Clinical trial results:
A Randomized, 3 Arm, Multicenter, Phase III Study to Evaluate the Efficacy and the Safety of T-DM1 Combined With Pertuzumab or T-DM1 Combined With Pertuzumab-Placebo (Blinded for Pertuzumab), Versus the Combination of Trastuzumab Plus Taxane, as First Line Treatment in HER2 Positive Progressive or Recurrent Locally Advanced or Metastatic Breast Cancer (MBC)

Summary

EudraCT number	2009-017905-13
Trial protocol	AT ES DE FR SE DK HU CZ GB IT BE PT GR
Global end of trial date	16 September 2016

Results information

Result version number	v2 (current)
This version publication date	30 August 2017
First version publication date	07 January 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	BO22589

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01120184
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, CH, Basel, Switzerland, Switzerland, 4070
Public contact	Medical Communications, Hoffmann-La Roche, +41 8008218590, genentech@druginfo.com
Scientific contact	Medical Communications, Hoffmann-La Roche, +41 8008218590, genentech@druginfo.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	15 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This randomized, three-arm, multicenter, Phase III study was designed to evaluate the efficacy and safety of trastuzumab emtansine with and without pertuzumab, versus the combination of trastuzumab with taxane therapy, among subjects with human epidermal growth factor receptor 2 (HER2)-positive locally advanced breast cancer (LABC) or metastatic breast cancer (MBC) who had not received prior chemotherapy for their metastatic disease.

Protection of trial subjects:

All investigators were trained according to applicable Sponsor Standard Operating Procedures (SOPs). Roche and the investigators strictly adhered to the stated provisions in these guidelines. This was documented by the investigator's signature on the protocol agreeing to carry out all of its terms in accordance with the applicable regulations and law and to follow International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 June 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	67 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 41
Country: Number of subjects enrolled	Korea, Republic of: 79
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Bahamas: 6
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Colombia: 5
Country: Number of subjects enrolled	Panama: 5
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United States: 131

Country: Number of subjects enrolled	Brazil: 88
Country: Number of subjects enrolled	Japan: 82
Country: Number of subjects enrolled	United Kingdom: 74
Country: Number of subjects enrolled	France: 72
Country: Number of subjects enrolled	Italy: 53
Country: Number of subjects enrolled	Russian Federation: 50
Country: Number of subjects enrolled	Spain: 43
Country: Number of subjects enrolled	Thailand: 39
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Bosnia and Herzegovina: 25
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Philippines: 23
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 21
Country: Number of subjects enrolled	Peru: 20
Country: Number of subjects enrolled	Czech Republic: 19
Country: Number of subjects enrolled	Hungary: 19
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Taiwan: 17
Country: Number of subjects enrolled	Mexico: 16
Country: Number of subjects enrolled	Guatemala: 12
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Malaysia: 10
Country: Number of subjects enrolled	New Zealand: 8
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Argentina: 6
Worldwide total number of subjects	1095
EEA total number of subjects	405

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)	912
From 65 to 84 years	179
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1629 subjects were screened, of whom 1095 were randomized. There were 534 subjects who failed screening, most often due to non-centrally confirmed HER2 status or abnormal laboratory results.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

The study was considered open-label with respect to trastuzumab and trastuzumab emtansine treatment; however, subjects and investigators were blinded with respect to pertuzumab or placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Trastuzumab + Taxane

Arm description:

Subjects received trastuzumab plus either docetaxel or paclitaxel. The regimen was chosen at the investigator's discretion. Option 1: trastuzumab 8 mg/kg via IV infusion on Day 1 of Cycle 1, then 6 mg/kg IV on Day 1 of each subsequent 3-week cycle; plus a minimum of 6 cycles with docetaxel 75 or 100 mg/m^2 IV on Day 1 of each 3-week cycle. Option 2: trastuzumab 4 mg/kg IV on Day 1 of Cycle 1, then 2 mg/kg IV weekly beginning on Day 8 of Cycle 1; plus a minimum of 18 weeks with paclitaxel 80 mg/m^2 IV weekly. Treatment continued until disease progression, unacceptable toxicity, or study termination. If trastuzumab or docetaxel were discontinued for toxicity, the other agent could be continued as monotherapy.

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

Dosage and administration details:

Trastuzumab was administered via IV infusion and dosed depending upon the taxane selected. Subjects received either 8 mg/kg on Day 1 of Cycle 1 followed by 6 mg/kg on Day 1 of each subsequent 3-week cycle, or 4 mg/kg on Day 1 of Cycle 1 followed by 2 mg/kg weekly beginning on Day 8 of Cycle 1.

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

Dosage and administration details:

Docetaxel was administered via IV infusion as 75 or 100 mg/m^2 on Day 1 of each 3-week cycle.

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

Dosage and administration details:

Paclitaxel was administered via IV infusion as 80 mg/m^2 weekly.

Arm title	Trastuzumab Emtansine + Placebo

Arm description:

Subjects received trastuzumab emtansine plus pertuzumab-placebo. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the placebo IV infusion, on Day 1 of each 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

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

Dosage and administration details:

Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion on Day 1 of each 3-week cycle.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received the placebo equivalent to pertuzumab via IV infusion on Day 1 of each 3-week cycle.

Arm title	Trastuzumab Emtansine + Pertuzumab

Arm description:

Subjects received trastuzumab emtansine plus pertuzumab. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the pertuzumab IV infusion, on Day 1 of each 3-week cycle. Pertuzumab was given as 840 mg IV on Day 1 of Cycle 1, then 420 mg IV on Day 1 of each subsequent 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

Arm type	Experimental
Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pertuzumab was administered via IV infusion as 840 mg on Day 1 of Cycle 1, followed by 420 mg on Day 1 of each subsequent 3-week cycle.

Investigational medicinal product name	Trastuzumab emtansine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion on Day 1 of each 3-week cycle.

Number of subjects in period 1	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab
Started	365	367	363
Treated	355	365	360
Completed	0	0	0
Not completed	365	367	363
Physician decision	9	1	3
Adverse event, non-fatal	-	1	-
Death	170	176	169
Sponsor Decision to Terminate Study	133	144	143
Subject/ Guardian Decision to Withdraw	32	29	25
Lost to follow-up	13	13	11
Reason not Specified	8	3	12

Baseline characteristics

Reporting groups	
Reporting group title	Trastuzumab + Taxane

Reporting group description:

Subjects received trastuzumab plus either docetaxel or paclitaxel. The regimen was chosen at the investigator's discretion. Option 1: trastuzumab 8 mg/kg via IV infusion on Day 1 of Cycle 1, then 6 mg/kg IV on Day 1 of each subsequent 3-week cycle; plus a minimum of 6 cycles with docetaxel 75 or 100 mg/m^2 IV on Day 1 of each 3-week cycle. Option 2: trastuzumab 4 mg/kg IV on Day 1 of Cycle 1, then 2 mg/kg IV weekly beginning on Day 8 of Cycle 1; plus a minimum of 18 weeks with paclitaxel 80 mg/m^2 IV weekly. Treatment continued until disease progression, unacceptable toxicity, or study termination. If trastuzumab or docetaxel were discontinued for toxicity, the other agent could be continued as monotherapy.

Reporting group title	Trastuzumab Emtansine + Placebo

Reporting group description:

Subjects received trastuzumab emtansine plus pertuzumab-placebo. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the placebo IV infusion, on Day 1 of each 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

Reporting group title	Trastuzumab Emtansine + Pertuzumab

Reporting group description:

Subjects received trastuzumab emtansine plus pertuzumab. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the pertuzumab IV infusion, on Day 1 of each 3-week cycle. Pertuzumab was given as 840 mg IV on Day 1 of Cycle 1, then 420 mg IV on Day 1 of each subsequent 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

Reporting group values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab
Number of subjects	365	367	363
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	303	306	303
From 65-84 years	59	61	59
85 years and over	3	0	1
Age Continuous Units: years			
arithmetic mean	54.2	52.6	52.2
standard deviation	± 11.3	± 11.4	± 12
Gender, Male/Female Units: Subjects			
Female	362	365	361
Male	3	2	2

Reporting group values	Total		

Number of subjects	1095		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	912		
From 65-84 years	179		
85 years and over	4		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: Subjects			
Female	1088		
Male	7		

End points

End points reporting groups

Reporting group title	Trastuzumab + Taxane

Reporting group description:

Subjects received trastuzumab plus either docetaxel or paclitaxel. The regimen was chosen at the investigator's discretion. Option 1: trastuzumab 8 mg/kg via IV infusion on Day 1 of Cycle 1, then 6 mg/kg IV on Day 1 of each subsequent 3-week cycle; plus a minimum of 6 cycles with docetaxel 75 or 100 mg/m^2 IV on Day 1 of each 3-week cycle. Option 2: trastuzumab 4 mg/kg IV on Day 1 of Cycle 1, then 2 mg/kg IV weekly beginning on Day 8 of Cycle 1; plus a minimum of 18 weeks with paclitaxel 80 mg/m^2 IV weekly. Treatment continued until disease progression, unacceptable toxicity, or study termination. If trastuzumab or docetaxel were discontinued for toxicity, the other agent could be continued as monotherapy.

Reporting group title	Trastuzumab Emtansine + Placebo

Reporting group description:

Subjects received trastuzumab emtansine plus pertuzumab-placebo. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the placebo IV infusion, on Day 1 of each 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

Reporting group title	Trastuzumab Emtansine + Pertuzumab

Reporting group description:

Subjects received trastuzumab emtansine plus pertuzumab. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the pertuzumab IV infusion, on Day 1 of each 3-week cycle. Pertuzumab was given as 840 mg IV on Day 1 of Cycle 1, then 420 mg IV on Day 1 of each subsequent 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

Subject analysis set title	Trastuzumab + Taxane
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received trastuzumab plus either docetaxel or paclitaxel. The regimen was chosen at the investigator's discretion. Option 1: trastuzumab 8 mg/kg via IV infusion on Day 1 of Cycle 1, then 6 mg/kg IV on Day 1 of each subsequent 3-week cycle; plus a minimum of 6 cycles with docetaxel 75 or 100 mg/m^2 IV on Day 1 of each 3-week cycle. Option 2: trastuzumab 4 mg/kg IV on Day 1 of Cycle 1, then 2 mg/kg IV weekly beginning on Day 8 of Cycle 1; plus a minimum of 18 weeks with paclitaxel 80 mg/m^2 IV weekly. Treatment continued until disease progression, unacceptable toxicity, or study termination. If trastuzumab or docetaxel were discontinued for toxicity, the other agent could be continued as monotherapy.

Subject analysis set title	Trastuzumab Emtansine + Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received trastuzumab emtansine plus pertuzumab-placebo. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the placebo IV infusion, on Day 1 of each 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

Subject analysis set title	Trastuzumab Emtansine + Pertuzumab
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received trastuzumab emtansine plus pertuzumab. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the pertuzumab IV infusion, on Day 1 of each 3-week cycle. Pertuzumab was given as 840 mg IV on Day 1 of Cycle 1, then 420 mg IV on Day 1 of each subsequent 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

Primary: Percentage of Subjects with Death or Disease Progression According to Independent Review Facility (IRF) Assessment

End point title	Percentage of Subjects with Death or Disease Progression According to Independent Review Facility (IRF) Assessment[1]

End point description:

Tumor assessments were performed according to Response Evaluation Criteria in Solid Tumors (RECIST)

version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. Disease progression was defined as a greater than or equal to (≥) 20 percent (%) and 5-millimeter (mm) increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). The percentage of subjects with death or disease progression was calculated as [number of subjects with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population (all subjects randomized in the study).

End point type	Primary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics only

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: percentage of subjects				
number (not applicable)	63.3	64.3	59.8	

Statistical analyses

No statistical analyses for this end point

Primary: Progression-Free Survival (PFS) According to IRF Assessment

End point title	Progression-Free Survival (PFS) According to IRF Assessment

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. PFS was defined as the time from randomization to first documented disease progression or death from any cause. Disease progression was defined as a ≥20% and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). Median duration of PFS was estimated using Kaplan-Meier analysis, and corresponding confidence intervals (CIs) were computed using the Brookmeyer-Crowley method. Analysis was performed on ITT population (all subjects randomized in the study).

End point type	Primary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: months				
median (confidence interval 95%)	13.7 (12.4 to 14.9)	14.1 (10.9 to 16.8)	15.2 (12.5 to 18.8)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Placebo versus Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3125 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.73
upper limit	1.13

Notes:

[2] - Test and p-value apply for superiority test. Two-sided significance level of 2.5% was used to adjust for independent comparison between each of the trastuzumab emtansine-containing arms and the trastuzumab + taxane arm.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Pertuzumab versus Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Pertuzumab
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1407 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.69
upper limit	1.08

Notes:

[3] - Test and p-value apply for superiority test. Two-sided significance level of 2.5% was used to adjust for independent comparison between each of the trastuzumab emtansine-containing arms and the trastuzumab + taxane arm.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Pertuzumab versus Trastuzumab Emtansine + Placebo. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab Emtansine + Pertuzumab
Number of subjects included in analysis	730
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3075 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.73
upper limit	1.13

Notes:

[4] - Test and p-value apply for superiority test. Primary endpoint did not meet superiority of PFS for trastuzumab emtansine + pertuzumab versus trastuzumab + taxane (two-sided significance level 2.5%); thus, tests and p-value are considered descriptive.

Secondary: Percentage of Subjects Who Died Prior to Clinical Cutoff

End point title	Percentage of Subjects Who Died Prior to Clinical Cutoff

End point description:

The percentage of subjects who died prior to clinical cutoff was calculated as [number of subjects with event divided by the number analyzed multiplied by 100]. Analysis was performed on ITT population (all subjects randomized in the study).

End point type	Secondary

End point timeframe:

Up to 70 months from randomization until clinical cutoff of 15-May-2016 (every 3 months until death, loss to follow-up, withdrawal, or study termination)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: percentage of subjects				
number (not applicable)	46.3	47.7	46.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) at Clinical Cutoff

End point title	Overall Survival (OS) at Clinical Cutoff

End point description:

OS was defined as the time from randomization to death from any cause. Median duration of OS was estimated using Kaplan-Meier analysis, and corresponding CIs were computed using the Brookmeyer-Crowley method. Here, "9999" represents that the value is not applicable because Median duration of OS was not reached due to insufficient follow-up. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Up to 70 months from randomization until clinical cutoff of 15-May-2016 (every 3 months until death, loss to follow-up, withdrawal, or study termination)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: months				
median (confidence interval 95%)	50.86 (44.75 to 60.75)	53.68 (48.36 to 64.36)	51.78 (47.87 to 9999)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Pertuzumab versus Trastuzmab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Pertuzumab
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.67
upper limit	1.11

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Placebo versus Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.73
upper limit	1.2

Secondary: Percentage of Subjects with Death or Disease Progression According to Investigator Assessment

End point title	Percentage of Subjects with Death or Disease Progression According to Investigator Assessment

End point description:

Tumor assessments were performed by the investigator according to RECIST version 1.1. Disease progression was defined as a ≥20% and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). The percentage of subjects with death or disease progression was calculated as [number of subjects with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population (all subjects randomized in the study).

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: percentage of subjects				
number (not applicable)	72.1	70.3	67.5	

Statistical analyses

No statistical analyses for this end point

Secondary: PFS According to Investigator Assessment

End point title	PFS According to Investigator Assessment

End point description:

Tumor assessments were performed by the investigator according to RECIST version 1.1. PFS was defined as the time from randomization to first documented disease progression or death from any cause. Disease progression was defined as a ≥20% and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). Median duration of PFS was estimated using Kaplan-Meier analysis, and corresponding CIs were computed using the Brookmeyer-Crowley method. Analysis was performed on ITT population (all subjects randomized in the study).

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: months				
median (confidence interval 95%)	12.5 (10.5 to 13.6)	14.1 (12.2 to 16.7)	14.8 (12.4 to 17.8)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Placebo versus Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.69
upper limit	1.04

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Pertuzumab versus Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Pertuzumab
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.63
upper limit	0.95

Secondary: Percentage of Subjects Experiencing Treatment Failure

End point title	Percentage of Subjects Experiencing Treatment Failure

End point description:

Treatment failure was defined as the discontinuation of all study medications in the treatment arm for any reason including disease progression, treatment toxicity, death, physician decision, or subject withdrawal. The percentage of subjects with treatment failure was calculated as [number of subjects with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population (all subjects randomized in the study).

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: percentage of subjects				
number (not applicable)	85.8	82.6	80.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure (TTF)

End point title	Time to Treatment Failure (TTF)

End point description:

Treatment failure was defined as the discontinuation of all study medications in the treatment arm for any reason including disease progression, treatment toxicity, death, physician decision, or subject withdrawal. TTF was defined as the time from randomization to treatment failure. Median TTF was estimated using Kaplan-Meier analysis, and corresponding CIs were computed using the Brookmeyer-Crowley method. Analysis was performed on ITT population (all subjects randomized in the study).

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: months				
median (confidence interval 95%)	10.2 (9.2 to 11.8)	12.1 (9.9 to 13.9)	11.8 (9.9 to 14.2)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Pertuzumab versus Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Pertuzumab
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.65
upper limit	0.95

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Placebo versus Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo

Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.66
upper limit	0.97

Secondary: One-Year Survival Rate

End point title	One-Year Survival Rate

End point description:

The percentage of subjects alive at 1 year after randomization was estimated as the one-year survival rate using Kaplan-Meier analysis, and corresponding CIs were computed using Greenwood's estimate of the standard error. Analysis was performed on ITT population (all subjects randomized in the study).

End point type	Secondary

End point timeframe:

From randomization until 1 year

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: percentage probability of being alive				
number (confidence interval 95%)	91.4 (88.44 to 94.41)	92.4 (89.62 to 95.15)	91.9 (89 to 94.77)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Grade ≥3 Adverse Events

End point title	Percentage of Subjects with Grade ≥3 Adverse Events

End point description:

Adverse events were graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activity of daily living with inability to perform bathing, dressing and undressing, feeding self, using the toilet, taking medications but not bedridden. Grade 4: An immediate threat to life. Urgent medical intervention is required in order to maintain survival. Grade 5: Death. Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

Up to 50 months from randomization until clinical cutoff of 16-Sept-2014 (continuously until 28 days after last dose]

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	353	361	366	
Units: percentage of subjects				
number (not applicable)	54.1	45.4	46.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Died at 2 Years

End point title	Percentage of Subjects Who Died at 2 Years

End point description:

Analysis was performed on ITT population (all subjects randomized in the study).

End point type	Secondary

End point timeframe:

From randomization until 2 years

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: percentage of subjects				
number (not applicable)	20.3	20.2	19.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Truncated at 2 Years

End point title	Overall Survival Truncated at 2 Years

End point description:

Overall Survival truncated at 2 years was defined as the time from the date of randomization to the date of death from any cause. Subjects who were alive at 2 years had been censored at 2 years. Overall survival truncated at 2 years was estimated using Kaplan-Meier analyses. Here, "9999" represents that data was not applicable because median was not reached at 2 years as most of the subjects were alive at that time point. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From randomization until 2 years

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)	9999 (9999 to 9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Grade 5 Adverse Events

End point title	Percentage of Subjects with Grade 5 Adverse Events

End point description:

Adverse events were graded according to NCI CTCAE version 4.0. Grade 5 adverse events are those events which led to death. Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

Up to 50 months from randomization until clinical cutoff of 16-Sept-2014 (continuously until 28 days after last dose

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	353	361	366	
Units: percentage of subjects				
number (not applicable)	1.7	1.1	1.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Grade 3-4 Laboratory Parameters

End point title	Percentage of Subjects with Grade 3-4 Laboratory Parameters

End point description:

Laboratory results were graded according to NCI CTCAE version 4.0. Grade 3: Severe or medically

significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activity of daily living with inability to perform bathing, dressing and undressing, feeding self, using the toilet, taking medications but not bedridden. Grade 4: An immediate threat to life. Urgent medical intervention is required in order to maintain survival. Analysis was performed on ITT population (all subjects randomized in the study).

End point type	Secondary

End point timeframe:

Day 1, 8, and 15 of Cycle 1–3 and on Day 1 of each subsequent cycle up to 50 months from randomization until clinical cutoff of 16-Sept-2014

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	353	361	366	
Units: percentage of subjects				
number (not applicable)				
Hemoglobin-Low: Grade 3	4.3	5.8	6.9	
Neutrophils-Low: Grade 3	20.2	5.5	5	
Neutrophils-Low: Grade 4	43.8	1.9	0.8	
Platelets-Low: Grade 3	0.9	12.7	12.9	
Platelets-Low: Grade 4	0.3	2.8	2.5	
Alkaline Phosphate-High: Grade 3	1.1	3.9	3	
Alanine Transaminase-High: Grade 3	3.4	9.1	8	
Alanine Transaminase-High: Grade 4	0	0.3	0.6	
Aspartate Aminotransferase-High: Grade 3	1.1	11.9	6.9	
Aspartate Aminotransferase-High: Grade 4	0	0.3	0.3	
Creatinine-High: Grade 3	0.9	0.3	1.1	
Creatinine-High: Grade 4	0	0	0.3	
Potassium-Low: Grade 3	4.3	4.7	5.2	
Potassium-Low: Grade 4	0.6	1.7	0.6	
Total Bilirubin-High: Grade 3	0.3	0.3	0.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Decline of ≥2 points from Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Status

End point title	Percentage of Subjects with Decline of ≥2 points from Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Status

End point description:

The ECOG performance status is a scale used to quantify cancer subjects' general well-being and activities of daily life. The scale ranges from 0 to 5, with 0 denoting perfect health and 5 indicating death. The 6 categories are 0=Asymptomatic (Fully active, able to carry on all predisease activities without restriction), 1=Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature), 2=Symptomatic, < 50% in bed during the day (Ambulatory and capable of all self-care but unable to carry out any work

activities. Up and about more than 50% of waking hours), 3=Symptomatic, > 50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours), 4=Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair), 5=Death. Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of every Cycle up to Clinical Data Cut (up to 48 months)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	353	361	366	
Units: percentage of subjects				
number (not applicable)	7.6	6.1	7.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Hospitalization Days

End point title	Hospitalization Days

End point description:

Hospitalization was defined as a non-administration-related hospitalization due to serious adverse event, while on study treatment. Reported values represent number of days admitted per subjects. Analysis was performed on safety population. Number of subjects analyzed=subjects with hospitalization and data available for calculation of the parameter.

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	353	361	366	
Units: days				
median (full range (min-max))	6 (1 to 50)	5 (1 to 117)	8 (1 to 381)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Hospitalization

End point title	Percentage of Subjects with Hospitalization

End point description:

Hospitalization was defined as a non-administration-related hospitalization due to serious adverse event, while on study treatment. Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	353	361	366	
Units: percentage of subjects				
number (confidence interval 95%)	21.8 (17.62 to 26.36)	20.2 (16.2 to 24.71)	22.1 (18.03 to 26.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Objective Response According to IRF Assessment

End point title	Percentage of Subjects with Objective Response According to IRF Assessment

End point description:

Objective response was defined as having complete response (CR) or partial response (PR), assessed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. CR was defined as the disappearance of all target and non-target lesions and short-axis reduction in pathological lymph nodes to <10 mm. PR was defined as a ≥30% decrease in sum of diameters of target lesions, taking as reference the Baseline sum. Response was determined using 2 consecutive tumor assessments at least 4 weeks apart. The percentage of subjects with a best overall response of CR or PR (ie, the objective response rate [ORR]) was calculated as [number of subjects meeting the respective criteria divided by the number analyzed] multiplied by 100. Corresponding CIs computed using the Blyth-Still-Casella exact method. Analysis performed on ITT population with measurable disease by IRF at Baseline.

End point type	Secondary

End point timeframe:

Up to 46 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	287	303	299	
Units: percentage of subjects				
number (confidence interval 95%)	67.9 (62.26 to 73.31)	59.7 (54.07 to 65.3)	64.2 (58.62 to 69.65)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Direction of comparison: Trastuzumab Emtansine + Placebo versus Trastuzumab + Taxane	
Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo
Number of subjects included in analysis	590
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Response Rate
Point estimate	-8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.9
upper limit	-0.5

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Direction of comparison: Trastuzumab Emtansine + Pertuzumab v Trastuzumab + Taxane	
Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Pertuzumab
Number of subjects included in analysis	586
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Response Rate
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.4
upper limit	3.9

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Direction of comparison: Trastuzumab Emtansine + Pertuzumab v Trastuzumab Emtansine + Placebo	
Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab Emtansine + Pertuzumab

Number of subjects included in analysis	602
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Response Rate
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	12.2

Secondary: Percentage of Subjects with Objective Response According to Investigator Assessment

End point title	Percentage of Subjects with Objective Response According to Investigator Assessment

End point description:

Objective response was defined as having CR or PR, assessed according to RECIST version 1.1, by investigator. CR was defined as the disappearance of all target and non-target lesions and short-axis reduction in pathological lymph nodes to <10 mm. PR was defined as a ≥30% decrease in sum of diameters of target lesions, taking as reference the Baseline sum. Response was determined using 2 consecutive tumor assessments at least 4 weeks apart. The percentage of subjects with a best overall response of CR or PR (ie, the ORR) was calculated as [number of subjects meeting the respective criteria divided by the number analyzed] multiplied by 100. Corresponding CIs were computed using the Blyth-Still-Casella exact method. Analysis was performed on ITT population (all subjects randomized in the study). Only subjects with measurable disease by investigator at Baseline were included.

End point type	Secondary

End point timeframe:

Up to 46 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	293	314	311	
Units: percentage of subjects				
number (confidence interval 95%)	69.3 (63.74 to 74.52)	64.6 (59.12 to 69.87)	67.5 (62.17 to 72.68)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane

Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo

Number of subjects included in analysis	607
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Response Rate
Point estimate	-4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.1
upper limit	2.8

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Direction of comparison: Trastuzumab Emtansine + Pertuzumab v Trastuzumab + Taxane	
Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Pertuzumab
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Response Rate
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	5.7

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Direction of comparison: Trastuzumab Emtansine + Pertuzumab v Trastuzumab Emtansine + Placebo	
Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab Emtansine + Pertuzumab
Number of subjects included in analysis	625
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Response Rate
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	10.3

Secondary: Duration of Response According to IRF Assessment

End point title	Duration of Response According to IRF Assessment

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. Duration of response was defined as the time from confirmed PR or CR to first documented disease progression or death from any cause. CR was defined as the disappearance of all target lesions and non-target lesions and short-axis reduction in pathological lymph nodes to <10 mm. PR was defined as a ≥30% decrease in sum of diameters of target lesions, taking as reference the Baseline sum. Response was determined using 2 consecutive tumor assessments at least 4 weeks apart. Median duration of response was estimated using Kaplan-Meier analysis, and corresponding CIs were computed using the Brookmeyer-Crowley method. Analysis was performed on ITT population. Only subjects achieving CR or PR were included in the analysis.

End point type	Secondary

End point timeframe:

Up to 46 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	195	181	192	
Units: months				
median (confidence interval 95%)	12.5 (10.5 to 16.6)	20.7 (14.8 to 25)	21.2 (15.8 to 29.3)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.43
upper limit	0.84

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Pertuzumab v Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Pertuzumab
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.45
upper limit	0.85

Secondary: Percentage of Subjects with a Best Overall Response of CR, PR, or Stable Disease (SD) According to IRF Assessment

End point title	Percentage of Subjects with a Best Overall Response of CR, PR, or Stable Disease (SD) According to IRF Assessment

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. CR was defined as the disappearance of all target and non-target lesions and short-axis reduction in pathological lymph nodes to <10 mm. PR was defined as a ≥30% decrease in sum of diameters of target lesions, taking as reference the Baseline sum. SD was defined as neither sufficient shrinkage to quality for PR nor sufficient (20%) increase to qualify for disease progression. Response was determined using 2 consecutive tumor assessments at least 4 weeks apart. The percentage of subjects with a best overall response of CR, PR, or SD was calculated as [number of subjects meeting the respective criteria divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Up to 46 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[5]	0[6]	0[7]	
Units: percentage of subjects				

Notes:

[5] - This outcome was removed because it was redundant to another prespecified secondary endpoint.

[6] - This outcome was removed because it was redundant to another prespecified secondary endpoint.

[7] - This outcome was removed because it was redundant to another prespecified secondary endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Experiencing a Clinically Significant Increase in Taxane-Related Treatment Symptoms as Measured by Taxane Subscale of the Functional Assessment of Cancer Therapy (FACT) Taxane (FACT-TaxS) Score

End point title	Percentage of Subjects Experiencing a Clinically Significant Increase in Taxane-Related Treatment Symptoms as Measured by Taxane Subscale of the Functional Assessment of Cancer Therapy (FACT) Taxane (FACT-TaxS) Score

End point description:

The FACT-Taxane is a self-reported instrument which measures the health-related quality of life (HRQOL) of subjects receiving taxane-containing chemotherapy. The FACT-TaxS consists of 16 items including 11 neurotoxicity-related questions and 5 additional questions assessing arthralgia, myalgia, and skin discoloration. Items are rated from 0 (not at all) to 4 (very much) and a total score is inversely derived. Scores may range from 0 to 64, with higher scores indicating fewer/no symptoms. A minimally clinically important difference in treatment-related symptoms was defined as a ≥5% decrease (ie, 3.2 points) in FACT-TaxS score from Baseline. The percentage of subjects with treatment-related symptoms was calculated using following formula: [number of subjects meeting the above threshold divided by the number analyzed] multiplied by 100. Corresponding CIs computed using the Blyth-Still-Casella exact method. Analysis included randomized subjects who entered after Protocol Amendment C.

End point type	Secondary

End point timeframe:

Up to 39 months from randomization until clinical cutoff of 16-Sept-2014 (at Baseline, on Day 1 of Cycles 2 to 8 and every even-numbered cycle thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	173	171	154	
Units: percentage of subjects				
number (confidence interval 95%)	93.1 (88.48 to 96.06)	60.8 (53.39 to 67.93)	68.8 (61.32 to 75.92)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Symptom Rate
Point estimate	-32.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-40
upper limit	-24

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Pertuzumab v Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Pertuzumab
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Symptom Rate
Point estimate	-24.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32
upper limit	-16

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Pertuzumab v Trastuzumab Emtansine + Placebo. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab Emtansine + Placebo v Trastuzumab Emtansine + Pertuzumab
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Symptom Rate
Point estimate	8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	18.4

Secondary: Percentage of Subjects Reporting Nausea According to the Relevant

Single Items of The FACT Colorectal Cancel (FACT-C) Module

End point title	Percentage of Subjects Reporting Nausea According to the Relevant Single Items of The FACT Colorectal Cancel (FACT-C) Module

End point description:

The FACT-C is a self-reported instrument which measures HRQOL pertaining to colorectal cancer. Response options on each question may range from 0 (not at all) to 4 (very much). The percentage of subjects with nausea was calculated using following formula: [number of subjects with any level of either symptom divided by the number analyzed] multiplied by 100. Analyses were performed on the Protocol Amendment C Subpopulation. Only subjects with a FACTC score at the designated visit (n) were included in the analysis.

End point type	Secondary

End point timeframe:

At Baseline, Day 8 of Cycle 1, and Days 1 and 8 of Cycle 2

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	173	171	154	
Units: percentage of subjects				
number (not applicable)				
Nausea, Baseline (n=166,166,150)	22.3	14.5	21.3	
Nausea, Cycle 1 Day 8 (n=121,114,95)	38	36	52.6	
Nausea, Cycle 2 Day 1 (n=147,151,138)	27.2	20.5	36.2	
Nausea, Cycle 2 Day 8 (n=122,121,105)	35.2	28.1	45.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Diarrhea According to the Relevant Single Items of The FACT-C Module

End point title	Percentage of Subjects Reporting Diarrhea According to the Relevant Single Items of The FACT-C Module

End point description:

The FACT-C is a self-reported instrument which measures HRQOL pertaining to colorectal cancer. Response options on each question may range from 0 (not at all) to 4 (very much). The percentage of subjects with diarrhea was calculated using following formula: [number of subjects with any level of either symptom divided by the number analyzed] multiplied by 100. Analyses were performed on the Protocol Amendment C Subpopulation. Only subjects with a FACTC score at the designated visit (n) were included in the analysis.

End point type	Secondary

End point timeframe:

At Baseline, Day 8 of Cycle 1, and Days 1 and 8 of Cycle 2

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	173	171	154	
Units: percentage of subjects				
number (not applicable)				
Diarrhea, Baseline (n=173,170,153)	15	7.6	11.8	
Diarrhea, Cycle 1 Day 8 (n=124,117,98)	34.7	17.9	34.7	
Diarrhea, Cycle 2 Day 1 (n=161,160,144)	24.2	11.3	39.6	
Diarrhea, Cycle 2 Day 8 (n=125,123,107)	34.4	8.1	41.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with a Clinically Significant Deterioration in Health Related Quality of Life (HRQoL) as measured by FACT Breast (FACT-B) Trial Outcome Index-Physical Function Breast (TOI-PFB) Score

End point title	Percentage of Subjects with a Clinically Significant Deterioration in Health Related Quality of Life (HRQoL) as measured by FACT Breast (FACT-B) Trial Outcome Index-Physical Function Breast (TOI-PFB) Score

End point description:

The FACT-B is a self-reported instrument which measures HRQOL of subjects with breast cancer. It consists of 5 subscales including physical well-being (PWB), social well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and a breast cancer subscale (BCS). The TOI-PFB score is taken by adding the scores from the PWB (7 items), FWB (7 items), and BCS (9 items) subscales. Items are rated from 0 (not at all) to 4 (very much) and a total score is derived. Scores may range from 0 to 92, with higher scores indicating better HRQOL. A 5 point change has been identified as the clinically minimal important difference (CMID) on the FACT-TOI-PFB scale. The percentage of subjects with deterioration was calculated as [number of subjects meeting the above threshold divided by the number analyzed] multiplied by 100. Analysis was performed on the ITT population with baseline and at least one post baseline FACT-B TOI-PFB score.

End point type	Secondary

End point timeframe:

Up to 39 months from randomization until clinical cutoff of 16-Sept-2014 (at Baseline, on Day 1 of Cycles 2 to 8 and every even-numbered cycle thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	327	352	338	
Units: percentage of subjects				
number (not applicable)	61.8	50.9	50.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration in HRQoL as Assessed by FACT-B TOI-PFB Score

End point title	Time to Deterioration in HRQoL as Assessed by FACT-B TOI-PFB Score

End point description:

The FACT-B is a self-reported instrument which measures HRQOL of subjects with breast cancer. It consists of 5 subscales including PWB, SWB, EWB, FWB, and BCS. The TOI-PFB score is taken by adding the scores from the PWB (7 items), FWB (7 items), and BCS (9 items) subscales. Items are rated from 0 (not at all) to 4 (very much) and a total score is derived. Scores may range from 0 to 92, with higher scores indicating better HRQOL. A 5 point change has been identified as the clinically minimal important difference (CMID) on the FACT-TOI-PFB scale. Time to deterioration was defined as the time from Baseline until the first decrease in FACT-B TOI-PFB score. Median time to deterioration was estimated using Kaplan-Meier analysis, and corresponding CIs were computed using the Brookmeyer-Crowley method. Analysis was performed on the ITT population with baseline and at least one post baseline FACT-B TOI-PFB score.

End point type	Secondary

End point timeframe:

Baseline up to 39 months from randomization until clinical cutoff of 16-Sept-2014

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	327	352	338	
Units: months				
median (confidence interval 95%)	3.6 (3 to 4.4)	7.7 (6.2 to 11.9)	9 (5.1 to 14.5)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Pertuzumab vs Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Pertuzumab
Number of subjects included in analysis	665
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.84

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Direction of comparison: Trastuzumab Emtansine + Placebo vs Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).	
Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo
Number of subjects included in analysis	679
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	0.86

Secondary: Change from Baseline in Rotterdam Symptom Checklist (RSCL) Activity Level Scale Score

End point title	Change from Baseline in Rotterdam Symptom Checklist (RSCL) Activity Level Scale Score
End point description:	
The RSCL is a self-reported instrument which consists of 4 domains including physical symptom distress, psychological distress, activity level, and overall global life quality. Only the activity level scale was collected and assessed. Scores may range from 0 to 100, with higher scores indicating increased burden of disease. Mean RSCL activity scale score changes were calculated as [mean score at the assessment visit minus mean score at Baseline]. The higher the score, the higher the level of impairment or burden. Analysis was performed on ITT population. Only subjects with available data at baseline and Cycle 7 (Week 18) were included.	
End point type	Secondary
End point timeframe:	
Baseline, Cycle 7 (Week 18)	

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	365	367	363	
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Baseline (n=344,355,344)	85 (82.9 to 87.2)	85.5 (83.3 to 87.8)	85.7 (83.5 to 87.8)	
Change From Baseline at Cycle 7 (n=261,252,261)	-1.6 (-4.2 to 1)	2.3 (0.4 to 4.2)	-0.2 (-2.1 to 1.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Work Productivity According to Work Productivity and Activity Impairment (WPAI) Questionnaire Score

End point title	Change From Baseline in Work Productivity According to Work Productivity and Activity Impairment (WPAI) Questionnaire Score

End point description:

The WPAI is a patient-reported measure which assesses the effect of general health and symptom severity on work productivity and regular activities. The General Health questionnaire asks subjects to estimate the number of hours missed from work due to reasons related and unrelated to their health problems, as well as the total number of hours actually worked in the preceding 7-day period. The percentage of subjects reporting that they were employed (working for pay) was assessed at baseline was assessed along with Absenteeism (work time missed), Presenteeism (impairment at work / reduced on-the-job effectiveness), Work productivity loss (overall work impairment / absenteeism plus presenteeism), and Activity Impairment. The reported changes represent change from baseline at Cycle 7. The score range for the scales of the WPAI is between 0 (no effect) to 100% (max effect). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Cycle 7 (Week 18)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	64	67	
Units: percent of work				
arithmetic mean (confidence interval 95%)				
% Work Time Missed at Baseline (n=66,63,67)	15.3 (9.2 to 21.4)	9.5 (4.2 to 14.8)	13.6 (7.7 to 19.6)	
Change in % Work Time Missed (n=35,33,36)	0.4 (-7.3 to 8.2)	0 (-4.5 to 4.5)	-4.3 (-13 to 4.6)	
% Impairment While Working at Baseline(n=67,64,67)	20 (14.1 to 25.9)	15.3 (9.5 to 21.1)	19.9 (13.6 to 26.1)	
Change in % Impairment While Working (n=34,32,35)	8.8 (2 to 15.6)	-0.3 (-11 to 10.5)	-2.7 (-11 to 5.2)	
% Overall Work Impairment at Baseline (n=65,62,66)	28.5 (20.7 to 36.2)	21.2 (13.8 to 28.7)	28.1 (20.3 to 35.9)	
Change in % Overall Work Impairment (n=34,31,35)	9.1 (-0.4 to 18.6)	-1.1 (-13 to 11)	-4.6 (-14 to 5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Activity Impairment According to Work Productivity and Activity Impairment (WPAI) Questionnaire Score

End point title	Change From Baseline in Activity Impairment According to Work Productivity and Activity Impairment (WPAI) Questionnaire Score

End point description:

The WPAI is a patient-reported measure which assesses the effect of general health and symptom severity on work productivity and regular activities. The General Health questionnaire asks subjects to estimate the number of hours missed from work due to reasons related and unrelated to their health problems, as well as the total number of hours actually worked in the preceding 7-day period. The percentage of subjects reporting that they were employed (working for pay) was assessed at baseline was assessed along with Absenteeism (work time missed), Presenteeism (impairment at work / reduced on-the-job effectiveness), Work productivity loss (overall work impairment / absenteeism plus presenteeism), and Activity Impairment. The reported changes represent change from baseline at Cycle 7. The score range for the scales of the WPAI is between 0 (no effect) to 100% (max effect). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Cycle 7 (Week 18)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	312	334	321	
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
% Activity Impairment at Baseline (n=312,334,321)	32.9 (29.6 to 36.3)	33.6 (30.2 to 37)	32.7 (29.5 to 36)	
Change in % Activity Impairment (n=227,222,234)	4.5 (0.2 to 8.7)	-5.3 (-9.5 to -1.1)	-3.7 (-7.2 to -0.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with a Best Overall Response of CR or PR According to IRF Assessment Among Those with High Human Epidermal Growth Factor Receptor 2 (HER2) Messenger Ribonucleic Acid (mRNA) Levels

End point title	Percentage of Subjects with a Best Overall Response of CR or PR According to IRF Assessment Among Those with High Human Epidermal Growth Factor Receptor 2 (HER2) Messenger Ribonucleic Acid (mRNA) Levels

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. CR was defined as the disappearance of all target and non-target lesions and short-axis reduction in pathological lymph nodes to <10 mm. PR was defined as a ≥30% decrease in sum of diameters of target lesions, taking as reference the Baseline sum. Response was determined

using 2 consecutive tumor assessments at least 4 weeks apart. The percentage of subjects with a best overall response of CR or PR (ie, the ORR) was calculated as [number of subjects meeting the respective criteria divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population with above the median HER2 mRNA expression (value greater than [>] 59.71). Only subjects with measurable disease at Baseline were included in the analysis.

End point type	Secondary

End point timeframe:

Up to 46 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	132	136	147	
Units: percentage of subjects				
number (not applicable)	75	66.9	63.9	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane

Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.15

Secondary: Percentage of Subjects with a Best Overall Response of CR or PR According to IRF Assessment Among Those with Low HER2 mRNA Levels

End point title	Percentage of Subjects with a Best Overall Response of CR or PR According to IRF Assessment Among Those with Low HER2 mRNA Levels

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. CR was defined as the disappearance of all target and non-target lesions and short-axis reduction in pathological lymph nodes to <10 mm. PR was defined as a ≥30% decrease in sum of diameters of target lesions, taking as reference the Baseline sum. Response was determined using 2 consecutive tumor assessments at least 4 weeks apart. The percentage of subjects with a best overall response of CR or PR (ie, the ORR) was calculated as [number of subjects meeting the respective criteria divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population

with below the median HER2 mRNA expression (value less than or equal to [≤] 59.71). Only subjects with measurable disease at Baseline were included in the analysis.

End point type	Secondary

End point timeframe:

Up to 46 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126	147	127	
Units: percentage of subjects				
number (not applicable)	61.9	51.7	66.1	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Placebo" vs Trastuzumab + Taxane

Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.07

Secondary: Percentage of Subjects with Death or Disease Progression According to IRF Assessment Among Those with High HER2 mRNA Levels

End point title	Percentage of Subjects with Death or Disease Progression According to IRF Assessment Among Those with High HER2 mRNA Levels

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. Disease progression was defined as a ≥20% and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). The percentage of subjects with death or disease progression was calculated as [number of subjects with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT Population (High HER2 mRNA Subpopulation).

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	165	173	
Units: percentage of subjects				
number (not applicable)	59.4	57.6	56.1	

Statistical analyses

No statistical analyses for this end point

Secondary: PFS According to IRF Assessment Among Those with High HER2 mRNA Levels

End point title	PFS According to IRF Assessment Among Those with High HER2 mRNA Levels

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. PFS was defined as the time from randomization to first documented disease progression or death from any cause. Disease progression was defined as a ≥20% and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). Median duration of PFS was estimated using Kaplan-Meier analysis. Analysis was performed on ITT Population (High HER2 mRNA Subpopulation).

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	165	173	
Units: months				
median (full range (min-max))	15.9 (0.1 to 46.4)	18.6 (0.1 to 46)	18.7 (0.1 to 48.1)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Direction of comparison: Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane	
Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.65
upper limit	1.25

Secondary: Percentage of Subjects with Death or Disease Progression According to IRF Assessment Among Those with Low HER2 mRNA Levels

End point title	Percentage of Subjects with Death or Disease Progression According to IRF Assessment Among Those with Low HER2 mRNA Levels

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. Disease progression was defined as a ≥20% and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). The percentage of subjects with death or disease progression was calculated as [number of subjects with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT Population (Low HER2 mRNA Subpopulation).

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	170	174	157	
Units: percentage of subjects				
number (not applicable)	66.5	70.1	62.4	

Statistical analyses

No statistical analyses for this end point

Secondary: PFS According to IRF Assessment Among Those with Low HER2 mRNA Levels

End point title	PFS According to IRF Assessment Among Those with Low HER2 mRNA Levels

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. PFS was defined as the time from randomization to first documented disease progression or death from any cause. Disease progression was defined as a ≥20% and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). Median duration of PFS was estimated using Kaplan-Meier analysis. Analysis was performed on ITT Population (Low HER2 mRNA Subpopulation).

End point type	Secondary

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	170	174	157	
Units: months				
median (full range (min-max))	12.4 (0.1 to 47.3)	10.2 (0.1 to 43.6)	14.5 (0.1 to 40.7)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane

Comparison groups	Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.74
upper limit	1.34

Secondary: Percentage of Subjects Who Died Prior to Clinical Cutoff Among Those with High HER2 mRNA Levels

End point title	Percentage of Subjects Who Died Prior to Clinical Cutoff Among Those with High HER2 mRNA Levels

End point description:

The percentage of subjects who died prior to clinical cutoff was calculated as [number of subjects with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population

(High HER2 mRNA Subpopulation).

End point type	Secondary

End point timeframe:

Up to 70 months from randomization until clinical cutoff of 15-May-2016 (every 3 months until death, loss to follow-up, withdrawal, or study termination)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	165	173	
Units: percentage of subjects				
number (not applicable)	38.8	41.2	45.1	

Statistical analyses

No statistical analyses for this end point

Secondary: OS at Clinical Cutoff Among Those with High HER2 mRNA Levels

End point title	OS at Clinical Cutoff Among Those with High HER2 mRNA Levels

End point description:

OS was defined as the time from randomization to death from any cause. Median duration of OS was estimated using Kaplan-Meier analysis. Here, "9999" represents that the value is not applicable because Median duration of OS was not reached due to insufficient follow up. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Up to 70 months from randomization until clinical cutoff of 15-May-2016 (every 3 months until death, loss to follow-up, withdrawal, or study termination)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	165	173	
Units: months				
median (full range (min-max))	9999 (50.86 to 9999)	65.97 (54.54 to 67.98)	55.39 (45.23 to 9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Died Prior to Clinical Cutoff Among Those with Low HER2 mRNA Levels

End point title	Percentage of Subjects Who Died Prior to Clinical Cutoff Among Those with Low HER2 mRNA Levels

End point description:

The percentage of subjects who died prior to clinical cutoff was calculated as [number of subjects with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Up to 70 months from randomization until clinical cutoff of 15-May-2016 (every 3 months until death, loss to follow-up, withdrawal, or study termination)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	170	174	157	
Units: percentage of subjects				
number (not applicable)	51.8	52.9	45.2	

Statistical analyses

No statistical analyses for this end point

Secondary: OS at Clinical Cutoff Among Those with Low HER2 mRNA Levels

End point title	OS at Clinical Cutoff Among Those with Low HER2 mRNA Levels

End point description:

OS was defined as the time from randomization to death from any cause. Median duration of OS was estimated using Kaplan-Meier analysis. Reported upper bound of confidence interval for "Trastuzumab Emtansine + Placebo" and confidence interval values for "Trastuzumab + Taxane" and "Trastuzumab Emtansine + Pertuzumab" are censored values. Here, "9999" represents that the value is not applicable because Median duration of OS was not reached due to insufficient follow up. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Up to 70 months from randomization until clinical cutoff of 15-May-2016 (every 3 months until death, loss to follow-up, withdrawal, or study termination)

End point values	Trastuzumab + Taxane	Trastuzumab Emtansine + Placebo	Trastuzumab Emtansine + Pertuzumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	170	174	157	
Units: months				
median (full range (min-max))	43.96 (37.19 to 54.87)	47.84 (42.09 to 53.85)	53.29 (46.75 to 9999)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 70 months from randomization until clinical cutoff of 16 September 2016 (every 3 months until death, loss to follow-up, withdrawal, or study termination).

Adverse event reporting additional description:

Safety Population: All randomized subjects who received at least one dose of study treatment. Subjects were analyzed based on the treatment received.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Trastuzumab Emtansine + Placebo

Reporting group description:

Subjects received trastuzumab emtansine plus pertuzumab-placebo. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the placebo IV infusion, on Day 1 of each 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

Reporting group title	Trastuzumab + Taxane

Reporting group description:

Subjects received trastuzumab plus either docetaxel or paclitaxel. The regimen was chosen at the investigator's discretion. Option 1: trastuzumab 8 mg/kg via IV infusion on Day 1 of Cycle 1, then 6 mg/kg IV on Day 1 of each subsequent 3-week cycle; plus a minimum of 6 cycles with docetaxel 75 or 100 mg/m^2 IV on Day 1 of each 3-week cycle. Option 2: trastuzumab 4 mg/kg IV on Day 1 of Cycle 1, then 2 mg/kg IV weekly beginning on Day 8 of Cycle 1; plus a minimum of 18 weeks with paclitaxel 80 mg/m^2 IV weekly. Treatment continued until disease progression, unacceptable toxicity, or study termination. If trastuzumab or docetaxel were discontinued for toxicity, the other agent could be continued as monotherapy.

Reporting group title	Trastuzumab Emtansine + Pertuzumab

Reporting group description:

Subjects received trastuzumab emtansine plus pertuzumab. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the pertuzumab IV infusion, on Day 1 of each 3-week cycle. Pertuzumab was given as 840 mg IV on Day 1 of Cycle 1, then 420 mg IV on Day 1 of each subsequent 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

Serious adverse events	Trastuzumab Emtansine + Placebo	Trastuzumab + Taxane	Trastuzumab Emtansine + Pertuzumab
Total subjects affected by serious adverse events			
subjects affected / exposed	86 / 361 (23.82%)	81 / 353 (22.95%)	93 / 366 (25.41%)
number of deaths (all causes)	174	170	170
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			

subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Breast neoplasm			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Colon neoplasm			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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 adenocarcinoma			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the cervix			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Uterine leiomyoma			

subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Basal Cell Carcinoma			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial Tumour Haemorrhage			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 361 (0.28%)	1 / 353 (0.28%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	2 / 361 (0.55%)	0 / 353 (0.00%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypertensive crisis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Aneurysm			

subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic Shock			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic Hypotension			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 361 (1.11%)	2 / 353 (0.57%)	5 / 366 (1.37%)
occurrences causally related to treatment / all	3 / 5	0 / 2	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 361 (0.28%)	3 / 353 (0.85%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 1	2 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	2 / 361 (0.55%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
General physical health deterioration			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	2 / 366 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pain			

subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	2 / 366 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site haematoma			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Peripheral swelling			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Adverse Drug Reaction			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden Death			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	2 / 361 (0.55%)	0 / 353 (0.00%)	2 / 366 (0.55%)
occurrences causally related to treatment / all	1 / 2	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	0 / 361 (0.00%)	2 / 353 (0.57%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytokine release syndrome			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic Shock			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Anaphylactoid Reaction			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hypertrophy			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Pleural effusion			
subjects affected / exposed	1 / 361 (0.28%)	3 / 353 (0.85%)	3 / 366 (0.82%)
occurrences causally related to treatment / all	0 / 1	2 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 361 (0.55%)	4 / 353 (1.13%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	1 / 2	1 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 361 (0.28%)	2 / 353 (0.57%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	1 / 1	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	3 / 366 (0.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 361 (0.28%)	1 / 353 (0.28%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	2 / 366 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Alveolitis allergic			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Nasal turbinate hypertrophy			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Pneumonitis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Pulmonary fibrosis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Acute Pulmonary Oedema			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	2 / 366 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			

subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	2 / 366 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide Attempt			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Mental Status Changes			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device Breakage			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	2 / 366 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	2 / 366 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Body temperature increased			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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

International normalised ratio increased			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Oxygen saturation decreased			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	7 / 361 (1.94%)	1 / 353 (0.28%)	13 / 366 (3.55%)
occurrences causally related to treatment / all	8 / 9	1 / 1	13 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	3 / 366 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial injury			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Contusion			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Fall			
subjects affected / exposed	2 / 361 (0.55%)	0 / 353 (0.00%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Femoral neck fracture			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
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 stoma complication			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Hip fracture			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Radiation retinopathy			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Subdural haematoma			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound secretion			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Injury			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot Fracture			

subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Stomal Hernia			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Uncoded serious adverse event	Additional description: Per investigator, this serious adverse event was, "gamma nail implant broke (status after femur fracture)."		
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Pericardial effusion			

subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Myocardial Infarction			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 361 (0.55%)	0 / 353 (0.00%)	2 / 366 (0.55%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 361 (0.55%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	1 / 361 (0.28%)	1 / 353 (0.28%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			

subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Depressed level of consciousness			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Guillain-Barre syndrome			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Paraparesis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Presyncope			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Somnolence			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular dementia			

subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Cerebral Haemorrhage			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Neuropathy Peripheral			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 361 (0.28%)	1 / 353 (0.28%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 361 (0.00%)	13 / 353 (3.68%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 0	15 / 15	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	5 / 361 (1.39%)	1 / 353 (0.28%)	6 / 366 (1.64%)
occurrences causally related to treatment / all	3 / 6	0 / 1	3 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	0 / 361 (0.00%)	5 / 353 (1.42%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 0	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	2 / 361 (0.55%)	0 / 353 (0.00%)	2 / 366 (0.55%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercoagulation			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Leukopenia			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	2 / 366 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Blindness transient			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Macular hole			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Ocular hypertension			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	0 / 361 (0.00%)	4 / 353 (1.13%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	4 / 366 (1.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 361 (0.28%)	2 / 353 (0.57%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	2 / 366 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Anal fistula			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Gastric haemorrhage			

subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Gastric ulcer			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Gastritis erosive			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Large intestine perforation			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth haemorrhage			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic artery aneurysm			

subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Umbilical hernia			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Abdominal Discomfort			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Haemorrhoidal Haemorrhage			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Fibrosis			

subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Hepatic Haematoma			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 361 (0.55%)	0 / 353 (0.00%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatomyositis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peau d'orange			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Cutaneous Lupus Erythematosus			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 361 (0.55%)	1 / 353 (0.28%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Back pain			
subjects affected / exposed	1 / 361 (0.28%)	1 / 353 (0.28%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 361 (0.28%)	2 / 353 (0.57%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 361 (0.28%)	1 / 353 (0.28%)	0 / 366 (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
Exostosis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Musculoskeletal chest pain			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Neck pain			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Pain in extremity			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Pathological fracture			

subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Tenosynovitis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 361 (0.83%)	4 / 353 (1.13%)	5 / 366 (1.37%)
occurrences causally related to treatment / all	2 / 3	2 / 4	1 / 6
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Cellulitis			
subjects affected / exposed	3 / 361 (0.83%)	3 / 353 (0.85%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	1 / 4	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	4 / 366 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Device related infection			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	2 / 366 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			

subjects affected / exposed	1 / 361 (0.28%)	1 / 353 (0.28%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	0 / 361 (0.00%)	3 / 353 (0.85%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 361 (0.28%)	2 / 353 (0.57%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
Bronchitis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	3 / 366 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 361 (0.00%)	2 / 353 (0.57%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 361 (0.28%)	1 / 353 (0.28%)	0 / 366 (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
Urinary tract infection			
subjects affected / exposed	0 / 361 (0.00%)	2 / 353 (0.57%)	0 / 366 (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
Wound infection			
subjects affected / exposed	1 / 361 (0.28%)	1 / 353 (0.28%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis infective			

subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Atypical pneumonia			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast abscess			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Chorioretinitis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Empyema			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			

subjects affected / exposed	1 / 361 (0.28%)	1 / 353 (0.28%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 361 (0.28%)	1 / 353 (0.28%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella sepsis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Localised infection			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Lung infection			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Mastitis			

subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Nasopharyngitis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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 pneumococcal			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Rectal abscess			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Tooth infection			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Abscess Limb			

subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Appendicitis Perforated			
subjects affected / exposed	1 / 361 (0.28%)	0 / 353 (0.00%)	0 / 366 (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
Catheter Site Infection			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Infection			
subjects affected / exposed	0 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	2 / 361 (0.55%)	0 / 353 (0.00%)	0 / 366 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Diabetic ketoacidosis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Hypercalcaemia			

subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Hypokalaemia			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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
Hyponatraemia			
subjects affected / exposed	0 / 361 (0.00%)	1 / 353 (0.28%)	0 / 366 (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 / 361 (0.00%)	0 / 353 (0.00%)	1 / 366 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 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	Trastuzumab Emtansine + Placebo	Trastuzumab + Taxane	Trastuzumab Emtansine + Pertuzumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	352 / 361 (97.51%)	342 / 353 (96.88%)	352 / 366 (96.17%)
Vascular disorders			
Hypertension			
subjects affected / exposed	37 / 361 (10.25%)	19 / 353 (5.38%)	43 / 366 (11.75%)
occurrences (all)	87	27	70
Hot flush			
subjects affected / exposed	16 / 361 (4.43%)	27 / 353 (7.65%)	12 / 366 (3.28%)
occurrences (all)	22	32	19
Lymphoedema			
subjects affected / exposed	7 / 361 (1.94%)	27 / 353 (7.65%)	8 / 366 (2.19%)
occurrences (all)	8	35	10
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	120 / 361 (33.24%)	128 / 353 (36.26%)	130 / 366 (35.52%)
occurrences (all)	273	247	276
Pyrexia			
subjects affected / exposed	96 / 361 (26.59%)	59 / 353 (16.71%)	118 / 366 (32.24%)
occurrences (all)	156	85	184
Asthenia			
subjects affected / exposed	62 / 361 (17.17%)	57 / 353 (16.15%)	63 / 366 (17.21%)
occurrences (all)	205	163	211
Chills			
subjects affected / exposed	55 / 361 (15.24%)	14 / 353 (3.97%)	97 / 366 (26.50%)
occurrences (all)	69	15	125
Oedema peripheral			
subjects affected / exposed	37 / 361 (10.25%)	98 / 353 (27.76%)	35 / 366 (9.56%)
occurrences (all)	56	177	44
Mucosal inflammation			
subjects affected / exposed	29 / 361 (8.03%)	40 / 353 (11.33%)	36 / 366 (9.84%)
occurrences (all)	46	56	54
Influenza like illness			
subjects affected / exposed	31 / 361 (8.59%)	17 / 353 (4.82%)	32 / 366 (8.74%)
occurrences (all)	49	33	73
Non-cardiac chest pain			
subjects affected / exposed	25 / 361 (6.93%)	24 / 353 (6.80%)	27 / 366 (7.38%)
occurrences (all)	36	29	35
Pain			
subjects affected / exposed	26 / 361 (7.20%)	29 / 353 (8.22%)	19 / 366 (5.19%)
occurrences (all)	29	38	24
Oedema			
subjects affected / exposed	11 / 361 (3.05%)	31 / 353 (8.78%)	3 / 366 (0.82%)
occurrences (all)	14	51	5
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	13 / 361 (3.60%)	18 / 353 (5.10%)	16 / 366 (4.37%)
occurrences (all)	13	27	19
Respiratory, thoracic and mediastinal disorders			

Epistaxis			
subjects affected / exposed	113 / 361 (31.30%)	53 / 353 (15.01%)	127 / 366 (34.70%)
occurrences (all)	266	85	295
Cough			
subjects affected / exposed	72 / 361 (19.94%)	74 / 353 (20.96%)	79 / 366 (21.58%)
occurrences (all)	103	132	118
Dyspnoea			
subjects affected / exposed	42 / 361 (11.63%)	56 / 353 (15.86%)	53 / 366 (14.48%)
occurrences (all)	73	89	74
Oropharyngeal pain			
subjects affected / exposed	31 / 361 (8.59%)	29 / 353 (8.22%)	30 / 366 (8.20%)
occurrences (all)	36	36	41
Rhinorrhoea			
subjects affected / exposed	21 / 361 (5.82%)	26 / 353 (7.37%)	32 / 366 (8.74%)
occurrences (all)	26	43	36
Psychiatric disorders			
Insomnia			
subjects affected / exposed	51 / 361 (14.13%)	51 / 353 (14.45%)	52 / 366 (14.21%)
occurrences (all)	77	62	77
Anxiety			
subjects affected / exposed	26 / 361 (7.20%)	22 / 353 (6.23%)	33 / 366 (9.02%)
occurrences (all)	33	42	41
Depression			
subjects affected / exposed	34 / 361 (9.42%)	17 / 353 (4.82%)	20 / 366 (5.46%)
occurrences (all)	42	18	23
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	54 / 361 (14.96%)	9 / 353 (2.55%)	28 / 366 (7.65%)
occurrences (all)	80	11	56
Alanine aminotranseferase increased			
subjects affected / exposed	41 / 361 (11.36%)	10 / 353 (2.83%)	35 / 366 (9.56%)
occurrences (all)	67	12	57
Weight decreased			
subjects affected / exposed	24 / 361 (6.65%)	7 / 353 (1.98%)	30 / 366 (8.20%)
occurrences (all)	44	10	41
Ejection fraction decreased			

subjects affected / exposed	7 / 361 (1.94%)	31 / 353 (8.78%)	16 / 366 (4.37%)
occurrences (all)	8	36	18
Gamma- glutamyltranseferase increased			
subjects affected / exposed	30 / 361 (8.31%)	1 / 353 (0.28%)	17 / 366 (4.64%)
occurrences (all)	38	1	23
Nervous system disorders			
Headache			
subjects affected / exposed	116 / 361 (32.13%)	80 / 353 (22.66%)	120 / 366 (32.79%)
occurrences (all)	281	165	261
Neuropathy peripheral			
subjects affected / exposed	52 / 361 (14.40%)	99 / 353 (28.05%)	69 / 366 (18.85%)
occurrences (all)	84	171	129
Peripheral sensory neuropathy			
subjects affected / exposed	47 / 361 (13.02%)	70 / 353 (19.83%)	46 / 366 (12.57%)
occurrences (all)	69	125	74
Dysgeusia			
subjects affected / exposed	30 / 361 (8.31%)	54 / 353 (15.30%)	50 / 366 (13.66%)
occurrences (all)	44	67	81
Paraesthesia			
subjects affected / exposed	31 / 361 (8.59%)	41 / 353 (11.61%)	43 / 366 (11.75%)
occurrences (all)	51	57	74
Dizziness			
subjects affected / exposed	38 / 361 (10.53%)	35 / 353 (9.92%)	38 / 366 (10.38%)
occurrences (all)	67	48	77
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	44 / 361 (12.19%)	74 / 353 (20.96%)	37 / 366 (10.11%)
occurrences (all)	186	174	152
Anaemia			
subjects affected / exposed	48 / 361 (13.30%)	39 / 353 (11.05%)	59 / 366 (16.12%)
occurrences (all)	74	61	142
Thrombocytopenia			
subjects affected / exposed	52 / 361 (14.40%)	0 / 353 (0.00%)	61 / 366 (16.67%)
occurrences (all)	145	0	185
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	17 / 361 (4.71%)	11 / 353 (3.12%)	21 / 366 (5.74%)
occurrences (all)	33	15	28
Eye disorders			
Lacrimation increased			
subjects affected / exposed	13 / 361 (3.60%)	48 / 353 (13.60%)	19 / 366 (5.19%)
occurrences (all)	19	58	22
Dry eye			
subjects affected / exposed	25 / 361 (6.93%)	13 / 353 (3.68%)	24 / 366 (6.56%)
occurrences (all)	26	14	28
Vision Blurred			
alternative assessment type: Systematic			
subjects affected / exposed	13 / 361 (3.60%)	10 / 353 (2.83%)	19 / 366 (5.19%)
occurrences (all)	15	15	24
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	174 / 361 (48.20%)	131 / 353 (37.11%)	192 / 366 (52.46%)
occurrences (all)	526	308	633
Diarrhoea			
subjects affected / exposed	92 / 361 (25.48%)	173 / 353 (49.01%)	178 / 366 (48.63%)
occurrences (all)	151	466	550
Vomiting			
subjects affected / exposed	80 / 361 (22.16%)	69 / 353 (19.55%)	111 / 366 (30.33%)
occurrences (all)	136	146	215
Constipation			
subjects affected / exposed	82 / 361 (22.71%)	72 / 353 (20.40%)	71 / 366 (19.40%)
occurrences (all)	150	119	138
Stomatitis			
subjects affected / exposed	37 / 361 (10.25%)	57 / 353 (16.15%)	42 / 366 (11.48%)
occurrences (all)	51	76	65
Dyspepsia			
subjects affected / exposed	33 / 361 (9.14%)	38 / 353 (10.76%)	48 / 366 (13.11%)
occurrences (all)	55	48	94
Abdominal pain upper			
subjects affected / exposed	39 / 361 (10.80%)	31 / 353 (8.78%)	46 / 366 (12.57%)
occurrences (all)	62	53	70

Dry mouth			
subjects affected / exposed	52 / 361 (14.40%)	13 / 353 (3.68%)	45 / 366 (12.30%)
occurrences (all)	74	21	55
Abdominal pain			
subjects affected / exposed	35 / 361 (9.70%)	31 / 353 (8.78%)	41 / 366 (11.20%)
occurrences (all)	51	44	70
Gingival bleeding			
subjects affected / exposed	31 / 361 (8.59%)	4 / 353 (1.13%)	25 / 366 (6.83%)
occurrences (all)	50	5	44
Haemorrhoids			
subjects affected / exposed	12 / 361 (3.32%)	9 / 353 (2.55%)	22 / 366 (6.01%)
occurrences (all)	20	9	44
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	26 / 361 (7.20%)	212 / 353 (60.06%)	33 / 366 (9.02%)
occurrences (all)	28	250	34
Rash			
subjects affected / exposed	62 / 361 (17.17%)	86 / 353 (24.36%)	89 / 366 (24.32%)
occurrences (all)	109	150	139
Pruritus			
subjects affected / exposed	28 / 361 (7.76%)	32 / 353 (9.07%)	51 / 366 (13.93%)
occurrences (all)	46	40	85
Nail disorder			
subjects affected / exposed	11 / 361 (3.05%)	39 / 353 (11.05%)	19 / 366 (5.19%)
occurrences (all)	12	45	20
Dry skin			
subjects affected / exposed	24 / 361 (6.65%)	24 / 353 (6.80%)	29 / 366 (7.92%)
occurrences (all)	26	30	41
Erythema			
subjects affected / exposed	13 / 361 (3.60%)	24 / 353 (6.80%)	20 / 366 (5.46%)
occurrences (all)	14	37	27
Dermatitis acneiform			
subjects affected / exposed	16 / 361 (4.43%)	6 / 353 (1.70%)	27 / 366 (7.38%)
occurrences (all)	16	6	41
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	6 / 361 (1.66%)	26 / 353 (7.37%)	11 / 366 (3.01%)
occurrences (all)	7	29	14
Nail discolouration			
subjects affected / exposed	5 / 361 (1.39%)	25 / 353 (7.08%)	1 / 366 (0.27%)
occurrences (all)	5	25	1
Onychoclasis			
subjects affected / exposed	19 / 361 (5.26%)	13 / 353 (3.68%)	17 / 366 (4.64%)
occurrences (all)	24	16	20
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	83 / 361 (22.99%)	91 / 353 (25.78%)	71 / 366 (19.40%)
occurrences (all)	138	145	103
Myalgia			
subjects affected / exposed	66 / 361 (18.28%)	82 / 353 (23.23%)	61 / 366 (16.67%)
occurrences (all)	152	163	117
Back pain			
subjects affected / exposed	60 / 361 (16.62%)	46 / 353 (13.03%)	63 / 366 (17.21%)
occurrences (all)	77	65	87
Pain in extremity			
subjects affected / exposed	53 / 361 (14.68%)	48 / 353 (13.60%)	54 / 366 (14.75%)
occurrences (all)	82	67	77
Muscle spasms			
subjects affected / exposed	32 / 361 (8.86%)	15 / 353 (4.25%)	62 / 366 (16.94%)
occurrences (all)	42	20	106
Musculoskeletal pain			
subjects affected / exposed	30 / 361 (8.31%)	23 / 353 (6.52%)	37 / 366 (10.11%)
occurrences (all)	38	29	50
Bone pain			
subjects affected / exposed	17 / 361 (4.71%)	33 / 353 (9.35%)	29 / 366 (7.92%)
occurrences (all)	21	51	69
Musculoskeletal chest pain			
subjects affected / exposed	13 / 361 (3.60%)	17 / 353 (4.82%)	20 / 366 (5.46%)
occurrences (all)	16	21	21
Neck Pain			

subjects affected / exposed	12 / 361 (3.32%)	12 / 353 (3.40%)	24 / 366 (6.56%)
occurrences (all)	13	13	31
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	50 / 361 (13.85%)	55 / 353 (15.58%)	66 / 366 (18.03%)
occurrences (all)	85	104	147
Nasopharyngitis			
subjects affected / exposed	52 / 361 (14.40%)	49 / 353 (13.88%)	66 / 366 (18.03%)
occurrences (all)	87	100	147
Urinary tract infection			
subjects affected / exposed	31 / 361 (8.59%)	29 / 353 (8.22%)	41 / 366 (11.20%)
occurrences (all)	55	43	72
Rhinitis			
subjects affected / exposed	25 / 361 (6.93%)	18 / 353 (5.10%)	24 / 366 (6.56%)
occurrences (all)	29	23	32
Influenza			
subjects affected / exposed	22 / 361 (6.09%)	14 / 353 (3.97%)	25 / 366 (6.83%)
occurrences (all)	24	19	36
Paronychia			
subjects affected / exposed	8 / 361 (2.22%)	22 / 353 (6.23%)	30 / 366 (8.20%)
occurrences (all)	11	31	56
Pharyngitis			
subjects affected / exposed	19 / 361 (5.26%)	14 / 353 (3.97%)	17 / 366 (4.64%)
occurrences (all)	21	14	18
Conjunctivitis			
subjects affected / exposed	14 / 361 (3.88%)	21 / 353 (5.95%)	17 / 366 (4.64%)
occurrences (all)	18	25	20
Bronchitis			
alternative assessment type: Systematic			
subjects affected / exposed	9 / 361 (2.49%)	14 / 353 (3.97%)	20 / 366 (5.46%)
occurrences (all)	9	15	22
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	84 / 361 (23.27%)	76 / 353 (21.53%)	84 / 366 (22.95%)
occurrences (all)	164	129	156
Hypokalaemia			

subjects affected / exposed occurrences (all)	19 / 361 (5.26%) 23	15 / 353 (4.25%) 18	30 / 366 (8.20%) 40

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2011	Updates to the protocol included truncation of OS at 2 years as a secondary endpoint, addition of several quality of life assessments including FACT instruments, changes in the assessment schedule, clarification of the study population and eligibility criteria, and addition of treatment guidelines for cases of study drug discontinuation.
11 October 2011	The protocol was amended to remove an interim futility analysis and to specify the new nonproprietary name 'trastuzumab emtansine' (formerly T-DM1).
29 May 2013	The protocol was revised in order to allow for formal comparison of both trastuzumab emtansine arms, specify statistical assumptions, evaluate OS within high and low HER2 mRNA subsets, remove the clinical benefit rate (CR/PR/SD) as a redundant secondary endpoint, clarify committee procedures, further update the schedule of assessments, and add the option for subjects to cross over to the best treatment arm if OS was more favorable in one of the trastuzumab emtansine arms.
01 November 2013	The protocol was modified to add safety guidance on hepatotoxicity, including updated language for hemorrhage and Hy's Law.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported