 28.5)		

Cycle 5: Sexual Enjoyment (n=147, 172)	2.3 (± 26.4)	-1.9 (± 24.6)		
Cycle 11: Sexual Enjoyment (n=128,137)	4.4 (± 27.5)	4.4 (± 24.5)		
FU Month 6: Sexual Enjoyment (n=104, 126)	3.2 (± 28.1)	0.3 (± 27.5)		
Month 12: Sexual Enjoyment (n=95, 114)	5.6 (± 26.0)	1.8 (± 26.2)		
Baseline: Sexual Function (n=550, 564)	20.2 (± 23.6)	22.0 (± 23.4)		
Cycle 5: Sexual Function (n=456, 466)	3.3 (± 20.0)	2.3 (± 20.0)		
Cycle 11: Sexual Function (n=393, 382)	3.1 (± 20.8)	1.9 (± 20.3)		
FU Month 6: Sexual Function (n=321, 360)	5.1 (± 23.9)	4.3 (± 23.1)		
FU Month 12: Sexual Function (n=289, 319)	5.9 (± 23.7)	5.2 (± 22.7)		
Baseline: Arm Symptoms (n=622,645)	24.6 (± 21.1)	24.5 (± 21.0)		
Cycle 5: Arm Symptoms (n=555, 571)	-2.8 (± 20.9)	-2.6 (± 23.0)		
Cycle 11: Arm Symptoms (n=493, 495)	-2.6 (± 21.2)	0.2 (± 24.2)		
FU Month 6: Arm Symptoms (n=409,462)	-3.0 (± 23.5)	-1.3 (± 24.2)		
FU Month 12: Arm Symptoms (n=383,428)	-5.7 (± 22.8)	-1.5 (± 22.6)		
Baseline: Breast Symptoms (n=622,645)	22.7 (± 19.1)	21.4 (± 17.9)		
Cycle 5: Breast Symptoms (n=555,571)	-1.1 (± 20.3)	-1.1 (± 19.1)		
Cycle 11: Breast Symptoms (n=493,495)	-3.7 (± 19.8)	-0.6 (± 19.5)		
FU Month 6: Breast Function (n=409,462)	-6.5 (± 20.0)	-2.2 (± 19.7)		
FU Month 12: Breast Function(n=383,428)	-8.3 (± 19.9)	-3.8 (± 19.2)		
Baseline: Systemic Therapy SE (n=622,645)	16.7 (± 13.7)	16.9 (± 14.1)		
Cycle 5: Systemic Therapy SE (n=555,571)	0.7 (± 13.0)	5.5 (± 15.3)		
Cycle 11: Systemic Therapy SE (n=493,495)	1.2 (± 12.2)	4.2 (± 15.4)		
FU Month 6: Systemic Therapy SE (n=409,462)	1.9 (± 13.9)	1.1 (± 15.3)		
FU Month 12: Systemic Therapy SE(n=383,428)	1.3 (± 13.9)	1.4 (± 16.3)		
Baseline: Upset by Hair Loss(n=77,96)	40.3 (± 35.6)	50.7 (± 38.4)		
Cycle 5: Upset by Hair Loss (n=13,17)	-5.1 (± 38.1)	-17.6 (± 39.3)		
Cycle 11: Upset by Hair Loss (n=14,14)	-28.6 (± 45.0)	-14.3 (± 33.9)		
FU Month 6: Upset by Hair Loss(n=25,22)	-12.0 (± 47.0)	-15.2 (± 42.1)		
FU Month 12: Upset by Hair Loss(n=23,21)	-2.9 (± 37.5)	-14.3 (± 41.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentrations of Trastuzumab Emtansine

End point title	Serum Concentrations of Trastuzumab Emtansine ^[1]
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End point description:

PK-evaluable population included all participants who received at least 1 dose of trastuzumab emtansine and had at least one evaluable post dose PK sample. Number analyzed is the number of participants with data available for analysis. n=unique number of participants out of all the assessed participants with data available for analysis at the specified timepoint. Different participants may have contributed data for each timepoint. 99999=The geometric mean and geometric coefficient of variation were not estimable as the samples were below the limit of quantification. The samples were taken prior to administration of the first dose.

End point type	Secondary
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End point timeframe:

Pre-infusion on Cycles 1, 2, 4 and 5; 15-30 minutes and 2 hours post-infusion on Cycles 1 and 4; treatment discontinuation/completion visit (up to approximately 64 months) (1 cycle = 21 days)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is reporting data for only the trastuzumab emtansine arm. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Trastuzumab Emtansine			
Subject group type	Reporting group			
Number of subjects analysed	406			
Units: micrograms per milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)				
Pre-infusion on Cycle 1 (n=406)	99999 ($\pm$ 99999)			
15-30 minutes post-infusion on Cycle 1 (n=402)	63.0 ($\pm$ 101.8)			
2 hours post-infusion on Cycle 1 (n=388)	67.4 ($\pm$ 60.0)			
Pre-infusion on Cycle 2 (n=383)	1.69 ($\pm$ 110.7)			
Pre-infusion on Cycle 4 (n=379)	1.73 ($\pm$ 95.7)			
15-30 minutes post-infusion on Cycle 4 (n=375)	68.5 ($\pm$ 59.4)			
2 hours post-infusion on Cycle 4 (n=358)	66.4 ($\pm$ 71.0)			
Pre-infusion on Cycle 5 (n=336)	1.67 ($\pm$ 99.3)			
Treatment Completion/Discontinuation (n=323)	0.323 ($\pm$ 265.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Deacetyl Mercapto 1-Oxopropyl Maytansine (DM1)

End point title	Plasma Concentrations of Deacetyl Mercapto 1-Oxopropyl Maytansine (DM1) ^[2]
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End point description:

Concentration of DM1 in plasma was measured through the samples obtained from participants randomized to the trastuzumab emtansine arm. DM1 is an ant-microtubule agent derived from maytansine. In transtuzumab entansine, DM1 is linked to the antibody transtuzumab thus helping the drug to specifically target the HER 2- positive cancer cells. PK trastuzumab emtansine evaluable population. Number analyzed is the number of participants with data available for analysis. n=unique number of participants out of all the assessed participants with data available for analysis at the specified timepoint. Different participants may have contributed data for each timepoint. 99999=The

geometric mean & geometric coefficient of variation were not estimable as majority of the values were lower than reportable. 9999=The geometric coefficient of variation was not estimable as majority of the values were lower than reportable or zero.

End point type	Secondary
End point timeframe:	
Pre-infusion, 15-30 minutes and 2 hour post-infusion on Cycles 1 and 4 (1 cycle = 21 days)	

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is reporting data for only the trastuzumab emtansine arm. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Trastuzumab Emtansine			
Subject group type	Reporting group			
Number of subjects analysed	417			
Units: nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Pre-infusion on Cycle 1 (n=401)	99999 (± 99999)			
15-30 minutes post-infusion on Cycle 1 (n=397)	4.21 (± 57.4)			
2 hours post-infusion on Cycle 1 (n=387)	3.44 (± 38.2)			
Pre-infusion on Cycle 4 (n=361)	0.372 (± 9999)			
15-30 minutes post-infusion on Cycle 4 (n=359)	4.81 (± 48.8)			
2 hours post-infusion on Cycle 4 (n=347)	3.70 (± 41.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentrations of Trastuzumab

End point title	Serum Concentrations of Trastuzumab ^[3]
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End point description:

PK-evaluable population included all participants who received at least 1 dose of trastuzumab and had at least one evaluable post dose PK sample. Number analyzed is the number of participants with data available for analysis. n=unique number of participants out of all the assessed participants with data available for analysis at the specified timepoint. Different participants may have contributed data for each timepoint. 9999=The geometric mean and geometric coefficient of variation were not estimable as the samples were below the limit of quantification. The samples were taken prior to administration of the first dose.

End point type	Secondary
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End point timeframe:

Pre-infusion and 15-30 minutes post-infusion on Cycles 1 and 4; Treatment completion/discontinuation visit (up to approximately 64 months) (1 cycle = 21 days)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is reporting data for only the trastuzumab arm. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	404			
Units: ug/mL				
geometric mean (geometric coefficient of variation)				
Pre-infusion on Cycle 1 (n=388)	9999 ($\pm$ 9999)			
15-30 minutes post-infusion on Cycle 1 (n=384)	208 ($\pm$ 43.1)			
Pre-infusion on Cycle 4 (n=361)	64.8 ($\pm$ 60.6)			
15-30 minutes post-infusion on Cycle 4 (n=355)	218 ($\pm$ 47.2)			
Treatment Completion/Discontinuation (n=325)	58.7 ($\pm$ 86.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentrations of Total Trastuzumab

End point title	Serum Concentrations of Total Trastuzumab ^[4]
End point description:	
Total trastuzumab is the sum of conjugated and unconjugated trastuzumab. Blood and serum samples were obtained from participants randomized to the trastuzumab arm. PK-evaluable population included all participants who received at least 1 dose of trastuzumab and had at least one evaluable post dose PK sample. Number analyzed is the number of participants with data available for analysis. n=unique number of participants out of all the assessed participants with data available for analysis at the specified timepoint. Different participants may have contributed data for each timepoint. 9999=The geometric mean and geometric coefficient of variation were not estimable as the samples were below the limit of quantification. The samples were taken prior to administration of the first dose.	
End point type	Secondary
End point timeframe:	
Pre-infusion on Day 1 of Cycles 1, 2, 4, and 5; 15-30 minutes and 2 hours post-infusion on Day 1 of Cycles 1 and 4 (1 cycle = 21 days)	
Notes:	
[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is reporting data for only the trastuzumab arm. Hence, statistics for all arms in the baseline period is not reported here.	

End point values	Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	421			
Units: ug/mL				
geometric mean (geometric coefficient of variation)				
Pre-infusion on Cycle 1 (n=390)	9999 ($\pm$ 9999)			
15-30 minutes post-infusion on Cycle 1 (n=418)	71.8 ($\pm$ 154.7)			
2 hours post-infusion on Cycle 1 (n=50)	81.4 ($\pm$ 74.3)			
Pre-infusion on Cycle 2 (n=42)	7.93 ($\pm$ 256.8)			
Pre-infusion on Cycle 4 (n=391)	13.7 ($\pm$ 78.0)			
15-30 minutes post-infusion on Cycle 4 (n=361)	76.9 ($\pm$ 46.5)			

2 hours post-infusion on Cycle 4 (n=37)	81.5 ($\pm$ 34.0)			
Pre-infusion on Cycle 5 (n=31)	8.90 ($\pm$ 125.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Duration of Trastuzumab Emtansine Exposure

End point title	Median Duration of Trastuzumab Emtansine Exposure ^[5]
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End point description:

Treatment duration was defined as the time between the first and the last infusion of trastuzumab emtansine. SE population included all randomized participants who received any amount of study treatment.

End point type	Secondary
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End point timeframe:

Up to 12 months

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is reporting data for only the trastuzumab emtansine arm. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Trastuzumab Emtansine			
Subject group type	Reporting group			
Number of subjects analysed	740			
Units: months				
median (full range (min-max))	10 (1 to 12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Positive Anti-drug Antibodies (ADAs) to Trastuzumab Emtansine

End point title	Number of Participants With Positive Anti-drug Antibodies (ADAs) to Trastuzumab Emtansine ^[6]
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End point description:

ADA-positive participants after drug administration were determined for participants exposed to trastuzumab emtansine. For determining post-baseline incidence, participants were considered to be ADA-positive if they were ADA-negative or had missing data at baseline but developed an ADA response following study drug exposure, or if they were ADA-positive at baseline and the titer of 1 or more post-baseline samples was at least 0.60 titer units (t.u.) greater than the baseline titer result. The total number of participants who developed ADAs to trastuzumab emtansine was determined by summing the ADA-positive participants across all timepoints. SE population included all randomized participants who received any amount of study treatment. Number analyzed is the number of participants with data available for analysis. n=number of participants with data available for analysis at the specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline (Day1 of Cycle1) and Post Baseline (Day 1 of Cycle 4 up to 3-4 months after last dose of the drug [up to approximately 13.6 months])

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is reporting data for only the trastuzumab emtansine arm. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Trastuzumab Emtansine			
Subject group type	Reporting group			
Number of subjects analysed	740			
Units: participants				
Baseline (n=410)	17			
Post-baseline (n=401)	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Positive ADAs to Trastuzumab

End point title	Number of Participants With Positive ADAs to Trastuzumab ^[7]
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End point description:

ADA-positive participants after drug administration were determined for participants exposed to trastuzumab. For determining post-baseline incidence, participants were considered to be ADA-positive if they were ADA-negative or had missing data at baseline but developed an ADA response following study drug exposure, or if they were ADA-positive at baseline and the titer of 1 or more post-baseline samples was at least 0.60 t.u. greater than the baseline titer result. The total number of participants who developed ADAs to trastuzumab was determined by summing the ADA-positive participants across all timepoints. SE Population included all randomized participants who received any amount of study treatment. Number analyzed is the number of participants with data available for analysis. n=number of participants with data available for analysis at the specified timepoint.

End point type	Secondary
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End point timeframe:

Baseline (Day1 of Cycle1) and Post Baseline (Day 1 of Cycle 4 up to 3-4 months after last dose of the drug [up to approximately 13.6 months])

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is reporting data for only the trastuzumab arm. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	720			
Units: participants				
Baseline (n=386)	11			
Post-baseline (392)	15			

Statistical analyses

Other pre-specified: IDFS Rate at 7 Years

End point title	IDFS Rate at 7 Years
End point description:	
IDFS=first occurrence of any 1 of following events: ipsilateral invasive breast tumor recurrence (i.e. an invasive breast cancer involving same breast parenchyma as original primary lesion); ipsilateral local-regional invasive breast cancer recurrence (i.e. an invasive breast cancer in axilla, regional lymph nodes, chest wall &/or skin of ipsilateral breast); distant recurrence (i.e. evidence of breast cancer in any anatomic site-other than 2 above-mentioned sites - that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer); contralateral invasive breast cancer; death attributable to any cause including breast cancer, non-breast cancer/unknown cause . 7-year IDFS rate in was estimated using Kaplan Meier (KM) method & percentage of participants who were event-free 7 years after randomization was estimated. ITT population included all participants who were randomized to the study regardless of whether they received any study treatment.	
End point type	Other pre-specified
End point timeframe:	
At Year 7	

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: percentage of participants				
number (confidence interval 95%)	67.11 (63.53 to 70.68)	80.82 (77.86 to 83.78)		

Statistical analyses

Statistical analysis title	Trastuzumab vs Trastuzumab Emtansine
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	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.66

Other pre-specified: IDFS Rate at 8 Years

End point title	IDFS Rate at 8 Years
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End point description:

IDFS=first occurrence of any 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 2 above-mentioned sites - that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer); contralateral invasive breast cancer; death attributable to any cause including breast cancer, non-breast cancer or unknown cause . 8-year IDFS rate in ITT population was estimated using KM method and the percentage of participants who were event-free 8 years after randomization was estimated. ITT population.

End point type	Other pre-specified
End point timeframe:	
At Year 8	

End point values	Trastuzumab	Trastuzumab Emtansine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	743	743		
Units: percentage of participants				
number (confidence interval 95%)	64.57 (60.90 to 68.23)	79.11 (76.03 to 82.19)		

Statistical analyses

Statistical analysis title	Trastuzumab vs Trastuzumab Emtansine
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	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.66

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of informed consent till the end of follow-up (up to approximately 131 months)

Adverse event reporting additional description:

SE Population. 1 participant randomized to trastuzumab arm was re-randomized to T-DM1 arm. Another participant received 13 cycles of trastuzumab & 1 of T-DM1. Both these participants were included in the trastuzumab ITT & T-DM1 safety analysis. 1 participant in T-DM1 received 9 cycles of trastuzumab & included in trastuzumab safety.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.0
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Reporting groups

Reporting group title	Trastuzumab
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Reporting group description: -

Reporting group title	Trastuzumab Emtansine
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Reporting group description: -

Serious adverse events	Trastuzumab	Trastuzumab Emtansine	
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 720 (8.06%)	94 / 740 (12.70%)	
number of deaths (all causes)	126	94	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
PITUITARY TUMOUR BENIGN			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENDOMETRIAL ADENOCARCINOMA			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLON CANCER STAGE I			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (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	1 / 720 (0.14%)	0 / 740 (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	3 / 720 (0.42%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATOMA			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSION			
subjects affected / exposed	1 / 720 (0.14%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 720 (0.14%)	3 / 740 (0.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYSTEMIC INFLAMMATORY RESPONSE SYNDROME			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA LIKE ILLNESS			

subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
HYPERSENSITIVITY			
subjects affected / exposed	0 / 720 (0.00%)	4 / 740 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
UTERINE OBSTRUCTION			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEAVY MENSTRUAL BLEEDING			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OVARIAN CYST			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (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	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UTERINE PROLAPSE			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
PULMONARY FIBROSIS			

subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (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	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPISTAXIS			
subjects affected / exposed	0 / 720 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
subjects affected / exposed	0 / 720 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
SUICIDAL IDEATION			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANXIETY			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

PLATELET COUNT DECREASED			
subjects affected / exposed	0 / 720 (0.00%)	10 / 740 (1.35%)	
occurrences causally related to treatment / all	0 / 0	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EJECTION FRACTION DECREASED			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TROPONIN T INCREASED			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
ANKLE FRACTURE			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TIBIA FRACTURE			
subjects affected / exposed	0 / 720 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
WRIST FRACTURE			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND COMPLICATION			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

SEROMA			
subjects affected / exposed	2 / 720 (0.28%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND DEHISCENCE			
subjects affected / exposed	1 / 720 (0.14%)	3 / 740 (0.41%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR FRACTURE			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ULNA FRACTURE			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIATION PNEUMONITIS			
subjects affected / exposed	0 / 720 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIUS FRACTURE			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
CARDIOGENIC SHOCK			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERICARDITIS			

subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE			
subjects affected / exposed	3 / 720 (0.42%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	0 / 720 (0.00%)	3 / 740 (0.41%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
NEURALGIA			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	0 / 720 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL MOTOR NEUROPATHY			
subjects affected / exposed	0 / 720 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIZZINESS			

subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (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	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ILEAL PERFORATION			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	1 / 720 (0.14%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	2 / 720 (0.28%)	3 / 740 (0.41%)	
occurrences causally related to treatment / all	0 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMPAIRED GASTRIC EMPTYING			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			

subjects affected / exposed	1 / 720 (0.14%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (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	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN			
subjects affected / exposed	1 / 720 (0.14%)	3 / 740 (0.41%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
NODULAR REGENERATIVE HYPERPLASIA			
subjects affected / exposed	0 / 720 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
GALLBLADDER POLYP			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATITIS			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC CYST			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS			

subjects affected / exposed	1 / 720 (0.14%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
TELANGIECTASIA			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PHOTOSENSITIVITY REACTION			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
BLADDER PAIN			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (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			
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACK PAIN			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ENTEROCOLITIS INFECTIOUS			

subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	1 / 720 (0.14%)	3 / 740 (0.41%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTED SEROMA			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABSCESS INTESTINAL			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN INFECTION			
subjects affected / exposed	1 / 720 (0.14%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	2 / 720 (0.28%)	6 / 740 (0.81%)	
occurrences causally related to treatment / all	0 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL BACTERAEMIA			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TONSILLITIS			

subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	0 / 720 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
subjects affected / exposed	0 / 720 (0.00%)	5 / 740 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTITIS			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (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	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS			
subjects affected / exposed	0 / 720 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMPLANT SITE CELLULITIS			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MASTITIS			
subjects affected / exposed	6 / 720 (0.83%)	8 / 740 (1.08%)	
occurrences causally related to treatment / all	0 / 7	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			

subjects affected / exposed	2 / 720 (0.28%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULAR DEVICE INFECTION			
subjects affected / exposed	0 / 720 (0.00%)	1 / 740 (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	0 / 720 (0.00%)	1 / 740 (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	0 / 720 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION			
subjects affected / exposed	2 / 720 (0.28%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIRECTAL ABSCESS			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 720 (0.28%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
HYPERGLYCAEMIA			
subjects affected / exposed	1 / 720 (0.14%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Trastuzumab	Trastuzumab Emtansine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	633 / 720 (87.92%)	719 / 740 (97.16%)	
Vascular disorders			
LYMPHOEDEMA			
subjects affected / exposed	48 / 720 (6.67%)	36 / 740 (4.86%)	
occurrences (all)	51	36	
HYPERTENSION			
subjects affected / exposed	34 / 720 (4.72%)	42 / 740 (5.68%)	
occurrences (all)	38	59	
HOT FLUSH			
subjects affected / exposed	144 / 720 (20.00%)	94 / 740 (12.70%)	
occurrences (all)	152	98	
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	29 / 720 (4.03%)	76 / 740 (10.27%)	
occurrences (all)	32	98	
CHILLS			
subjects affected / exposed	14 / 720 (1.94%)	39 / 740 (5.27%)	
occurrences (all)	16	57	
PAIN			
subjects affected / exposed	92 / 720 (12.78%)	90 / 740 (12.16%)	
occurrences (all)	113	107	
FATIGUE			
subjects affected / exposed	243 / 720 (33.75%)	363 / 740 (49.05%)	
occurrences (all)	276	456	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	86 / 720 (11.94%)	100 / 740 (13.51%)	
occurrences (all)	96	138	
OEDEMA PERIPHERAL			
subjects affected / exposed	52 / 720 (7.22%)	29 / 740 (3.92%)	
occurrences (all)	56	33	
Reproductive system and breast disorders			

BREAST PAIN subjects affected / exposed occurrences (all)	41 / 720 (5.69%) 49	52 / 740 (7.03%) 55	
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all) OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all) EPISTAXIS subjects affected / exposed occurrences (all) DYSпноEA subjects affected / exposed occurrences (all)	86 / 720 (11.94%) 93 33 / 720 (4.58%) 36 25 / 720 (3.47%) 30 52 / 720 (7.22%) 57	100 / 740 (13.51%) 112 37 / 740 (5.00%) 39 158 / 740 (21.35%) 225 62 / 740 (8.38%) 69	
Psychiatric disorders ANXIETY subjects affected / exposed occurrences (all) INSOMNIA subjects affected / exposed occurrences (all) DEPRESSION subjects affected / exposed occurrences (all)	42 / 720 (5.83%) 44 86 / 720 (11.94%) 95 44 / 720 (6.11%) 47	27 / 740 (3.65%) 29 101 / 740 (13.65%) 110 41 / 740 (5.54%) 44	
Investigations PLATELET COUNT DECREASED subjects affected / exposed occurrences (all) NEUTROPHIL COUNT DECREASED subjects affected / exposed occurrences (all) ALANINE AMINOTRANSFERASE INCREASED subjects affected / exposed occurrences (all)	17 / 720 (2.36%) 21 36 / 720 (5.00%) 47 41 / 720 (5.69%) 51	206 / 740 (27.84%) 261 61 / 740 (8.24%) 78 172 / 740 (23.24%) 209	

WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	41 / 720 (5.69%)	61 / 740 (8.24%)	
occurrences (all)	61	82	
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	13 / 720 (1.81%)	61 / 740 (8.24%)	
occurrences (all)	14	68	
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	2 / 720 (0.28%)	49 / 740 (6.62%)	
occurrences (all)	2	74	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	40 / 720 (5.56%)	210 / 740 (28.38%)	
occurrences (all)	44	255	
Injury, poisoning and procedural complications			
RADIATION SKIN INJURY			
subjects affected / exposed	199 / 720 (27.64%)	186 / 740 (25.14%)	
occurrences (all)	207	196	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	57 / 720 (7.92%)	69 / 740 (9.32%)	
occurrences (all)	61	77	
PARAESTHESIA			
subjects affected / exposed	40 / 720 (5.56%)	56 / 740 (7.57%)	
occurrences (all)	43	68	
HEADACHE			
subjects affected / exposed	124 / 720 (17.22%)	209 / 740 (28.24%)	
occurrences (all)	148	289	
DYSGEUSIA			
subjects affected / exposed	11 / 720 (1.53%)	57 / 740 (7.70%)	
occurrences (all)	12	58	
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	50 / 720 (6.94%)	136 / 740 (18.38%)	
occurrences (all)	51	146	
Blood and lymphatic system disorders			

ANAEMIA subjects affected / exposed occurrences (all)	60 / 720 (8.33%) 79	74 / 740 (10.00%) 90	
Eye disorders LACRIMATION INCREASED subjects affected / exposed occurrences (all)	13 / 720 (1.81%) 13	41 / 740 (5.54%) 44	
Gastrointestinal disorders DRY MOUTH subjects affected / exposed occurrences (all) DIARRHOEA subjects affected / exposed occurrences (all) VOMITING subjects affected / exposed occurrences (all) CONSTIPATION subjects affected / exposed occurrences (all) ABDOMINAL PAIN subjects affected / exposed occurrences (all) STOMATITIS subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all)	9 / 720 (1.25%) 9 89 / 720 (12.36%) 116 37 / 720 (5.14%) 45 59 / 720 (8.19%) 66 42 / 720 (5.83%) 49 25 / 720 (3.47%) 28 93 / 720 (12.92%) 111	100 / 740 (13.51%) 109 91 / 740 (12.30%) 117 107 / 740 (14.46%) 140 125 / 740 (16.89%) 151 55 / 740 (7.43%) 66 80 / 740 (10.81%) 96 308 / 740 (41.62%) 441	
Skin and subcutaneous tissue disorders PRURITUS subjects affected / exposed occurrences (all) RASH MACULO-PAPULAR subjects affected / exposed occurrences (all) DERMATITIS ACNEIFORM	42 / 720 (5.83%) 44 26 / 720 (3.61%) 27	52 / 740 (7.03%) 58 43 / 740 (5.81%) 50	

subjects affected / exposed	21 / 720 (2.92%)	39 / 740 (5.27%)	
occurrences (all)	23	44	
DRY SKIN			
subjects affected / exposed	36 / 720 (5.00%)	48 / 740 (6.49%)	
occurrences (all)	40	52	
Musculoskeletal and connective tissue disorders			
MYALGIA			
subjects affected / exposed	80 / 720 (11.11%)	113 / 740 (15.27%)	
occurrences (all)	87	126	
ARTHRALGIA			
subjects affected / exposed	158 / 720 (21.94%)	202 / 740 (27.30%)	
occurrences (all)	175	233	
BONE PAIN			
subjects affected / exposed	35 / 720 (4.86%)	51 / 740 (6.89%)	
occurrences (all)	38	54	
BACK PAIN			
subjects affected / exposed	66 / 720 (9.17%)	53 / 740 (7.16%)	
occurrences (all)	73	57	
MUSCLE SPASMS			
subjects affected / exposed	45 / 720 (6.25%)	33 / 740 (4.46%)	
occurrences (all)	45	36	
PAIN IN EXTREMITY			
subjects affected / exposed	71 / 720 (9.86%)	87 / 740 (11.76%)	
occurrences (all)	82	99	
Infections and infestations			
URINARY TRACT INFECTION			
subjects affected / exposed	37 / 720 (5.14%)	64 / 740 (8.65%)	
occurrences (all)	39	79	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	53 / 720 (7.36%)	59 / 740 (7.97%)	
occurrences (all)	65	70	
Metabolism and nutrition disorders			
HYPOKALAEMIA			
subjects affected / exposed	14 / 720 (1.94%)	48 / 740 (6.49%)	
occurrences (all)	20	61	
DECREASED APPETITE			

subjects affected / exposed	16 / 720 (2.22%)	65 / 740 (8.78%)	
occurrences (all)	19	74	

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 participants 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 participant 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.
09 July 2014	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.
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.
18 June 2021	Study TDM4788g/BO22589 was finalized, so information about median OS was added. The study completion was extended from 10 years post-FPI to 12 years post-FPI. Scheduled follow-up assessments was updated to collect more OS events. The protocol sections covering the determination of sample size and interim analyses were updated to reflect the extension of the study. The details of the planned interim and final analyses of OS was updated accordingly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported