Clinical trial results:
A Randomized, Multicenter, Adaptive Phase II/III Study to Evaluate The Efficacy And Safety of Trastuzumab Emtansine (T-DM1) Versus Taxane (Docetaxel or Paclitaxel) In Patients With Previously Treated Locally Advanced or Metastatic Her2-Positive Gastric Cancer, Including Adenocarcinoma of the Gastroesophageal Junction

Summary

EudraCT number	2012-000660-22
Trial protocol	BE CZ DE HU GB ES FI PL IT
Global end of trial date	30 April 2016

Results information

Result version number	v2 (current)
This version publication date	14 April 2017
First version publication date	16 July 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	BO27952

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01641939
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, 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	30 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 April 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective for this study was to compare the Overall Survival (OS) of subjects treated with the selected trastuzumab emtansine arm to the OS of subjects treated with physician's choice of taxane (docetaxel or paclitaxel) in subjects with human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (AGC), defined as unresectable and locally advanced or metastatic gastric cancer, including adenocarcinoma of the gastroesophageal junction (GEJ).

Protection of trial subjects:

This study was conducted in full conformance with the International Conference of Harmonization (ICH) E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 September 2012
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	Poland: 4
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	China: 11
Country: Number of subjects enrolled	Japan: 82
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 83
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Philippines: 1
Country: Number of subjects enrolled	Singapore: 4
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	Guatemala: 4
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Panama: 1
Country: Number of subjects enrolled	Peru: 1
Country: Number of subjects enrolled	Romania: 9

Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Spain: 35
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	United Kingdom: 34
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	415
EEA total number of subjects	162

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)	246
From 65 to 84 years	169
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 415 subjects were randomized, of these 117 subjects in taxane arm, 228 subjects in 2.4 milligram per kilogram (mg/kg) trastuzumab emtansine arm (across both phase 2 and 3), and 70 subjects (phase-dose selection portion of the study) in 3.6 mg/kg trastuzumab emtansine arm received at least one dose of the treatment.

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	Standard Taxane Therapy

Arm description:

Docetaxel was administered at 75 milligram per meter square (mg/m^2) intravenously (IV) on Day 1 of a 21-day cycle, or paclitaxel was administered at 80 mg/m^2 IV weekly (Days 1, 8, and 15 of a 21 day cycle) as per investigator's choice, until progression of disease, intolerable toxicity, initiation of another anticancer therapy, or subjects and/or physician decision to discontinue.

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

Dosage and administration details:

Docetaxel 75 mg/m^2 IV every 3 weeks.

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

Dosage and administration details:

Paclitaxel 80 mg/m^2 weekly IV.

Arm title	Trastuzumab Emtansine 2.4 mg

Arm description:

Trastuzumab emtansine was administered on Days 1, 8, and 15 of a 21-day cycle at 2.4 milligram per kilogram (mg/kg) IV infusion until progression of disease, intolerable toxicity, initiation of another anticancer therapy, or subjects and/or physician decision to discontinue.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab emtansine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab emtansine 2.4 mg/kg IV once a week.

Arm title	Trastuzumab Emtansine 3.6 mg

Arm description:

Trastuzumab emtansine was administered on Days 1 of a 21-day cycle at 3.6 mg/kg IV infusion until progression of disease, intolerable toxicity, initiation of another anticancer therapy, or subjects and/or physician decision to discontinue.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab emtansine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab emtansine 3.6 mg/kg IV every 3 weeks.

Number of subjects in period 1	Standard Taxane Therapy	Trastuzumab Emtansine 2.4 mg	Trastuzumab Emtansine 3.6 mg
Started	117	228	70
Stage 1	37	75	70
Stage 2	80	153	0
Completed	0	0	0
Not completed	117	228	70
Consent withdrawn by subject	14	11	5
Study terminated by Sponsor	10	28	3
Death	90	187	61
Lost to follow-up	3	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Standard Taxane Therapy
Reporting group description:	
Docetaxel was administered at 75 milligram per meter square (mg/m^2) intravenously (IV) on Day 1 of a 21-day cycle, or paclitaxel was administered at 80 mg/m^2 IV weekly (Days 1, 8, and 15 of a 21 day cycle) as per investigator's choice, until progression of disease, intolerable toxicity, initiation of another anticancer therapy, or subjects and/or physician decision to discontinue.	
Reporting group title	Trastuzumab Emtansine 2.4 mg
Reporting group description:	
Trastuzumab emtansine was administered on Days 1, 8, and 15 of a 21-day cycle at 2.4 milligram per kilogram (mg/kg) IV infusion until progression of disease, intolerable toxicity, initiation of another anticancer therapy, or subjects and/or physician decision to discontinue.	
Reporting group title	Trastuzumab Emtansine 3.6 mg
Reporting group description:	
Trastuzumab emtansine was administered on Days 1 of a 21-day cycle at 3.6 mg/kg IV infusion until progression of disease, intolerable toxicity, initiation of another anticancer therapy, or subjects and/or physician decision to discontinue.	

Reporting group values	Standard Taxane Therapy	Trastuzumab Emtansine 2.4 mg	Trastuzumab Emtansine 3.6 mg
Number of subjects	117	228	70
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 62.1 ± 10.3	 60.5 ± 10.9	 61.2 ± 11.4
Gender categorical Units: Subjects			
Female	22	51	17
Male	95	177	53

Reporting group values	Total		
Number of subjects	415		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 -		
Gender categorical Units: Subjects			
Female	90		
Male	325		

End points

End points reporting groups

Reporting group title	Standard Taxane Therapy

Reporting group description:

Docetaxel was administered at 75 milligram per meter square (mg/m^2) intravenously (IV) on Day 1 of a 21-day cycle, or paclitaxel was administered at 80 mg/m^2 IV weekly (Days 1, 8, and 15 of a 21 day cycle) as per investigator's choice, until progression of disease, intolerable toxicity, initiation of another anticancer therapy, or subjects and/or physician decision to discontinue.

Reporting group title	Trastuzumab Emtansine 2.4 mg

Reporting group description:

Trastuzumab emtansine was administered on Days 1, 8, and 15 of a 21-day cycle at 2.4 milligram per kilogram (mg/kg) IV infusion until progression of disease, intolerable toxicity, initiation of another anticancer therapy, or subjects and/or physician decision to discontinue.

Reporting group title	Trastuzumab Emtansine 3.6 mg

Reporting group description:

Trastuzumab emtansine was administered on Days 1 of a 21-day cycle at 3.6 mg/kg IV infusion until progression of disease, intolerable toxicity, initiation of another anticancer therapy, or subjects and/or physician decision to discontinue.

Primary: Overall Survival (OS) - Phase 3

End point title	Overall Survival (OS) - Phase 3[1]

End point description:

Overall survival was defined as the time between the date of randomisation and date of death due to any cause. Kaplan-Meier estimates were used for analysis. Subjects for whom no death was reported prior to an analysis cutoff (30 June 2015) was censored at the latest date before the cutoff in which they were known to be alive. All data from the standard taxane therapy and trastuzumab emtansine 2.4 mg (selected treatment arm) from phase 2 and phase 3 (Stage 2) are combined into phase 3 data, and thus cumulative data are provided within the results presented for phase 3. The confirmatory analyses are restricted to comparisons between the taxane arm and the selected trastuzumab emtansine arm (2.4 mg). ITT population.

End point type	Primary

End point timeframe:

Date of randomisation until death (up to 2 years 3 months)

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: The data for reporting groups "Standard Taxane Therapy and Trastuzumab Emtansine 2.4 mg" were planned to be reported for the endpoint.

End point values	Standard Taxane Therapy	Trastuzumab Emtansine 2.4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	228		
Units: months				
median (confidence interval 95%)	8.6 (7.1 to 11.2)	7.9 (6.7 to 9.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The unstratified Cox proportional hazards model was used to estimate the hazard ratio. The 95% Confidence Interval (CI) for median was computed using the method of Brookmeyer and Crowley. Reference group: Standard Taxane Therapy.

Comparison groups	Standard Taxane Therapy v Trastuzumab Emtansine 2.4 mg
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8589 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.6

Notes:

[2] - One sided p-value with correction for interim treatment selection due to adaptive seamless phase design.

Primary: Overall Survival (OS) - Phase 2

End point title	Overall Survival (OS) - Phase 2

End point description:

Overall survival was defined as the time between the date of randomisation and date of death due to any cause. Kaplan-Meier estimates were used for analysis. Subjects for whom no death was reported prior to an analysis cutoff (10 August 2013) was censored at the latest date before the cutoff in which they were known to be alive. Analysis population included all subjects that had been enrolled in phase 2 (stage 1) up to a clinical cut-off date of 10 August 2013; subjects grouped according to the therapy they were randomized to receive. Here, N (number of subjects analyzed)=number of evaluable subjects during phase 2 up to 10 August 2013. The value "99999" represents non evaluable (NE) data, the upper limit of the 95% CI could not be calculated due to the large number of censored events.

End point type	Primary

End point timeframe:

Date of randomisation until death (up to 1 year)

End point values	Standard Taxane Therapy	Trastuzumab Emtansine 2.4 mg	Trastuzumab Emtansine 3.6 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	64	58	
Units: months				
median (confidence interval 95%)	28 (24 to 99999)	36.3 (23 to 99999)	23 (18 to 99999)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The unstratified Cox proportional hazards model was used to estimate the hazard ratio. The 95% CI for median was computed using the method of Brookmeyer and Crowley. Reference group: Trastuzumab Emtansine 3.6 mg

Comparison groups	Standard Taxane Therapy v Trastuzumab Emtansine 2.4 mg
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	2.03

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

The unstratified Cox proportional hazards model was used to estimate the hazard ratio. The 95% CI for median was computed using the method of Brookmeyer and Crowley. Reference group: Standard Taxane Therapy.

Comparison groups	Trastuzumab Emtansine 3.6 mg v Trastuzumab Emtansine 2.4 mg
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.96

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The unstratified Cox proportional hazards model was used to estimate the hazard ratio. The 95% CI for median was computed using the method of Brookmeyer and Crowley. Reference group: Standard Taxane Therapy.

Comparison groups	Standard Taxane Therapy v Trastuzumab Emtansine 3.6 mg
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	2.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	4.92

Secondary: Percentage of Subjects with Disease Progression According to Modified Response Evaluation Criteria in Solid Tumors (mRECIST v1.1) - Phase 3

End point title	Percentage of Subjects with Disease Progression According to Modified Response Evaluation Criteria in Solid Tumors (mRECIST v1.1) - Phase 3[3]

End point description:

Progressive disease could base on symptom deterioration or was defined as at least a 20 percent (%) increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since treatment started or the appearance of one or more new lesions and/or the unequivocal progression of existing non-target lesions. Tumor assessment was performed using modified RECIST v1.1. Cumulative data (up to primary analysis cut-off date of 30-June-2015) are provided for both phase 2 and phase 3 within the results of this measure. ITT population.

End point type	Secondary

End point timeframe:

Date of randomisation until disease progression or death, whichever occurred first (assessed at baseline, every 6 weeks up to 2 years 3 months)

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: The data for reporting groups "Standard Taxane Therapy and Trastuzumab Emtansine 2.4 mg" were planned to be reported for the endpoint.

End point values	Standard Taxane Therapy	Trastuzumab Emtansine 2.4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	228		
Units: percentage of subjects				
number (not applicable)	88.9	93		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) According to Modified Response Evaluation Criteria in Solid Tumors (mRECIST v1.1) - Phase 3

End point title	Progression Free Survival (PFS) According to Modified Response Evaluation Criteria in Solid Tumors (mRECIST v1.1) - Phase 3[4]

End point description:

Progression-free survival was defined as the time between the date of randomisation and the first date of documented progression or date of death due to any cause, whichever occurred first. Tumor assessment was performed using modified RECIST v1.1. Progressive disease could base on symptom deterioration or was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since treatment started or the appearance of one or more new lesions and/or the unequivocal progression of existing non-target lesions. Kaplan-Meier estimates were used for analysis. Cumulative data (up to primary analysis cut-off

date of 30-June-2015) are provided for both phase 2 and phase 3 within the results of this measure. The confirmatory analyses are restricted to comparisons between the taxane arm and the selected trastuzumab emtansine arm (2.4 mg). ITT population.

End point type	Secondary

End point timeframe:

Date of randomisation until disease progression or death, whichever occurred first (assessed at baseline, every 6 weeks up to 2 years 3 months)

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: The data for reporting groups "Standard Taxane Therapy and Trastuzumab Emtansine 2.4 mg" were planned to be reported for the endpoint.

End point values	Standard Taxane Therapy	Trastuzumab Emtansine 2.4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	228		
Units: months				
median (confidence interval 95%)	2.89 (2.76 to 4.01)	2.66 (1.61 to 2.79)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The unstratified Cox proportional hazards model was used to estimate the hazard ratio. The 95% CI for median was computed using the method of Brookmeyer and Crowley. Reference group: Standard Taxane Therapy.

Comparison groups	Standard Taxane Therapy v Trastuzumab Emtansine 2.4 mg
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.308
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.43

Secondary: Percentage of Subjects With Objective Response According to mRECIST v1.1 - Phase 3

End point title	Percentage of Subjects With Objective Response According to mRECIST v1.1 - Phase 3[5]

End point description:

Objective response referred to subjects with complete response (CR) or partial response (PR). CR: disappearance of all target lesions, non-target lesions, and normalization of tumor marker level. PR: greater than or equal to (>=) 30% decrease in sum of the longest diameter (LD) of all target lesions

taking as reference the screening sum LD. To be assigned a status of PR or CR, changes in tumor measurements had to be confirmed by repeat assessments that should have been performed no less than 4 weeks after the criteria for response were first met. Longer intervals as determined by the study protocol were also appropriate. Cumulative data (up to primary analysis cut-off date of 30-June-2015) are provided for both phase 2 and phase 3 within the results of this measure. ITT population. Here, N=number of subjects with measurable disease were included in analysis of this outcome measure.

End point type	Secondary

End point timeframe:

Date of randomisation until disease progression or death, whichever occurred first (assessed at baseline, every 6 weeks up to 2 years 3 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: The data for reporting groups "Standard Taxane Therapy and Trastuzumab Emtansine 2.4 mg" were planned to be reported for the endpoint.

End point values	Standard Taxane Therapy	Trastuzumab Emtansine 2.4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	204		
Units: percentage of subjects				
number (confidence interval 95%)	19.6 (12.56 to 28.07)	20.6 (15.26 to 26.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response - Phase 3

End point title	Duration of Objective Response - Phase 3[6]

End point description:

DOR: time from the date when a clinical response [CR or PR] was first documented to the date of first documented progressive disease (PD) or death. CR:disappearance of all target lesions, non-target lesions, normalization of tumor marker level. PR: >= 30% decrease in sum of the LD of all target lesions taking as reference the screening sum LD. PD: could base on symptom deterioration or at least a 20% increase in the sum of diameters of target or non-target lesions and new lesions, taking as reference the smallest sum on study (nadir), including baseline. To be assigned a status of PR or CR, changes in tumor measurements had to be confirmed by repeat assessments that should have been performed no less than 4 weeks after the criteria for response were first met. Cumulative data (up to primary analysis cut-off date of 30-June-2015) are provided for both phase 2 and phase 3 within the results of this measure. ITT population. N=number of subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Date of randomisation until disease progression or death, whichever occurred first (assessed at baseline, every 6 weeks up to 2 years 3 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: The data for reporting groups "Standard Taxane Therapy and Trastuzumab Emtansine 2.4 mg" were planned to be reported for the endpoint.

End point values	Standard Taxane Therapy	Trastuzumab Emtansine 2.4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	204		
Units: months				
median (confidence interval 95%)	3.65 (2.76 to 5.55)	4.27 (3.02 to 6.83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With European Organisation for Research and Treatment of Cancer Quality of Life Core Module 30 (EORTC QLQ-C30) Score - Phase 3

End point title	Percentage of Subjects With European Organisation for Research and Treatment of Cancer Quality of Life Core Module 30 (EORTC QLQ-C30) Score - Phase 3[7]

End point description:

EORTC QLQ-C30: a validated, cancer-specific 30-item patient-reported measure, contains 14 domains to assess the impact of cancer treatment on 5 aspects of subjects functioning (physical,role,cognitive,emotional,social), 9 aspects of disease/treatment-related symptoms (fatigue,nausea and vomiting,pain,dyspnea,insomnia,loss of appetite,constipation,diarrhea) and a global QoL/overall health status scale. Questions used 4 point scale (1 'Not at all' - 4 'Very much'; with exception of QoL/health status scale which uses 7-point scale (1 'very poor' - 7 'Excellent'). Each scale is transformed on a scale of 0-100; higher score=better level of functioning or greater degree of symptoms. Change of >= 10-points has been found to be clinically significant. Cumulative data (up to primary analysis cut-off date of 30-June-2015) are provided for both phase 2 and phase 3 within the results of this measure. ITT population. N=number of subject with baseline at least 1 post-baseline valid

End point type	Secondary

End point timeframe:

Day 1 of each treatment cycle and at the study drug completion visit, and thereafter at survival follow-up (up to 2 years 3 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: The data for reporting groups "Standard Taxane Therapy and Trastuzumab Emtansine 2.4 mg" were planned to be reported for the endpoint.

End point values	Standard Taxane Therapy	Trastuzumab Emtansine 2.4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	189		
Units: percentage of subjects				
number (confidence interval 95%)				
Appetite loss	39.6 (29.57 to 50)	30.2 (23.97 to 37.23)		
Cognitive Functioning	31.9 (22.49 to 42)	28 (21.76 to 34.68)		
Constipation	40.7 (30.48 to 51.47)	25.9 (19.84 to 32.66)		
Diarrhoea	23.1 (14.89 to 32.53)	21.7 (16.23 to 28.15)		
Dyspnea	19.8 (12.16 to 29.19)	21.7 (16.23 to 28.15)		

Emotional Functioning	24.2 (15.98 to 33.56)	29.1 (22.74 to 35.78)		
Fatigue	46.2 (36.17 to 56.92)	40.7 (33.67 to 47.81)		
Nausea/Vomiting	33 (24.04 to 43.08)	28 (21.76 to 34.68)		
Pain	49.5 (38.8 to 60.14)	33.9 (27.36 to 40.84)		
Physical Functioning	17.6 (10.4 to 26.44)	25.9 (19.84 to 32.66)		
Role Functioning	29.7 (20.55 to 39.86)	30.7 (24.2 to 37.75)		
Social Functioning	34.1 (24.45 to 44.16)	37.6 (30.8 to 44.48)		
Insomnia	33 (24.04 to 43.08)	33.3 (26.83 to 40.32)		
Global Health Status/QoL	44 (33.56 to 54.75)	34.4 (27.65 to 41.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Quality of Life Questionnaire Stomach Cancer Module 22 (QLQ-STO22) Score - Phase 3

End point title	Percentage of Subjects With Quality of Life Questionnaire Stomach Cancer Module 22 (QLQ-STO22) Score - Phase 3[8]

End point description:

The Quality of Life Questionnaire Stomach Cancer Module 22 (QLQ-STO22) supplements the EORTC QLQ-C30 to assess symptoms and treatment-related side effects commonly reported in subjects. There are 22 questions which comprise 5 scales (dysphagia, pain, reflux symptom, dietary restrictions, and anxiety) and 4 single items (dry mouth, hair loss, taste, body image). Most questions use 4-point scale (1 'Not at all' to 4 'Very much'; 1 question was a yes or no answer). A linear transformation was used to standardize all scores and single-items to a scale of 0 to 100; higher score=better level of functioning or greater degree of symptoms. Change of >=10 points has been found to be clinically significant. Cumulative data (up to primary analysis cut-off date of 30-June-2015) are provided for both phase 2 and phase 3 within the results of this measure. ITT population. Here, N=number of subjects with baseline and at least one post-baseline valid score.

End point type	Secondary

End point timeframe:

Day 1 of each treatment cycle, at the study drug completion visit, and thereafter at survival follow-up (up to 2 years 3 months)

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: The data for reporting groups "Standard Taxane Therapy and Trastuzumab Emtansine 2.4 mg" were planned to be reported for the endpoint.

End point values	Standard Taxane Therapy	Trastuzumab Emtansine 2.4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	185		
Units: percentage of subjects				
median (confidence interval 95%)				
Overall	88.9 (81.15 to 94.54)	88.1 (82.64 to 92.4)		

Body image	20 (12.31 to 29.33)	29.7 (23.25 to 36.52)		
Dry Mouth	30 (20.79 to 40.35)	21.1 (15.44 to 27.28)		
Dietary Restrictions	41.1 (30.84 to 51.98)	32.4 (25.75 to 39.66)		
Dysphagia	35.6 (25.74 to 45.8)	23.8 (17.84 to 30.31)		
Hair Loss	11.1 (5.46 to 18.85)	22.7 (17.07 to 29.29)		
Pain/discomfort	52.2 (41.43 to 62.45)	45.4 (38.28 to 52.87)		
Specific Emotional Problems	63.3 (53.09 to 73.25)	57.8 (50.71 to 65.05)		
Upper Gastrointestinal Symptoms	46.7 (36.52 to 57.49)	42.7 (35.47 to 50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Advanced Gastric Cancer (AGC) Symptom Progression - Phase 3

End point title	Percentage of Subjects With Advanced Gastric Cancer (AGC) Symptom Progression - Phase 3[9]

End point description:

AGC symptomatic progression: a worsening of >=10-points in any 1 of the abdominal discomfort, loss of appetite, weakness and fatigue, upper abdominal pain, change in bowel movement, and/or weight loss scales of the EORTC QLQ-C30 and QLQ-STO22 (supplements EORTC QLQ-C30 to assess symptoms and commonly reported treatment-related side effects). There are 22 questions comprise 5 scales (dysphagia, pain, reflux symptom, diet restrictions, anxiety), 4 single items (dry mouth, hair loss, taste, body image), which are related to the symptoms of the disease. Most questions used 4-point scale (1 'Not at all' - 4 'Very much'). All scores and single-items transformed to a scale of 0-100; higher score=better level of functioning or greater degree of symptoms. Cumulative data (up to primary analysis cut-off date of 30-June-2015) are provided for both phase 2 and phase 3 within the results of this measure. ITT population. Here, N=number of subjects evaluable for this measure.

End point type	Secondary

End point timeframe:

Day 1 of each treatment cycle, at the study drug completion visit, and thereafter at survival follow-up (up to 2 years 3 months)

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: The data for reporting groups "Standard Taxane Therapy and Trastuzumab Emtansine 2.4 mg" were planned to be reported for the endpoint.

End point values	Standard Taxane Therapy	Trastuzumab Emtansine 2.4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	228		
Units: percentage of subjects				
number (not applicable)	90.6	93		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Advanced Gastric Cancer (AGC) Symptom Progression - Phase 3

End point title	Time to Advanced Gastric Cancer (AGC) Symptom Progression - Phase 3[10]

End point description:

Time to AGC symptom were defined as the time from randomization to the first documentation of an increase in at least one of the pre-specified abdominal discomfort, loss of appetite, weakness and fatigue, upper abdominal pain, change in bowel movement, and weight loss subscales of the QLQ STO22 and EORTC QLQ-C30. Cumulative data (up to primary analysis cut-off date of 30-June-2015) are provided for both phase 2 and phase 3 within the results of this measure. ITT population. Here, N=number of subjects evaluable for this measure.

End point type	Secondary

End point timeframe:

Day 1 of each treatment cycle, at the study drug completion visit, and thereafter at survival follow-up (up to 2 years 3 months)

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: The data for reporting groups "Standard Taxane Therapy and Trastuzumab Emtansine 2.4 mg" were planned to be reported for the endpoint.

End point values	Standard Taxane Therapy	Trastuzumab Emtansine 2.4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	228		
Units: months				
median (confidence interval 95%)	1.61 (1.41 to 2.17)	1.51 (1.41 to 1.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Trastuzumab Emtansine (T-DM1) and Total Trastuzumab - Stage 1

End point title	Maximum Observed Plasma Concentration (Cmax) of Trastuzumab Emtansine (T-DM1) and Total Trastuzumab - Stage 1[11]

End point description:

Maximum observed plasma concentration of Trastuzumab Emtansine (T-DM1) and total trastuzumab were reported. Stage 1 consists of all subjects recruited before the regimen selection decision, which was carried out after 12 weeks of randomization. Subjects who had at least one PK parameter estimated were included for analysis. Here, n=number of subjects evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Day 1 (D1) of Cycle 1 (C1) and C4, C1D2, C1D3, C1D4/C1D5, C1D8, C1D15, C2D1 (up to 12 weeks)

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: The data for reporting groups "Trastuzumab Emtansine 2.4 mg and Trastuzumab

Emtansine 3.6 mg" were planned to be reported for the endpoint.

End point values	Trastuzumab Emtansine 2.4 mg	Trastuzumab Emtansine 3.6 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	37		
Units: microgram per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
T-DM1 Cycle 1 First Dose (n=41, 37)	43 (± 11.8)	58.6 (± 12.9)		
T-DM1 Cycle 4 First Dose (n=25, 10)	52.6 (± 19.4)	61.6 (± 14.5)		
Total trastuzumab Cycle 1 First Dose (n=41, 37)	46.8 (± 12.3)	61.2 (± 14.6)		
Total trastuzumab Cycle 4 First Dose (n=25, 10)	71.2 (± 23.2)	66.3 (± 14.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Trastuzumab Emtansine (T-DM1) and Total Trastuzumab - Stage 2

End point title	Maximum Observed Plasma Concentration (Cmax) of Trastuzumab Emtansine (T-DM1) and Total Trastuzumab - Stage 2[12]

End point description:

Stage 2 consists of all subjects recruited after the regimen selection decision. Subjects who had at least one PK parameter estimated were included for analysis. Here, n=number of subjects evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

C1D1; C4D1

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: The data for reporting group "Trastuzumab Emtansine 2.4 mg" was planned to be reported for the endpoint.

End point values	Trastuzumab Emtansine 2.4 mg			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: mcg/mL				
arithmetic mean (standard deviation)				
T-DM1 Cycle 1 First Dose	34.1 (± 15.2)			
T-DM1 Cycle 4 First Dose	38 (± 13.4)			
Total trastuzumab Cycle 1 First Dose	44.5 (± 15.4)			
Total trastuzumab Cycle 4 First Dose	69.7 (± 21.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time Zero to Extrapolated Infinite Time [AUCinf] - Stage 1

End point title	Area Under the Curve From Time Zero to Extrapolated Infinite Time [AUCinf] - Stage 1[13]

End point description:

AUCinf= Area under the plasma concentration versus time curve (AUC) from time zero (pre-dose) to extrapolated infinite time (0 - inf). It is obtained from AUC (0 - t) plus AUC (t - inf). Stage 1 consists of all subjects recruited before the regimen selection decision. Regimen selection analysis was carried out after 12 weeks of randomisation. Subjects who had at least one PK parameter estimated were included for analysis.

End point type	Secondary

End point timeframe:

D1C1 and D1C4, C1D2, C1D3, C1D4/C1D5, C1D8, C1D15, C2D1 (up to 12 weeks)

Notes:

[13] - 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: The data for reporting groups "Trastuzumab Emtansine 2.4 mg and Trastuzumab Emtansine 3.6 mg" were planned to be reported for the endpoint.

End point values	Trastuzumab Emtansine 2.4 mg	Trastuzumab Emtansine 3.6 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	37		
Units: day*µg/mL				
arithmetic mean (standard deviation)				
T-DM1	179 (± 51)	262 (± 90.3)		
Total trastuzumab	289 (± 129)	403 (± 237)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Decay Half-Life (t1/2) - Stage 1

End point title	Plasma Decay Half-Life (t1/2) - Stage 1[14]

End point description:

Plasma decay half-life is the time measured for the plasma concentration to decrease by one half. Stage 1 consists of all subjects recruited before the regimen selection decision. Regimen selection analysis was carried out after 12 weeks of randomisation. Subjects who had at least one PK parameter estimated were included for analysis.

End point type	Secondary

End point timeframe:

D1C1 and D1C4, C1D2, C1D3, C1D4/C1D5, C1D8, C1D15, C2D1 (up to 12 weeks)

Notes:

[14] - 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: The data for reporting groups "Trastuzumab Emtansine 2.4 mg and Trastuzumab Emtansine 3.6 mg" were planned to be reported for the endpoint.

End point values	Trastuzumab Emtansine 2.4 mg	Trastuzumab Emtansine 3.6 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	37		
Units: days				
arithmetic mean (standard deviation)				
T-DM1	3.48 (± 0.747)	3.33 (± 1.21)		
Total trastuzumab	5.22 (± 1.53)	5.4 (± 2.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution at Steady State (Vss) - Stage 1

End point title	Volume of Distribution at Steady State (Vss) - Stage 1[15]

End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a drug. Steady state volume of distribution (Vss) is the apparent volume of distribution at steady-state. Stage 1 consists of all subjects recruited before the regimen selection decision. Regimen selection analysis was carried out after 12 weeks of randomisation. Subjects who had at least one PK parameter estimated were included for analysis.

End point type	Secondary

End point timeframe:

D1C1 and D1C4, C1D2, C1D3, C1D4/C1D5, C1D8, C1D15, C2D1 (up to 12 weeks)

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: The data for reporting groups "Trastuzumab Emtansine 2.4 mg and Trastuzumab Emtansine 3.6 mg" were planned to be reported for the endpoint.

End point values	Trastuzumab Emtansine 2.4 mg	Trastuzumab Emtansine 3.6 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	37		
Units: millilitre per kilogram (mL/kg)				
arithmetic mean (standard deviation)				
T-DM1	66.2 (± 19.2)	67.7 (± 14)		
Total trastuzumab	65.9 (± 21.9)	72.1 (± 16.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Systemic Clearance (CL) - Stage 1

End point title	Systemic Clearance (CL) - Stage 1[16]

End point description:

CL is a quantitative measure of the rate at which a drug substance is removed from the body. Stage 1 consists of all subjects recruited before the regimen selection decision. Regimen selection analysis was carried out after 12 weeks of randomisation. Subjects who had at least one PK parameter estimated were included for analysis.

End point type	Secondary

End point timeframe:

D1C1 and D1C4, C1D2, C1D3, C1D4/C1D5, C1D8, C1D15, C2D1 (up to 12 weeks)

Notes:

[16] - 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: The data for reporting groups "Trastuzumab Emtansine 2.4 mg and Trastuzumab Emtansine 3.6 mg" were planned to be reported for the endpoint.

End point values	Trastuzumab Emtansine 2.4 mg	Trastuzumab Emtansine 3.6 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	37		
Units: mL/day/kg				
arithmetic mean (standard deviation)				
T-DM1	14.6 (± 4.64)	15.4 (± 5.61)		
Total trastuzumab	10.2 (± 4.87)	11.3 (± 5.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of N2'-Deacetyl-N2'-(3-mercapto-1-oxopropyl)-Maytansine (DM1) - Stage 1

End point title	Maximum Observed Plasma Concentration (Cmax) of N2'-Deacetyl-N2'-(3-mercapto-1-oxopropyl)-Maytansine (DM1) - Stage 1[17]

End point description:

Maximum observed plasma concentration of DM1 were reported. Stage 1 consists of all subjects recruited before the regimen selection decision. Regimen selection analysis was carried out after 12 weeks of randomisation. Subjects who had at least one PK parameter estimated were included for analysis. Here, n=number of subjects evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

C1D1 and C1C4, C1D2, C1D3, C1D4/C1D5, C1D8, C1D15, C2D1 (up to 12 weeks)

Notes:

[17] - 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: The data for reporting groups "Trastuzumab Emtansine 2.4 mg and Trastuzumab Emtansine 3.6 mg" were planned to be reported for the endpoint.

End point values	Trastuzumab Emtansine 2.4 mg	Trastuzumab Emtansine 3.6 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	35		
Units: nanogram per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
DM1 Cycle 1 First Dose (n=40, 35)	2.47 (± 1.05)	4.61 (± 6.26)		
DM1 Cycle 4 First Dose (n=22, 9)	3.41 (± 1.61)	3.86 (± 0.83)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to data cut-off date 30-April-2016 (up to 3 years 8 months)

Adverse event reporting additional description:

Safety Analysis Population included all subjects who received at least one dose of study medication. The safety parameters were analyzed and presented according to the therapy subjects received. Cumulative data (up to primary analysis cut-off date of 30-April-2016) are provided for both phase 2 and phase 3.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Standard Taxane Therapy

Reporting group description:

Docetaxel was administered at 75 milligram per meter square (mg/m^2) intravenously (IV) on Day 1 of a 21-day cycle, or paclitaxel was administered at 80 mg/m^2 IV weekly (Days 1, 8, and 15 of a 21 day cycle).

Reporting group title	Trastuzumab Emtansine 2.4 mg

Reporting group description:

Trastuzumab emtansine was administered on Days 1, 8, and 15 of a 21-day cycle at 2.4 milligram per kilogram (mg/kg) IV infusion until progression of disease, intolerable toxicity, initiation of another anticancer therapy, or subject and/or physician decision to discontinue.

Reporting group title	Trastuzumab Emtansine 3.6 mg

Reporting group description:

Trastuzumab emtansine was administered on Days 1 of a 21-day cycle at 3.6 mg/kg IV infursion until progression of disease, intolerable toxicity, initiation of another anticancer therapy, or subject and/or physician decision to discontinue.

Serious adverse events	Standard Taxane Therapy	Trastuzumab Emtansine 2.4 mg	Trastuzumab Emtansine 3.6 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 111 (27.93%)	65 / 224 (29.02%)	23 / 69 (33.33%)
number of deaths (all causes)	87	185	61
number of deaths resulting from adverse events	4	8	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			

subjects affected / exposed	0 / 111 (0.00%)	0 / 224 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Tumour haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 111 (0.90%)	0 / 224 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	2 / 111 (1.80%)	0 / 224 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 111 (0.00%)	0 / 224 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 111 (0.90%)	2 / 224 (0.89%)	3 / 69 (4.35%)
occurrences causally related to treatment / all	1 / 1	0 / 2	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	2 / 111 (1.80%)	0 / 224 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	1 / 111 (0.90%)	0 / 224 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	1 / 111 (0.90%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 111 (0.90%)	2 / 224 (0.89%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 111 (0.90%)	0 / 224 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 111 (0.90%)	0 / 224 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Aspiration			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 111 (0.00%)	4 / 224 (1.79%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 111 (0.00%)	2 / 224 (0.89%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	1 / 111 (0.90%)	0 / 224 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			

subjects affected / exposed	0 / 111 (0.00%)	0 / 224 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 111 (0.00%)	0 / 224 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Supraventricular tachycardia			
subjects affected / exposed	1 / 111 (0.90%)	0 / 224 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	0 / 111 (0.00%)	2 / 224 (0.89%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			

subjects affected / exposed	0 / 111 (0.00%)	0 / 224 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Syncope			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 111 (2.70%)	8 / 224 (3.57%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	2 / 3	3 / 9	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coagulopathy			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	4 / 111 (3.60%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	3 / 111 (2.70%)	0 / 224 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 111 (0.00%)	3 / 224 (1.34%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 111 (0.90%)	0 / 224 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 111 (0.90%)	2 / 224 (0.89%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	2 / 111 (1.80%)	6 / 224 (2.68%)	4 / 69 (5.80%)
occurrences causally related to treatment / all	1 / 2	0 / 8	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 1
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	0 / 224 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 111 (0.90%)	5 / 224 (2.23%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal ulcer			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	0 / 111 (0.00%)	2 / 224 (0.89%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jejunal perforation			
subjects affected / exposed	1 / 111 (0.90%)	0 / 224 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 111 (0.90%)	0 / 224 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 111 (0.00%)	0 / 224 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	3 / 224 (1.34%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Regurgitation			

subjects affected / exposed	1 / 111 (0.90%)	0 / 224 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	8 / 224 (3.57%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	4 / 10	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Vomiting			
subjects affected / exposed	1 / 111 (0.90%)	1 / 224 (0.45%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			
subjects affected / exposed	0 / 111 (0.00%)	0 / 224 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 111 (0.90%)	0 / 224 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Myalgia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cellulitis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 224 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia infection			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 111 (0.00%)	2 / 224 (0.89%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			

subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 111 (0.00%)	0 / 224 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 224 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	5 / 111 (4.50%)	7 / 224 (3.13%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	2 / 5	1 / 7	0 / 2
deaths causally related to treatment / all	1 / 2	0 / 2	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 111 (0.90%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 111 (0.00%)	2 / 224 (0.89%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 224 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral Discitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 111 (0.00%)	0 / 224 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophagia			
subjects affected / exposed	0 / 111 (0.00%)	0 / 224 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Standard Taxane Therapy	Trastuzumab Emtansine 2.4 mg	Trastuzumab Emtansine 3.6 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	105 / 111 (94.59%)	211 / 224 (94.20%)	62 / 69 (89.86%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 111 (3.60%)	21 / 224 (9.38%)	5 / 69 (7.25%)
occurrences (all)	8	34	8
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 111 (4.50%)	36 / 224 (16.07%)	10 / 69 (14.49%)
occurrences (all)	6	49	15
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 111 (2.70%)	8 / 224 (3.57%)	5 / 69 (7.25%)
occurrences (all)	4	12	6
Blood bilirubin increased			
subjects affected / exposed	3 / 111 (2.70%)	13 / 224 (5.80%)	1 / 69 (1.45%)
occurrences (all)	4	18	2
Weight decereased			
subjects affected / exposed	8 / 111 (7.21%)	13 / 224 (5.80%)	3 / 69 (4.35%)
occurrences (all)	9	13	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 111 (4.50%)	14 / 224 (6.25%)	5 / 69 (7.25%)
occurrences (all)	5	17	6
Headache			
subjects affected / exposed	6 / 111 (5.41%)	24 / 224 (10.71%)	2 / 69 (2.90%)
occurrences (all)	6	31	3
Dysgeusia			
subjects affected / exposed	11 / 111 (9.91%)	18 / 224 (8.04%)	5 / 69 (7.25%)
occurrences (all)	11	18	5
Neuropathy peripheral			
subjects affected / exposed	11 / 111 (9.91%)	22 / 224 (9.82%)	2 / 69 (2.90%)
occurrences (all)	14	24	2
Peripheral sensory neuropathy			
subjects affected / exposed	22 / 111 (19.82%)	21 / 224 (9.38%)	4 / 69 (5.80%)
occurrences (all)	22	23	4
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	35 / 111 (31.53%)	75 / 224 (33.48%)	15 / 69 (21.74%)
occurrences (all)	47	98	17
Leukopenia			
subjects affected / exposed	10 / 111 (9.01%)	2 / 224 (0.89%)	1 / 69 (1.45%)
occurrences (all)	23	7	2
Febrile neutropenia			
subjects affected / exposed	7 / 111 (6.31%)	1 / 224 (0.45%)	0 / 69 (0.00%)
occurrences (all)	7	1	0
Neutropenia			
subjects affected / exposed	55 / 111 (49.55%)	24 / 224 (10.71%)	7 / 69 (10.14%)
occurrences (all)	108	55	9
Thrombocytopenia			
subjects affected / exposed	3 / 111 (2.70%)	60 / 224 (26.79%)	18 / 69 (26.09%)
occurrences (all)	3	110	26
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 111 (8.11%)	39 / 224 (17.41%)	9 / 69 (13.04%)
occurrences (all)	18	49	11
Chills			
subjects affected / exposed	2 / 111 (1.80%)	12 / 224 (5.36%)	4 / 69 (5.80%)
occurrences (all)	2	17	4
Malaise			
subjects affected / exposed	5 / 111 (4.50%)	12 / 224 (5.36%)	1 / 69 (1.45%)
occurrences (all)	8	13	1
Fatigue			
subjects affected / exposed	51 / 111 (45.95%)	68 / 224 (30.36%)	24 / 69 (34.78%)
occurrences (all)	71	87	37
Oedema peripheral			
subjects affected / exposed	16 / 111 (14.41%)	14 / 224 (6.25%)	5 / 69 (7.25%)
occurrences (all)	19	18	5
Mucosal inflammation			
subjects affected / exposed	7 / 111 (6.31%)	8 / 224 (3.57%)	1 / 69 (1.45%)
occurrences (all)	8	8	1
Pain			

subjects affected / exposed	11 / 111 (9.91%)	6 / 224 (2.68%)	3 / 69 (4.35%)
occurrences (all)	14	6	3
Pyrexia			
subjects affected / exposed	17 / 111 (15.32%)	44 / 224 (19.64%)	11 / 69 (15.94%)
occurrences (all)	19	61	14
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 111 (3.60%)	10 / 224 (4.46%)	6 / 69 (8.70%)
occurrences (all)	4	10	6
Abdominal pain			
subjects affected / exposed	12 / 111 (10.81%)	42 / 224 (18.75%)	10 / 69 (14.49%)
occurrences (all)	12	46	13
Abdominal pain upper			
subjects affected / exposed	8 / 111 (7.21%)	19 / 224 (8.48%)	6 / 69 (8.70%)
occurrences (all)	10	23	6
Constipation			
subjects affected / exposed	22 / 111 (19.82%)	47 / 224 (20.98%)	10 / 69 (14.49%)
occurrences (all)	25	59	11
Diarrhoea			
subjects affected / exposed	27 / 111 (24.32%)	33 / 224 (14.73%)	10 / 69 (14.49%)
occurrences (all)	42	47	11
Dry mouth			
subjects affected / exposed	2 / 111 (1.80%)	20 / 224 (8.93%)	4 / 69 (5.80%)
occurrences (all)	3	20	4
Dyspepsia			
subjects affected / exposed	11 / 111 (9.91%)	17 / 224 (7.59%)	6 / 69 (8.70%)
occurrences (all)	11	18	6
Dysphagia			
subjects affected / exposed	4 / 111 (3.60%)	9 / 224 (4.02%)	4 / 69 (5.80%)
occurrences (all)	4	9	4
Nausea			
subjects affected / exposed	30 / 111 (27.03%)	57 / 224 (25.45%)	15 / 69 (21.74%)
occurrences (all)	42	73	19
Stomatitis			
subjects affected / exposed	21 / 111 (18.92%)	14 / 224 (6.25%)	3 / 69 (4.35%)
occurrences (all)	23	16	5

Vomiting			
subjects affected / exposed	15 / 111 (13.51%)	41 / 224 (18.30%)	17 / 69 (24.64%)
occurrences (all)	24	59	24
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 111 (10.81%)	13 / 224 (5.80%)	7 / 69 (10.14%)
occurrences (all)	16	13	9
Epistaxis			
subjects affected / exposed	6 / 111 (5.41%)	26 / 224 (11.61%)	7 / 69 (10.14%)
occurrences (all)	6	37	10
Dyspnoea			
subjects affected / exposed	9 / 111 (8.11%)	21 / 224 (9.38%)	10 / 69 (14.49%)
occurrences (all)	9	23	12
Hiccups			
subjects affected / exposed	8 / 111 (7.21%)	5 / 224 (2.23%)	6 / 69 (8.70%)
occurrences (all)	10	5	9
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	57 / 111 (51.35%)	7 / 224 (3.13%)	1 / 69 (1.45%)
occurrences (all)	60	7	1
Nail disorder			
subjects affected / exposed	7 / 111 (6.31%)	4 / 224 (1.79%)	0 / 69 (0.00%)
occurrences (all)	7	4	0
Palmar−plantar erythrodysaesthesia syndrome			
subjects affected / exposed	8 / 111 (7.21%)	8 / 224 (3.57%)	2 / 69 (2.90%)
occurrences (all)	10	8	2
Rash			
subjects affected / exposed	12 / 111 (10.81%)	15 / 224 (6.70%)	3 / 69 (4.35%)
occurrences (all)	16	16	3
Pruritus			
subjects affected / exposed	11 / 111 (9.91%)	7 / 224 (3.13%)	4 / 69 (5.80%)
occurrences (all)	13	7	4
Psychiatric disorders			
Insominia			
subjects affected / exposed	10 / 111 (9.01%)	18 / 224 (8.04%)	5 / 69 (7.25%)
occurrences (all)	14	21	5

Depression			
subjects affected / exposed	0 / 111 (0.00%)	5 / 224 (2.23%)	4 / 69 (5.80%)
occurrences (all)	0	5	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 111 (11.71%)	13 / 224 (5.80%)	6 / 69 (8.70%)
occurrences (all)	16	17	6
Back pain			
subjects affected / exposed	6 / 111 (5.41%)	13 / 224 (5.80%)	6 / 69 (8.70%)
occurrences (all)	7	13	6
Myalgia			
subjects affected / exposed	18 / 111 (16.22%)	13 / 224 (5.80%)	6 / 69 (8.70%)
occurrences (all)	21	16	6
Metabolism and nutrition disorders			
Deceased appetite			
subjects affected / exposed	32 / 111 (28.83%)	57 / 224 (25.45%)	22 / 69 (31.88%)
occurrences (all)	37	60	26
Hypoalbuminaemia			
subjects affected / exposed	5 / 111 (4.50%)	13 / 224 (5.80%)	3 / 69 (4.35%)
occurrences (all)	5	14	3
Hypokalaemia			
subjects affected / exposed	1 / 111 (0.90%)	22 / 224 (9.82%)	3 / 69 (4.35%)
occurrences (all)	1	29	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2012	The distinctions between "Stage 1" and "Stage 2" were clarified; methods for study conduct (taxane selection, concomitant therapies, cycle length, PK and pharmacodynamic sampling, and dosing instructions) were clarified; the dose modification guidance was aligned with the most current, harmonized standards across the trastuzumab emtansine clinical program; the description of the futility analysis was updated; the eligibility criteria were revised.
13 January 2014	The IDMC regimen selection recommendation from 14 October 2013, to continue with the 2.4mg/kg qw regimen was added; important safety language updates for severe bleeding events, severe hepatotoxicity, and risk of left ventricular ejection fraction (LVEF), as well as dose modification guideline updates were included; the allowed use of HER2 testing from other studies for eligibility was been clarified.
19 June 2014	Option to open an extension cohort to enroll in China after the last patient in (LPI) had been enrolled into the main study (this option has not been implemented). The study exclusion criteria were also modified to disallow prior enrollment in Study BO25114 (NCT01774786 and EudraCT 2012-003554-83).
21 April 2015	This version was released to clearly spell out the study end rules for the main study, and the China extension cohort in the event this was initiated.

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 study was terminated by the Sponsor as the primary analysis results did not meet the primary endpoint.

Notes: