Clinical trial results:
A Randomized, Multicenter, Open-Label, Two-Arm, Phase III Neoadjuvant Study Evaluating Trastuzumab Emtansine Plus Pertuzumab Compared With Chemotherapy Plus Trastuzumab and Pertuzumab for Patients With HER2-Positive Breast Cancer

Summary

EudraCT number	2012-004879-38
Trial protocol	BE ES DE FR IE
Global end of trial date	

Results information

Result version number	v1
This version publication date	19 December 2016
First version publication date	19 December 2016

Trial information

Trial identification

Sponsor protocol code	BO28408

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02131064
WHO universal trial number (UTN)	-
Other trial identifiers	Other identifier: TRIO021

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, Roche Trial Information Hotline, +41 61 6878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, Roche Trial Information Hotline, +41 61 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	03 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 December 2015
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of the trial were to compare the total pathological Complete Response (tpCR) rate (ypT0/is, ypN0) and safety among chemotherapy, Trastuzumab (TCH) + Pertuzumab (P) (Arm A) and Trastuzumab Emtansine (T-DM1) + P (Arm B).

Protection of trial subjects:

This study was conducted in full conformance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 guideline for Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study complied with the
requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), and was conducted under a U.S. Investigational New Drug application, complying with Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	United States: 83
Country: Number of subjects enrolled	Korea, Republic of: 59
Country: Number of subjects enrolled	Russian Federation: 61
Country: Number of subjects enrolled	Ukraine: 5
Country: Number of subjects enrolled	Belgium: 30
Country: Number of subjects enrolled	Spain: 88
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	Taiwan: 42
Country: Number of subjects enrolled	Germany: 24
Worldwide total number of subjects	444
EEA total number of subjects	169

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)	398
From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 574 participants were screened at 68 sites in 10 countries, of which 444 participants were randomized in two arms: TCH + P (Arm A) and T-DM1 + P (Arm B).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TCH + P

Arm description:

Participants received pertuzumab 840 milligrams (mg) (loading dose) and 420 mg (maintenance dose) intravenous (IV) infusion, trastuzumab 8 milligrams per kilogram (mg/kg) (loading dose) and 6 mg/kg (maintenance dose) IV infusion, docetaxel 75 milligrams per square meter (mg/m^2) IV infusion and carboplatin at a dose to achieve an area under the curve (AUC) of 6 milligrams per milliliter* minute (mg/mL*min) IV infusion every 3 weeks (q3w) for 6 cycles in neoadjuvant period. Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab 8 mg/kg (loading dose) and 6 mg/kg (maintenance dose) IV infusion q3w for rest of the cycles (12 cycles) in adjuvant period (up to a total of 18 cycles).

Arm type	Active comparator
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herceptin®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab 8 mg/kg (loading dose); and 6 mg/kg (maintenance dose) IV infusion q3w

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

Dosage and administration details:

Carboplatin IV infusion at a dose to achieve an AUC of 6 mg*min/mL q3w

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

Dosage and administration details:

Docetaxel 75 mg/m^2 IV infusion q3w

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	RO4368451
Other name	Perjeta®
Pharmaceutical forms	Concentrate for solution for infusion

Routes of administration	Intravenous use

Dosage and administration details:

Pertuzumab 840 mg (loading dose); and 420 mg (maintenance dose) IV infusion q3w

Arm title	T-DM1 + P

Arm description:

Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab emtansine 3.6 mg/kg IV infusion q3w for a total of 18 cycles (6 cycles of neoadjuvant period and 12 cycles of adjuvant period).

Arm type	Experimental
Investigational medicinal product name	Trastuzumab Emtansine
Investigational medicinal product code	RO5304020
Other name	Kadcyla®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab Emtansine 3.6 mg/kg IV infusion q3w

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	RO4368451
Other name	Perjeta®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pertuzumab 840 mg (loading dose); and 420 mg (maintenance dose) IV infusion q3w

Number of subjects in period 1	TCH + P	T-DM1 + P
Started	221	223
Completed	0	0
Not completed	221	223
Consent withdrawn by subject	6	14
Death	-	1
Ongoing	214	207
Unspecified	1	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	TCH + P
Reporting group description:	
Participants received pertuzumab 840 milligrams (mg) (loading dose) and 420 mg (maintenance dose) intravenous (IV) infusion, trastuzumab 8 milligrams per kilogram (mg/kg) (loading dose) and 6 mg/kg (maintenance dose) IV infusion, docetaxel 75 milligrams per square meter (mg/m^2) IV infusion and carboplatin at a dose to achieve an area under the curve (AUC) of 6 milligrams per milliliter* minute (mg/mL*min) IV infusion every 3 weeks (q3w) for 6 cycles in neoadjuvant period. Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab 8 mg/kg (loading dose) and 6 mg/kg (maintenance dose) IV infusion q3w for rest of the cycles (12 cycles) in adjuvant period (up to a total of 18 cycles).	
Reporting group title	T-DM1 + P
Reporting group description:	
Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab emtansine 3.6 mg/kg IV infusion q3w for a total of 18 cycles (6 cycles of neoadjuvant period and 12 cycles of adjuvant period).	

Reporting group values	TCH + P	T-DM1 + P	Total
Number of subjects	221	223	444
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	49.3	50.5	
standard deviation	± 11.2	± 10.6	-
Gender categorical Units: Subjects			
Female	221	222	443
Male	0	1	1

End points

End points reporting groups

Reporting group title	TCH + P

Reporting group description:

Participants received pertuzumab 840 milligrams (mg) (loading dose) and 420 mg (maintenance dose) intravenous (IV) infusion, trastuzumab 8 milligrams per kilogram (mg/kg) (loading dose) and 6 mg/kg (maintenance dose) IV infusion, docetaxel 75 milligrams per square meter (mg/m^2) IV infusion and carboplatin at a dose to achieve an area under the curve (AUC) of 6 milligrams per milliliter* minute (mg/mL*min) IV infusion every 3 weeks (q3w) for 6 cycles in neoadjuvant period. Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab 8 mg/kg (loading dose) and 6 mg/kg (maintenance dose) IV infusion q3w for rest of the cycles (12 cycles) in adjuvant period (up to a total of 18 cycles).

Reporting group title	T-DM1 + P

Reporting group description:

Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab emtansine 3.6 mg/kg IV infusion q3w for a total of 18 cycles (6 cycles of neoadjuvant period and 12 cycles of adjuvant period).

Primary: Percentage of Participants With tpCR Assessed Based on Tumor Samples

End point title	Percentage of Participants With tpCR Assessed Based on Tumor Samples

End point description:

tpCR was assessed by local pathology review on samples taken at surgery following completion of neoadjuvant therapy. tpCR was defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes (that is [i.e.], ypT0/is, ypN0 in the American Joint Committee on Cancer [AJCC] staging system, 7th edition). Percentage of participants with tpCR was reported. Intent-to-treat (ITT) population comprised all randomized participants, whether or not they received any study treatment or completed a full course of study treatment. Participants were analyzed according to their randomized treatment.

End point type	Primary

End point timeframe:

Pre-surgery (within 6 weeks after neoadjuvant therapy; up to approximately 6 months)

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	223		
Units: percentage of participants				
number (confidence interval 95%)	55.7 (48.84 to 62.32)	44.4 (37.76 to 51.18)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

95% CI for the difference in tPCR rates between treatment arms was calculated using normal approximation. The Cochran-Mantel-Haenszel Chi-square test was used and stratified by local hormone receptor status and clinical stage at presentation.

Comparison groups	TCH + P v T-DM1 + P
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0155 [1]
Method	Cochran-Mantel-Haenszel Chi-Square
Parameter estimate	Difference in tpCR rate
Point estimate	-11.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.5
upper limit	-2.02

Notes:

[1] - Threshold for significance at 5%

Secondary: Event-free Survival (EFS) Assessed by Investigator Based on Radiological, Clinical and Histological Assessment

End point title	Event-free Survival (EFS) Assessed by Investigator Based on Radiological, Clinical and Histological Assessment

End point description:

EFS is defined as the time from randomization to disease progression or disease recurrence (local, regional, distant, or contralateral, invasive or non-invasive), or death from any cause.

End point type	Secondary

End point timeframe:

From randomization up to disease progression or recurrence or death (up to approximately 45 months)

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: months				
median (full range (min-max))	(to)	(to)		

Notes:

[2] - The data for this endpoint will be reported after final analysis.

[3] - The data for this endpoint will be reported after final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Invasive Disease-free Survival (IDFS)

End point title	Invasive Disease-free Survival (IDFS)

End point description:

IDFS is defined only for participants who undergo surgery. Participants who do not undergo surgery will be excluded from the analysis. IDFS is defined as the time from surgery to the first documented occurrence of an IDFS event, defined as: Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast 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, excluding ipsilateral invasive or local-regional breast cancer, in any anatomic site that has been either histologically confirmed or clinically diagnosed as recurrent invasive breast cancer); Contralateral

invasive breast cancer; and death from any cause.

End point type	Secondary

End point timeframe:

From surgery to the first documented occurrence of IDFC event (up to approximately 45 months)

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: months				
median (full range (min-max))	(to)	(to)		

Notes:

[4] - The data for this endpoint will be reported after final analysis.

[5] - The data for this endpoint will be reported after final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival is defined as the time from randomization to death from any cause.

End point type	Secondary

End point timeframe:

From randomization until death (up to approximately 45 months)

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: months				
median (full range (min-max))	(to)	(to)		

Notes:

[6] - The data for this endpoint will be reported after final analysis.

[7] - The data for this endpoint will be reported after final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Received Breast-Conserving Surgery (BCS)

End point title	Percentage of Participants Who Received Breast-Conserving Surgery (BCS)

End point description:

BCS rate was defined as the percentage of participants who achieve BCS out of the ITT population of participants without inflammatory breast cancer. A subset of ITT population including participants who had non-inflammatory breast cancer at baseline. Participants were analyzed according to their

randomized treatment.

End point type	Secondary

End point timeframe:

6 months

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	218		
Units: percentage of participants				
number (confidence interval 95%)	52.6 (45.65 to 59.45)	41.7 (35.12 to 48.33)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

95% CI for the difference in BCS rate between treatment arms was calculated using normal approximation.

Comparison groups	TCH + P v T-DM1 + P
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in BCS rate
Point estimate	-10.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.21
upper limit	-1.47

Secondary: Percentage of Participants With Selected Adverse Events (AEs)

End point title	Percentage of Participants With Selected Adverse Events (AEs)

End point description:

Selected AEs included hepatotoxicity, pulmonary toxicity, cardiac dysfunction, neutropenia, thrombocytopenia, peripheral neuropathy, hemorrhage, infusion related reaction (IRR)/hypersensitivity, IRR/hypersensitivity symptoms, rash, diarrhoea and mucositis. Safety population comprised all participants who received at least one full or partial dose of any study treatment. Participants were analyzed according to the treatment they actually received. An AE was defined as any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, regardless of causal attribution.

End point type	Secondary

End point timeframe:

Neoadjuvant phase (Baseline up to Cycle 6, each cycle = 21 days)

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	223		
Units: percentage of participants				
number (not applicable)				
Hepatotoxicity	11.9	24.2		
Pulmonary Toxicity	0	0.9		
Cardiac Dysfunction	0.9	0.4		
Neutropenia	45.2	0.9		
Thrombocytopenia	21.9	7.6		
Peripheral Neuropathy	30.1	9.9		
Hemorrhage	14.6	20.2		
IRR/Hypersensitivity	11.9	17.9		
IRR/Hypersensitivity symptoms	5.9	13.9		
Rash	34.7	21.5		
Diarrhoea	73.5	33.2		
Mucositis	40.2	15.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Response for Neuropathy Single Item

End point title	Percentage of Participants by Response for Neuropathy Single Item

End point description:

Participants answered the question "Did you have tingling hands/feet?", from the Modified Quality of Life Questionnaire Breast Cancer 23 (mQLQ-BR23), on a 4-point scale (1 'Not at all', 2 'a little', 3 'quite a bit' 4 'Very much'). Percentage of participants by each response was reported. ITT population. Participants were analyzed according to their randomized treatment. Number of participants analyzed = participants evaluable for this outcome measure. Here 'n' signifies number of participants evaluable for specified categories. Percentage values are based on ITT N.

End point type	Secondary

End point timeframe:

Baseline, Cycle 3, Cycle 5 of neoadjuvant period (each cycle = 21 days); pre-surgery visit (within 6 weeks after neoadjuvant therapy; up to approximately 6 months)

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	205		
Units: percentage of participants				
number (not applicable)				
Not at all: Baseline (n= 194, 205)	76.9	80.7		
A little bit: Baseline (n= 194, 205)	9.5	10.3		

Somewhat: Baseline (n= 194, 205)	0	0		
Quite a bit: Baseline (n= 194, 205)	0.9	0.9		
Very much: Baseline (n= 194, 205)	0.5	0		
Not at all: Cycle 3 (n= 181, 190)	55.2	61.9		
A little bit: Cycle 3 (n= 181, 190)	20.8	20.2		
Somewhat: Cycle 3 (n= 181, 190)	0	0		
Quite a bit: Cycle 3 (n= 181, 190)	3.6	2.7		
Very much: Cycle 3 (n= 181, 190)	2.3	0.4		
Not at all: Cycle 5 (n= 181, 182)	37.1	55.2		
A little bit: Cycle 5 (n= 181, 182)	29.9	22		
Somewhat: Cycle 5 (n= 181, 182)	0	0		
Quite a bit: Cycle 5 (n= 181, 182)	8.1	2.7		
Very much: Cycle 5 (n= 181, 182)	6.8	1.8		
Not at all: Pre-Surgery (n= 172, 176)	24	53.4		
A little bit: Pre-Surgery (n= 172, 176)	28.1	18.8		
Somewhat: Pre-Surgery (n= 172, 176)	0	0		
Quite a bit: Pre-Surgery (n= 172, 176)	15.8	5.4		
Very much: Pre-Surgery (n= 172, 176)	10	1.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Response for Skin Problem Single Items

End point title	Percentage of Participants by Response for Skin Problem Single Items

End point description:

Participants answered the Question 1 "Did itching skin bother you?" and Question 2 "Have you had skin problems?", from the mQLQ-BR23, on a 4-point scale (1 'Not at all', 2 'a little', 3 'quite a bit' 4 'Very much'). Percentage of participants by each response was reported. ITT population. Participants were analyzed according to their randomized treatment. Number of participants analyzed = participants evaluable for this outcome measure. Here 'n' signifies number of participants evaluable for specified categories. Percentage values are based on ITT N.

End point type	Secondary

End point timeframe:

Baseline, Cycle 3, Cycle 5 of neoadjuvant period (each cycle = 21 days); pre-surgery visit (within 6 weeks after neoadjuvant therapy; up to approximately 6 months)

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	205		
Units: percentage of participants				
number (not applicable)				
Question 1: Not at all: Baseline (n= 193, 205)	70.6	72.6		
Question 1: A little bit: Baseline (n= 193, 205)	14.5	16.6		
Question 1: Somewhat: Baseline (n= 193, 205)	0	0		

Question 1: Quite a bit: Baseline (n= 193, 205)	2.3	2.2		
Question 1: Very much: Baseline (n= 193, 205)	0	0.4		
Question 1: Not at all: Cycle 3 (n= 180, 190)	35.3	50.7		
Question 1: A little bit: Cycle 3 (n= 180, 190)	32.1	28.3		
Question 1: Somewhat: Cycle 3 (n= 180, 190)	0	0		
Question 1: Quite a bit: Cycle 3 (n= 180, 190)	11.8	4.5		
Question 1: Very much: Cycle 3 (n= 180, 190)	2.3	1.8		
Question 1: Not at all: Cycle 5 (n= 180, 182)	48.9	48		
Question 1: A little bit: Cycle 5 (n= 180, 182)	22.6	25.6		
Question 1: Somewhat: Cycle 5 (n= 180, 182)	0	0		
Question 1: Quite a bit: Cycle 5 (n= 180, 182)	7.7	6.7		
Question 1: Very much: Cycle 5 (n= 180, 182)	2.3	1.3		
Question 1: Not at all: Pre-Surgery (n= 172, 176)	40.7	49.3		
Question 1:A little bit: Pre-Surgery (n= 172, 176)	27.1	22.4		
Question 1: Somewhat: Pre-Surgery (n= 172, 176)	0	0		
Question 1: Quite a bit: Pre-Surgery (n= 172, 176)	7.7	5.8		
Question 1: Very much: Pre-Surgery (n= 172, 176)	2.3	1.3		
Question 2: Not at all: Baseline (n= 194, 205)	64.3	66.8		
Question 2: A little bit: Baseline (n= 194, 205)	19.9	18.4		
Question 2: Somewhat: Baseline (n= 194, 205)	0	0		
Question 2: Quite a bit: Baseline (n= 194, 205)	3.2	6.3		
Question 2: Very much: Baseline (n= 194, 205)	0.5	0.4		
Question 2: Not at all: Cycle 3 (n= 181, 190)	13.6	25.1		
Question 2: A little bit: Cycle 3 (n= 181, 190)	40.7	40.4		
Question 2: Somewhat: Cycle 3 (n= 181, 190)	0	0		
Question 2: Quite a bit: Cycle 3 (n= 181, 190)	20.4	15.2		
Question 2: Very much: Cycle 3 (n= 181, 190)	7.2	4.5		
Question 2: Not at all: Cycle 5 (n= 181, 182)	21.3	26.9		
Question 2: A little bit: Cycle 5 (n= 181, 182)	35.7	37.2		
Question 2: Somewhat: Cycle 5 (n= 181, 182)	0	0		
Question 2: Quite a bit: Cycle 5 (n= 181, 182)	19.9	13.5		

Question 2: Very much: Cycle 5 (n= 181, 182)	5	4		
Question 2: Not at all: Pre-Surgery (n= 172, 176)	20.8	28.7		
Question 2:A little bit: Pre-Surgery (n= 172, 176)	33.9	37.2		
Question 2: Somewhat: Pre-Surgery (n= 172, 176)	0	0		
Question 2: Quite a bit: Pre-Surgery (n= 172, 176)	16.7	9		
Question 2: Very much: Pre-Surgery (n= 172, 176)	6.3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Response for Hair Loss Single Item

End point title	Percentage of Participants by Response for Hair Loss Single Item

End point description:

Participants answered the Question "Have you lost any hair?", from the mQLQ-BR23, on a 4-point scale (1 'Not at all', 2 'a little', 3 'quite a bit' 4 'Very much'). Percentage of participants by each response was reported. ITT population. Participants were analyzed according to their randomized treatment. Number of participants analyzed = participants evaluable for this outcome measure. Here 'n' signifies number of participants evaluable for specified categories. Percentage values are based on ITT N.

End point type	Secondary

End point timeframe:

Baseline, Cycle 3, Cycle 5 of neoadjuvant period (each cycle = 21 days); pre-surgery visit (within 6 weeks after neoadjuvant therapy; up to approximately 6 months)

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	205		
Units: percentage of participants				
number (not applicable)				
Not at all: Baseline (n= 194, 205)	79.6	87.4		
A little bit: Baseline (n= 194, 205)	7.7	4.5		
Somewhat: Baseline (n= 194, 205)	0	0		
Quite a bit: Baseline (n= 194, 205)	0.5	0		
Very much: Baseline (n= 194, 205)	0	0		
Not at all: Cycle 3 (n= 181, 190)	8.6	67.3		
A little bit: Cycle 3 (n= 181, 190)	11.8	17.5		
Somewhat: Cycle 3 (n= 181, 190)	0	0		
Quite a bit: Cycle 3 (n= 181, 190)	20.8	0.4		
Very much: Cycle 3 (n= 181, 190)	40.7	0		
Not at all: Cycle 5 (n= 181, 182)	20.4	59.2		
A little bit: Cycle 5 (n= 181, 182)	19.9	20.2		
Somewhat: Cycle 5 (n= 181, 182)	0	0		
Quite a bit: Cycle 5 (n= 181, 182)	15.4	1.8		

Very much: Cycle 5 (n= 181, 182)	26.2	0.4		
Not at all: Pre-Surgery (n= 172, 176)	31.7	51.6		
A little bit: Pre-Surgery (n= 172, 176)	12.7	25.1		
Somewhat: Pre-Surgery (n= 172, 176)	0	0		
Quite a bit: Pre-Surgery (n= 172, 176)	11.3	2.2		
Very much: Pre-Surgery (n= 172, 176)	22.2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Clinically Meaningful Deterioration in Global Health Status (GHS)/Quality of Life (QoL) Score

End point title	Percentage of Participants With a Clinically Meaningful Deterioration in Global Health Status (GHS)/Quality of Life (QoL) Score

End point description:

Participants rated their quality of life (global health status) on European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ- C30), with total scores ranging from 0 (worst) to 100 (best); where higher score indicates better quality of life. Clinically meaningful deterioration in GHS/QoL was defined as a decrease in score of 10 points in GHS/QoL. ITT population. Participants were analyzed according to their randomized treatment. Number of participants analyzed = Number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

From Baseline (Day 1 Cycle 1) to Cycle 6 (each cycle = 21 days) in neoadjuvant period

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	205		
Units: percentage of participants				
number (not applicable)	69.9	45.4		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

95% CI for the difference in clinically meaningful deterioration in GHS/QoL score between treatment arms was calculated using normal approximation.

Comparison groups	TCH + P v T-DM1 + P

Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Deterioration
Point estimate	-24.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.98
upper limit	-15.19

Secondary: Time to Clinically Meaningful Deterioration in GHS/QoL Score

End point title	Time to Clinically Meaningful Deterioration in GHS/QoL Score

End point description:

Participants rated their quality of life (global health status) on EORTC QLQ C-30, with total scores ranging from 0 (worst) to 100 (best); where higher score indicates better quality of life. Time to deterioration was defined as the time from baseline to first 10-point (or greater) decrease as measured by GHS/QoL. All valid GHS/QoL questionnaires of the neoadjuvant phase including surgery were used. Participants without deterioration were censored at the time of completing the last GHS/QoL plus 1 day. Median time to deterioration was estimated with Kaplan-Meier method. The 95% confidence interval (CI) for the median was computed using the method of Brookmeyer and Crowley. ITT population. Participants were analyzed according to their randomized treatment. Number of participants analyzed = Number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

From Baseline (Day 1 Cycle 1) to Cycle 6 (each cycle = 21 days) in neoadjuvant period

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	200		
Units: months				
median (confidence interval 95%)	3.02 (2.83 to 3.38)	4.63 (4.11 to 7.98)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified cox proportional hazards regression model was used to estimate Hazard Ratio and CI. Stratification by hormonal receptor status and clinical stage at presentation (stratification factors).

Comparison groups	TCH + P v T-DM1 + P

Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.78

Secondary: Percentage of Participants With a Clinically Meaningful Deterioration in Function Subscales

End point title	Percentage of Participants With a Clinically Meaningful Deterioration in Function Subscales

End point description:

Participants rated their function on EORTC QLQ C-30, with total scores ranging from 0 (worst) to 100 (best); where higher score indicates better functioning. Clinically meaningful deterioration was defined as a decrease in score of 10 points in physical function and HRQoL; decrease of 7 points in cognitive function and decrease of 14 points in role function. ITT population. Participants were analyzed according to their randomized treatment. Number of participants analyzed = Number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

From Baseline (Day 1 Cycle 1) to Cycle 6 (each cycle = 21 days) in neoadjuvant period

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	205		
Units: percentage of participants				
number (not applicable)				
Cognitive Functioning	59.1	42.4		
Physical Functioning	72.5	40		
Role Functioning	76.7	47.8		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

This is the statistical analysis for cognitive functioning. 95% CI for the difference in clinically meaningful deterioration in function subscales between treatment arms was calculated using normal approximation.

Comparison groups	TCH + P v T-DM1 + P

Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Deterioration
Point estimate	-16.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.32
upper limit	-6.94

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

This is the statistical analysis for physical functioning. 95% CI for the difference in clinically meaningful deterioration in function subscales between treatment arms was calculated using normal approximation.

Comparison groups	TCH + P v T-DM1 + P
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Deterioration
Point estimate	-32.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.74
upper limit	-23.34

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

This is the statistical analysis for role functioning. 95% CI for the difference in clinically meaningful deterioration in function subscales between treatment arms was calculated using normal approximation.

Comparison groups	TCH + P v T-DM1 + P
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Deterioration
Point estimate	-28.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.95
upper limit	-19.8

Secondary: Time to Clinically Meaningful Deterioration in Function Subscale

End point title	Time to Clinically Meaningful Deterioration in Function Subscale

End point description:

Participants rated their function on EORTC QLQ C-30, with total scores ranging from 0 (worst) to 100 (best); where higher score indicates better functioning. Time to deterioration was defined as the time from baseline to first 10-point (or greater) decrease as measured by physical function; to first 14-point (or greater) decrease as measured by role function, to first 7-point (or greater) decrease as measured by cognitive function. Median time to deterioration was estimated with Kaplan-Meier method. The 95% CI for the median was computed using the method of Brookmeyer and Crowley. ITT population. Participants were analyzed according to their randomized treatment. Number of participants analyzed = Number of participants evaluable for this outcome measure. Here, 99999 represents data not estimable.

End point type	Secondary

End point timeframe:

From Baseline (Day 1 Cycle 1) to Cycle 6 (each cycle = 21 days) in neoadjuvant period

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	200		
Units: months				
median (confidence interval 95%)				
Physical Function	2.79 (2.79 to 2.96)	4.86 (4.4 to 7.98)		
Role Function	2.79 (2.17 to 2.89)	4.44 (4.04 to 4.53)		
Cognitive Function	3.42 (3.02 to 4.24)	4.44 (4.21 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Clinically Meaningful Increase in Symptom Subscales

End point title	Percentage of Participants With a Clinically Meaningful Increase in Symptom Subscales

End point description:

Participants rated their symptoms on EORTC QLQ C-30 and mQLQ-BR23, with total scores ranging from 0 (worst) to 100 (best); where higher score indicates greater degree of symptoms. Clinically meaningful increase in symptoms was defined as an increase in score (deterioration) of 11 points in nausea and vomiting, pain, dyspnoea; increase of 9 points in insomnia; increase of 14 points in appetite loss; increase of 15 points in diarrhoea, constipation; increase of 10 points in fatigue, systemic therapy side effects, hair loss. ITT population. Participants were analyzed according to their randomized treatment. Number of participants analyzed = Number of participants evaluable for this outcome measure. Here ‘n’ signifies number of participants evaluable for specified categories.

End point type	Secondary

End point timeframe:

From Baseline (Day 1 Cycle 1) to Cycle 6 (each cycle = 21 days) in neoadjuvant period

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	205		
Units: percentage of participants				
number (not applicable)				
Appetitle Loss (n=193, 205)	61.1	47.8		
Any Hair Loss (n=194, 205)	91.2	40.5		
Systemic Therapy Sise-Effects (n=194, 205)	89.7	75.1		
Constipation (n=193, 205)	33.2	32.7		
Diarrhoea (n=193, 205)	79.3	50.7		
Dyspnea (n=193, 205)	56	31.2		
Fatigue (n=193, 205)	87.6	68.8		
Nausea/Vomiting (n=193, 205)	66.3	43.9		
Pain (n=193, 205)	56	36.6		
Insomnia (n=193, 205)	42.5	30.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) of Trastuzumab

End point title	Maximum Observed Serum Concentration (Cmax) of Trastuzumab[8]

End point description:

Only participants who received trastuzumab were to be analyzed for this outcome. Pharmacokinetic (PK) population comprised all participants who received at least one treatment dose of trastuzumab emtansine (in T-DM1 + P arm) or trastuzumab (in TCH + P arm), and had at least one post-treatment serum or plasma sample. Number of participants analyzed = Number of participants in PK Population evaluable for this outcome. Here 'n' signifies number of participants evaluable for specified category.

End point type	Secondary

End point timeframe:

15-30 minutes (min) post-study treatment infusion (infusion duration = 90 min) on Day 1 of Cycle 1 and 6 (each cycle = 21 days) in neoadjuvant period

Notes:

[8] - 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: Trastuzumab was administered in this arm only.

End point values	TCH + P			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: micrograms per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
Cycle 1 (n=162)	167 (± 47.1)			
Cycle 6 (n=155)	148 (± 44.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Trastuzumab Emtansine and Total Trastuzumab

End point title	Cmax of Trastuzumab Emtansine and Total Trastuzumab[9]

End point description:

Only participants who received trastuzumab emtansine were to be analyzed for this outcome. PK population. Number of participants analyzed = Number of participants in the PK Population evaluable for this outcome measure. Here 'n' signifies number of participants evaluable for specified category.

End point type	Secondary

End point timeframe:

15-30 min post-study treatment infusion (infusion duration = 90 min) on Day 1 of Cycle 1 and 6 (each cycle = 21 days) in neoadjuvant period

Notes:

[9] - 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: Trastuzumab emtansine was administered in this arm only.

End point values	T-DM1 + P			
Subject group type	Reporting group			
Number of subjects analysed	207			
Units: mcg/mL				
arithmetic mean (standard deviation)				
Trastuzumab emtansine: Cycle 1 (n=206)	80.3 (± 26.6)			
Trastuzumab emtansine: Cycle 6 (n=179)	72.3 (± 30)			
Total Trastuzumab: Cycle 1 (n=207)	79 (± 25.7)			
Total Trastuzumab: Cycle 6 (n=179)	79.5 (± 30.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Concentration (Cmin) of Trastuzumab Emtansine and Total Trastuzumab

End point title	Minimum Observed Serum Concentration (Cmin) of Trastuzumab Emtansine and Total Trastuzumab[10]

End point description:

Only participants who received trastuzumab emtansine were to be analyzed for this outcome. PK population. Number of participants analyzed = Number of participants in the PK population evaluable for this outcome measure. Here 'n' signifies number of participants evaluable for specified category.

End point type	Secondary

End point timeframe:

Pre-study treatment infusion (0 hours [hr]) (infusion duration = 90 min) on Day 1 of Cycle 6 (cycle length = 21 days) in neoadjuvant period

Notes:

[10] - 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: Trastuzumab emtansine was administered in this arm only.

End point values	T-DM1 + P			
Subject group type	Reporting group			
Number of subjects analysed	191			
Units: mcg/mL				
arithmetic mean (standard deviation)				
Trastuzumab emtansine: (n=190) Total Trastuzumab: (n=191)	3.06 (± 7.68) 12.5 (± 8.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmin of Trastuzumab

End point title	Cmin of Trastuzumab[11]

End point description:

Only participants who received trastuzumab were to be analyzed for this outcome. PK population. Number of participants analyzed = Number of participants in PK Population with evaluable samples at a given timepoint.

End point type	Secondary

End point timeframe:

Pre-study treatment infusion (0 hr) (infusion duration = 90 min) on Day 1 of Cycle 6 (cycle length = 21 days) in neoadjuvant period

Notes:

[11] - 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: Trastuzumab was administered in this arm only.

End point values	TCH + P			
Subject group type	Reporting group			
Number of subjects analysed	165			
Units: mcg/mL				
arithmetic mean (standard deviation)	45.8 (± 17.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma N2'-Deacetyl-N2'-(3-mercapto-1-oxopropyl)-Maytansine (DM1) Concentrations

End point title	Plasma N2'-Deacetyl-N2'-(3-mercapto-1-oxopropyl)-Maytansine (DM1) Concentrations[12]

End point description:

DM1 is the metabolite of trastuzumab emtansine. Only participants who received trastuzumab emtansine were to be analyzed for this outcome. PK population. Number of participants analyzed = Number of participants in the PK population evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-study treatment infusion (0 hr) (infusion duration = 90 min) on Day 1 of Cycle 1 (cycle length = 21

days); 15-30 min post-study treatment infusion on Day 1 of Cycle 1 and 6 in neoadjuvant period

Notes:

[12] - 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: Trastuzumab emtansine was administered in this arm only.

End point values	T-DM1 + P			
Subject group type	Reporting group			
Number of subjects analysed	221			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1: Pre-dose (n=211)	0.0841 (± 0.881)			
Cycle 1: 15-30 min post-dose (n=209)	4.98 (± 2.82)			
Cycle 6: 15-30 min post-dose (n=180)	4.85 (± 2.74)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Levels of Plasma DM1-Containing Catabolites Concentrations (in ng/mL) (Nonreducible Thioether Linker [MCC]-DM1 and Lysine [Lys]-MCC-DM1)

End point title	Serum Levels of Plasma DM1-Containing Catabolites Concentrations (in ng/mL) (Nonreducible Thioether Linker [MCC]-DM1 and Lysine [Lys]-MCC-DM1)

End point description:

End point type	Secondary

End point timeframe:

Pre-study treatment infusion (0 hr) (infusion duration = 90 min) on Day 1 of Cycle 1 (cycle length = 21 days) in neoadjuvant period; 15-30 min post-study treatment infusion on Day 1 of Cycle 1 and 6 in neoadjuvant and adjuvant period

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[13]	0[14]		
Units: mcg/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[13] - The data for this endpoint will be reported after final analysis.

[14] - The data for this endpoint will be reported after final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-Therapeutic Antibodies (ATA) to

TDM-1

End point title	Percentage of Participants With Anti-Therapeutic Antibodies (ATA) to TDM-1[15]

End point description:

Participants were considered post-baseline ATA positive if they had ATAs post-baseline that were either treatment-induced or treatment-enhanced. Participants had treatment-induced ATAs if they had a negative or missing ATA result at baseline, and at least one positive ATA result post-baseline. Participants had treatment-enhanced ATAs if they had a positive ATA result at baseline, and at least one positive ATA result post-baseline that was greater than or equal to (>/=) 0.60 titer units higher than the result at baseline. ITT population, including participants from T-DM1 + P arm only. Number of participants analyzed = participants evaluable for this outcome measure. Here 'n' signifies number of participants evaluable for specified category.

End point type	Secondary

End point timeframe:

Baseline (Pre-TDM-1 [0 hr] infusion [infusion duration = 90 min] on Day 1 of Cycle 1); post-baseline (Pre-TDM-1 infusion [0 hr] on Day 1 of Cycle 6) (each cycle = 21 days) in neoadjuvant

Notes:

[15] - 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: Trastuzumab emtansine was administered in this arm only.

End point values	T-DM1 + P			
Subject group type	Reporting group			
Number of subjects analysed	216			
Units: percentage of participants				
number (not applicable)				
Neoadjuvant Phase: At Baseline (n=216)	5.6			
Neoadjuvant Phase: At Post-Baseline (n=201)	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With ATA to Trastuzumab

End point title	Percentage of Participants With ATA to Trastuzumab

End point description:

End point type	Secondary

End point timeframe:

Baseline (Pre-trastuzumab [0 hr] infusion [infusion duration = 90 min] on Day 1 of Cycle 1); post-baseline (Pre-trastuzumab infusion [0 hr] on Day 1 of Cycle 6) (each cycle = 21 days) in neoadjuvant and adjuvant period

End point values	TCH + P	T-DM1 + P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[16]	0[17]		
Units: percentage of participants				
number (not applicable)				

Notes:

[16] - The data for this endpoint will be reported after final analysis.

[17] - The data for this endpoint will be reported after final analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Baseline (Day 1 Cycle 1) to Cycle 6 (each cycle = 21 days) in neoadjuvant period	
Adverse event reporting additional description:	
Safety population was analyzed.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	T-DM1 + P
Reporting group description:	
Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab emtansine 3.6 mg/kg IV infusion q3w for a total of 18 cycles (6 cycles of neoadjuvant period and 12 cycles of adjuvant period).	
Reporting group title	TCH + P
Reporting group description:	
Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion, trastuzumab 8 mg/kg (loading dose) and 6 mg/kg (maintenance dose) IV infusion, docetaxel 75 mg/m^2 IV infusion and carboplatin at a dose to achieve an AUC of 6 mg/mL*min IV infusion q3w for 6 cycles in neoadjuvant period. Participants received pertuzumab 840 mg (loading dose) and 420 mg (maintenance dose) IV infusion followed by trastuzumab 8 mg/kg (loading dose) and 6 mg/kg (maintenance dose) IV infusion q3w for rest of the cycles (12 cycles) in adjuvant period (up to a total of 18 cycles).	

Serious adverse events	T-DM1 + P	TCH + P	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 223 (4.93%)	63 / 219 (28.77%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			

subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 223 (0.00%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adenomyosis			

subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast haematoma			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (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			
Pleural effusion			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 223 (0.90%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Ejection fraction decreased			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 223 (0.00%)	3 / 219 (1.37%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Procedural intestinal perforation			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous haematoma			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 223 (0.45%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			

subjects affected / exposed	1 / 223 (0.45%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	3 / 223 (1.35%)	26 / 219 (11.87%)	
occurrences causally related to treatment / all	0 / 3	33 / 33	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	3 / 223 (1.35%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 223 (0.00%)	7 / 219 (3.20%)	
occurrences causally related to treatment / all	0 / 0	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 223 (0.45%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 223 (0.00%)	3 / 219 (1.37%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 223 (0.00%)	9 / 219 (4.11%)	
occurrences causally related to treatment / all	0 / 0	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 223 (0.45%)	4 / 219 (1.83%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cellulitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	0 / 223 (0.00%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
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 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			

subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 223 (0.90%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 223 (0.00%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 223 (0.45%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	2 / 223 (0.90%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypermagnesaemia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 223 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 223 (0.00%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	T-DM1 + P	TCH + P	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	198 / 223 (88.79%)	215 / 219 (98.17%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	17 / 223 (7.62%)	30 / 219 (13.70%)	
occurrences (all)	20	32	
Hypertension			
subjects affected / exposed	10 / 223 (4.48%)	14 / 219 (6.39%)	
occurrences (all)	10	16	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	39 / 223 (17.49%)	57 / 219 (26.03%)	
occurrences (all)	59	102	
Chills			

subjects affected / exposed	23 / 223 (10.31%)	9 / 219 (4.11%)	
occurrences (all)	26	9	
Fatigue			
subjects affected / exposed	74 / 223 (33.18%)	93 / 219 (42.47%)	
occurrences (all)	106	133	
Influenza like illness			
subjects affected / exposed	13 / 223 (5.83%)	6 / 219 (2.74%)	
occurrences (all)	15	7	
Mucosal inflammation			
subjects affected / exposed	18 / 223 (8.07%)	30 / 219 (13.70%)	
occurrences (all)	21	36	
Oedema peripheral			
subjects affected / exposed	5 / 223 (2.24%)	27 / 219 (12.33%)	
occurrences (all)	5	34	
Pyrexia			
subjects affected / exposed	30 / 223 (13.45%)	29 / 219 (13.24%)	
occurrences (all)	41	39	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	15 / 223 (6.73%)	9 / 219 (4.11%)	
occurrences (all)	16	9	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	26 / 223 (11.66%)	15 / 219 (6.85%)	
occurrences (all)	31	18	
Epistaxis			
subjects affected / exposed	35 / 223 (15.70%)	24 / 219 (10.96%)	
occurrences (all)	62	29	
Dyspnoea			
subjects affected / exposed	13 / 223 (5.83%)	14 / 219 (6.39%)	
occurrences (all)	15	18	
Oropharyngeal pain			
subjects affected / exposed	7 / 223 (3.14%)	11 / 219 (5.02%)	
occurrences (all)	8	14	
Psychiatric disorders			

Depression			
subjects affected / exposed	8 / 223 (3.59%)	14 / 219 (6.39%)	
occurrences (all)	8	14	
Insomnia			
subjects affected / exposed	32 / 223 (14.35%)	29 / 219 (13.24%)	
occurrences (all)	36	31	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	39 / 223 (17.49%)	18 / 219 (8.22%)	
occurrences (all)	50	31	
Alanine aminotransferase increased			
subjects affected / exposed	52 / 223 (23.32%)	23 / 219 (10.50%)	
occurrences (all)	65	33	
Neutrophil count decreased			
subjects affected / exposed	4 / 223 (1.79%)	22 / 219 (10.05%)	
occurrences (all)	5	40	
Platelet count decreased			
subjects affected / exposed	13 / 223 (5.83%)	27 / 219 (12.33%)	
occurrences (all)	25	38	
Weight decreased			
subjects affected / exposed	13 / 223 (5.83%)	22 / 219 (10.05%)	
occurrences (all)	13	22	
White blood cell count decreased			
subjects affected / exposed	4 / 223 (1.79%)	15 / 219 (6.85%)	
occurrences (all)	4	16	
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	9 / 223 (4.04%)	20 / 219 (9.13%)	
occurrences (all)	9	20	
Nervous system disorders			
Dizziness			
subjects affected / exposed	18 / 223 (8.07%)	25 / 219 (11.42%)	
occurrences (all)	24	27	
Dysgeusia			
subjects affected / exposed	30 / 223 (13.45%)	43 / 219 (19.63%)	
occurrences (all)	38	54	

Headache			
subjects affected / exposed	62 / 223 (27.80%)	35 / 219 (15.98%)	
occurrences (all)	96	43	
Hypoaesthesia			
subjects affected / exposed	5 / 223 (2.24%)	14 / 219 (6.39%)	
occurrences (all)	6	15	
Neuropathy peripheral			
subjects affected / exposed	15 / 223 (6.73%)	27 / 219 (12.33%)	
occurrences (all)	19	31	
Paraesthesia			
subjects affected / exposed	4 / 223 (1.79%)	19 / 219 (8.68%)	
occurrences (all)	5	23	
Peripheral sensory neuropathy			
subjects affected / exposed	16 / 223 (7.17%)	22 / 219 (10.05%)	
occurrences (all)	17	23	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	9 / 223 (4.04%)	58 / 219 (26.48%)	
occurrences (all)	11	85	
Anaemia			
subjects affected / exposed	30 / 223 (13.45%)	78 / 219 (35.62%)	
occurrences (all)	33	97	
Thrombocytopenia			
subjects affected / exposed	16 / 223 (7.17%)	21 / 219 (9.59%)	
occurrences (all)	18	27	
Eye disorders			
Dry eye			
subjects affected / exposed	14 / 223 (6.28%)	11 / 219 (5.02%)	
occurrences (all)	14	13	
Lacrimation increased			
subjects affected / exposed	4 / 223 (1.79%)	17 / 219 (7.76%)	
occurrences (all)	6	19	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	18 / 223 (8.07%)	29 / 219 (13.24%)	
occurrences (all)	24	38	
Abdominal pain upper			

subjects affected / exposed	4 / 223 (1.79%)	18 / 219 (8.22%)	
occurrences (all)	5	25	
Diarrhoea			
subjects affected / exposed	83 / 223 (37.22%)	159 / 219 (72.60%)	
occurrences (all)	157	354	
Constipation			
subjects affected / exposed	25 / 223 (11.21%)	39 / 219 (17.81%)	
occurrences (all)	38	42	
Dry mouth			
subjects affected / exposed	23 / 223 (10.31%)	2 / 219 (0.91%)	
occurrences (all)	29	2	
Dyspepsia			
subjects affected / exposed	22 / 223 (9.87%)	15 / 219 (6.85%)	
occurrences (all)	25	18	
Gastrooesophageal reflux disease			
subjects affected / exposed	7 / 223 (3.14%)	15 / 219 (6.85%)	
occurrences (all)	8	17	
Nausea			
subjects affected / exposed	95 / 223 (42.60%)	132 / 219 (60.27%)	
occurrences (all)	200	235	
Haemorrhoids			
subjects affected / exposed	4 / 223 (1.79%)	14 / 219 (6.39%)	
occurrences (all)	4	16	
Vomiting			
subjects affected / exposed	29 / 223 (13.00%)	68 / 219 (31.05%)	
occurrences (all)	35	86	
Stomatitis			
subjects affected / exposed	21 / 223 (9.42%)	47 / 219 (21.46%)	
occurrences (all)	28	65	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	31 / 223 (13.90%)	142 / 219 (64.84%)	
occurrences (all)	31	145	
Dry skin			
subjects affected / exposed	27 / 223 (12.11%)	23 / 219 (10.50%)	
occurrences (all)	28	28	

Dermatitis acneiform			
subjects affected / exposed	7 / 223 (3.14%)	13 / 219 (5.94%)	
occurrences (all)	8	13	
Nail disorder			
subjects affected / exposed	6 / 223 (2.69%)	14 / 219 (6.39%)	
occurrences (all)	6	15	
Nail discolouration			
subjects affected / exposed	0 / 223 (0.00%)	14 / 219 (6.39%)	
occurrences (all)	0	15	
Pruritus			
subjects affected / exposed	13 / 223 (5.83%)	16 / 219 (7.31%)	
occurrences (all)	15	22	
Rash			
subjects affected / exposed	42 / 223 (18.83%)	54 / 219 (24.66%)	
occurrences (all)	55	70	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 223 (8.52%)	30 / 219 (13.70%)	
occurrences (all)	24	41	
Bone pain			
subjects affected / exposed	4 / 223 (1.79%)	14 / 219 (6.39%)	
occurrences (all)	4	22	
Back pain			
subjects affected / exposed	8 / 223 (3.59%)	17 / 219 (7.76%)	
occurrences (all)	12	18	
Muscle spasms			
subjects affected / exposed	12 / 223 (5.38%)	7 / 219 (3.20%)	
occurrences (all)	13	9	
Myalgia			
subjects affected / exposed	26 / 223 (11.66%)	29 / 219 (13.24%)	
occurrences (all)	35	31	
Musculoskeletal pain			
subjects affected / exposed	7 / 223 (3.14%)	12 / 219 (5.48%)	
occurrences (all)	7	14	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	22 / 223 (9.87%)	15 / 219 (6.85%)	
occurrences (all)	24	18	
Urinary tract infection			
subjects affected / exposed	9 / 223 (4.04%)	14 / 219 (6.39%)	
occurrences (all)	12	16	
Upper respiratory tract infection			
subjects affected / exposed	16 / 223 (7.17%)	9 / 219 (4.11%)	
occurrences (all)	17	9	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	10 / 223 (4.48%)	20 / 219 (9.13%)	
occurrences (all)	14	22	
Decreased appetite			
subjects affected / exposed	26 / 223 (11.66%)	39 / 219 (17.81%)	
occurrences (all)	31	46	
Hypomagnesaemia			
subjects affected / exposed	0 / 223 (0.00%)	11 / 219 (5.02%)	
occurrences (all)	0	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 September 2014	- Surgery was to be performed no later than 6 weeks after the last dose of neoadjuvant treatment instead of no later than 9 weeks. - The inclusion criterion was updated to clarify that participants with multifocal tumors must have had all discrete tumors sampled and centrally confirmed as Human Epidermal Growth Factor Receptor 2 (HER2)-positive. - Exclusion criteria were updated to clarify the eligibility of participants with prior breast in situ cancers (lobular carcinoma in situ, ductal carcinoma in situ) and participants who have received prior local and/or systemic therapies for the treatment and prevention of breast cancer. - Language was added to allow for the use of hematopoietic growth factors for primary prophylaxis as per National Comprehensive Cancer Network (NCCN)/European Society for Medical Oncology (ESMO) guidelines at the investigator's discretion for patients in the TCH + P arm, and to allow for the use hematopoietic growth factors for secondary prophylaxis for participants in either treatment arm. - For participants in the T-DM1 + P arm who receive optional adjuvant chemotherapy, language was included to prohibit treatment with trastuzumab in conjunction with anthracyclines. - Language was added to clarify that any participant diagnosed with drug related interstitial lung disease/pneumonitis must discontinue treatment with trastuzumab
06 July 2015	- To ensure integrity of the benefit-risk assessment in light of evolving data, language regarding the optional adjuvant chemotherapy for participants in the T-DM1 + P arm was updated from stating that adjuvant chemotherapy was allowed, to recommending adjuvant chemotherapy for participants in the T-DM1 + P arm. Clarification was added regarding participants for whom chemotherapy was recommended, including participants who did not achieve tpCR, and had residual tumor less than (>) 1 centimeter (cm) and/or had residual nodal disease. - Language was updated to recommend the use of hematopoietic growth factors for primary prophylaxis for participants in the TCH + P. - An interim evaluation of total pCR rates by the independent Data Monitoring Committee (iDMC) was specified to be performed to further ensure maintenance of a favorable benefit-risk profile. - Language regarding patient-reported outcomes (PROs) was updated to further specify key treatment-related symptoms and the treatment impact for participants with early breast cancer (EBC).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The reported results are interim only.

Notes: