



Clinical trial results:

A Two-Cohort, Open-Label, Multicenter, Study of Trastuzumab Emtansine (T-DM1) in HER2-Positive Locally Advanced or Metastatic Breast Cancer Patients Who Have Received Prior Anti-HER2 and Chemotherapy-Based Treatment

Summary

EudraCT number	2012-001628-37
Trial protocol	DE BE ES SE GB DK HU PT NO AT FI IT GR IE SI BG NL EE IS
Global end of trial date	31 July 2020

Results information

Result version number	v2 (current)
This version publication date	30 July 2021
First version publication date	14 October 2017

Version creation reason

Trial information

Trial identification

Sponsor protocol code	MO28231
-----------------------	---------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01702571
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 July 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To gain better understanding of the safety profile of trastuzumab emtansine in this study the safety and tolerability of trastuzumab emtansine was investigated in human epidermal growth factor receptor 2 (HER2)-positive locally advanced breast cancer (LABC) and metastatic breast cancer (mBC) patients who had received prior anti-HER2 and chemotherapy-based treatment.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 515
Country: Number of subjects enrolled	Spain: 182
Country: Number of subjects enrolled	United Kingdom: 164
Country: Number of subjects enrolled	Italy: 153
Country: Number of subjects enrolled	Germany: 120
Country: Number of subjects enrolled	Turkey: 71
Country: Number of subjects enrolled	Poland: 55
Country: Number of subjects enrolled	Netherlands: 54
Country: Number of subjects enrolled	Brazil: 50
Country: Number of subjects enrolled	Canada: 50
Country: Number of subjects enrolled	Mexico: 48
Country: Number of subjects enrolled	Australia: 46
Country: Number of subjects enrolled	Ireland: 45
Country: Number of subjects enrolled	Portugal: 39
Country: Number of subjects enrolled	Belgium: 36
Country: Number of subjects enrolled	Denmark: 34
Country: Number of subjects enrolled	Greece: 31
Country: Number of subjects enrolled	Hungary: 30
Country: Number of subjects enrolled	Norway: 24
Country: Number of subjects enrolled	Taiwan: 22

Country: Number of subjects enrolled	Austria: 21
Country: Number of subjects enrolled	Bulgaria: 20
Country: Number of subjects enrolled	Finland: 20
Country: Number of subjects enrolled	Panama: 17
Country: Number of subjects enrolled	Slovenia: 17
Country: Number of subjects enrolled	Sweden: 16
Country: Number of subjects enrolled	Slovakia: 15
Country: Number of subjects enrolled	Argentina: 14
Country: Number of subjects enrolled	Peru: 12
Country: Number of subjects enrolled	Croatia: 8
Country: Number of subjects enrolled	Ecuador: 7
Country: Number of subjects enrolled	Estonia: 7
Country: Number of subjects enrolled	Guatemala: 7
Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Iceland: 4
Country: Number of subjects enrolled	Luxembourg: 4
Country: Number of subjects enrolled	United Arab Emirates: 4
Country: Number of subjects enrolled	Dominican Republic: 1
Country: Number of subjects enrolled	China: 155
Country: Number of subjects enrolled	Indonesia: 12
Country: Number of subjects enrolled	Korea, Republic of: 25
Country: Number of subjects enrolled	Thailand: 15
Country: Number of subjects enrolled	Venezuela, Bolivarian Republic of: 10
Worldwide total number of subjects	2185
EEA total number of subjects	1450

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)	1802
From 65 to 84 years	379
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

For one participant, the site incorrectly answered the question 'Did the participant complete follow-up as per protocol?' It was answered No, however the participant was in survival follow-up and the site should have answered Yes. This participant is wrongly counted in the 'discontinued from study' number.

Pre-assignment

Screening details:

Subjects with HER2-positive disease with invasive breast cancer and prior treatment (both chemotherapy, alone or with another agent, and an anti-HER2 agent, alone or with another agent) with disease progression during or after the most recent treatment for LABC/mBC or within 6 months of completing adjuvant therapy were included in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Trastuzumab Emtansine (All Participants)

Arm description:

This cohort (Cohort 1) enrolled all subjects with human epidermal growth factor receptor 2 (HER2) positive, unresectable, locally advanced breast cancer (LABC) or metastatic breast cancer (mBC) who had received prior anti-HER2 and chemotherapy treatment and had progressed on or after the most recent treatment for LABC or mBC, or within 6 months of completing adjuvant therapy. Subjects received trastuzumab emtansine every 3 weeks until unacceptable toxicity, withdrawal of consent, or disease progression.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab emtansine
Investigational medicinal product code	
Other name	RO5304020, T-DM1, Kadcyla,
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received trastuzumab emtansine 3.6 milligrams per kilogram (mg/kg) intravenously (IV) on Day 1 of a 3-week cycle every 3 weeks until unacceptable toxicity, withdrawal of consent, or disease progression.

Arm title	Trastuzumab Emtansine (Asian Participants)
------------------	--

Arm description:

This cohort (Cohort 2) enrolled Asian race participants with HER2-positive, unresectable, LABC or mBC who had received prior anti-HER2 and chemotherapy treatment and had progressed on or after the most recent treatment for LABC or mBC, or within 6 months of completing adjuvant therapy. Participants received trastuzumab emtansine every 3 weeks until unacceptable toxicity, withdrawal of consent, or disease progression.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab emtansine
Investigational medicinal product code	
Other name	RO5304020, T-DM1, Kadcyla,
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received trastuzumab emtansine 3.6 milligrams per kilogram (mg/kg) intravenously (IV) on

Day 1 of a 3-week cycle every 3 weeks until unacceptable toxicity, withdrawal of consent, or disease progression.

Number of subjects in period 1	Trastuzumab Emtansine (All Participants)	Trastuzumab Emtansine (Asian Participants)
Started	2003	182
Completed	494	65
Not completed	1509	117
On Study Treatment At Lplv/Cohort 1	93	-
On Study Treatment At Lplv/Cohort 2	-	1
Not Classifiable	1	-
Death	1067	76
Lost to Follow-up	144	10
Adverse Event/Unacceptable Toxicity	4	-
Progressive Disease	3	-
Termination By Sponsor	4	-
Withdrawal by Subject	177	29
Investigator Decision	5	-
Protocol Violation	2	-
Safety FU Done < 3 Months Prior To CCOD	9	1

Baseline characteristics

Reporting groups

Reporting group title	Trastuzumab Emtansine (All Participants)
-----------------------	--

Reporting group description:

This cohort (Cohort 1) enrolled all subjects with human epidermal growth factor receptor 2 (HER2) positive, unresectable, locally advanced breast cancer (LABC) or metastatic breast cancer (mBC) who had received prior anti-HER2 and chemotherapy treatment and had progressed on or after the most recent treatment for LABC or mBC, or within 6 months of completing adjuvant therapy. Subjects received trastuzumab emtansine every 3 weeks until unacceptable toxicity, withdrawal of consent, or disease progression.

Reporting group title	Trastuzumab Emtansine (Asian Participants)
-----------------------	--

Reporting group description:

This cohort (Cohort 2) enrolled Asian race participants with HER2-positive, unresectable, LABC or mBC who had received prior anti-HER2 and chemotherapy treatment and had progressed on or after the most recent treatment for LABC or mBC, or within 6 months of completing adjuvant therapy. Participants received trastuzumab emtansine every 3 weeks until unacceptable toxicity, withdrawal of consent, or disease progression.

Reporting group values	Trastuzumab Emtansine (All Participants)	Trastuzumab Emtansine (Asian Participants)	Total
Number of subjects	2003	182	2185
Age categorical Units: Subjects			
Preterm newborn infants (gestational age <37 weeks)	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)	1630	172	1802
From 65-84 years	369	10	379
85 years and over	4	0	4
Age Continuous Units: years			
arithmetic mean	54.5	49.1	
standard deviation	± 11.35	± 10.1	-
Gender, Male/Female Units: Subjects			
Female	1989	182	2171
Male	14	0	14
Race Units: Subjects			
Caucasian	1397	0	1397
Black	21	0	21
Asian	72	182	254
Native American	41	0	41
N/A as per local regulation	466	0	466
Unknown	3	0	3
Other	2	0	2
Missing	1	0	1

Ethnicity			
Units: Subjects			
Hispanic/Latino	300	0	300
Chinese	29	147	176
N/A as per local regulation	997	16	1013
Other	417	19	436
Mixed	9	0	9
Indian (Indian subcontinent)	4	0	4
Unknown	247	0	247

End points

End points reporting groups

Reporting group title	Trastuzumab Emtansine (All Participants)
Reporting group description: This cohort (Cohort 1) enrolled all subjects with human epidermal growth factor receptor 2 (HER2) positive, unresectable, locally advanced breast cancer (LABC) or metastatic breast cancer (mBC) who had received prior anti-HER2 and chemotherapy treatment and had progressed on or after the most recent treatment for LABC or mBC, or within 6 months of completing adjuvant therapy. Subjects received trastuzumab emtansine every 3 weeks until unacceptable toxicity, withdrawal of consent, or disease progression.	
Reporting group title	Trastuzumab Emtansine (Asian Participants)
Reporting group description: This cohort (Cohort 2) enrolled Asian race participants with HER2-positive, unresectable, LABC or mBC who had received prior anti-HER2 and chemotherapy treatment and had progressed on or after the most recent treatment for LABC or mBC, or within 6 months of completing adjuvant therapy. Participants received trastuzumab emtansine every 3 weeks until unacceptable toxicity, withdrawal of consent, or disease progression.	

Primary: Percentage of Participants with Adverse Events of Primary Interest (AEPIs)

End point title	Percentage of Participants with Adverse Events of Primary Interest (AEPIs) ^[1]
End point description: The AEPIs in this study were defined as the following: adverse events (AEs) Grade ≥ 3 , specifically, hepatic events, allergic reactions, thrombocytopenia and hemorrhage events, all Grade ≥ 3 AEs related to trastuzumab emtansine and pneumonitis events of all grades. The safety population included all participants who had received at least 1 dose of study medication.	
End point type	Primary
End point timeframe: Baseline up to approximately 7 years	
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: Statistical analysis is not applicable to this study.	

End point values	Trastuzumab Emtansine (All Participants)	Trastuzumab Emtansine (Asian Participants)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2002	181		
Units: Percentage of Participants				
number (confidence interval 95%)	23.1 (21.2 to 25.0)	51.4 (43.9 to 58.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Specific AEPIs

End point title	Percentage of Participants with Specific AEPIs
End point description: The AEPIs in this study were defined as the following: adverse events (AEs) Grade ≥ 3 , specifically, hepatic events, allergic reactions, thrombocytopenia and hemorrhage events, all Grade ≥ 3 AEs related to trastuzumab emtansine and pneumonitis events of all grades. The safety population included all participants who had received at least 1 dose of study medication.	
End point type	Secondary
End point timeframe: Baseline up to approximately 7 years	

End point values	Trastuzumab Emtansine (All Participants)	Trastuzumab Emtansine (Asian Participants)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2002	181		
Units: Percentage of Participants				
number (not applicable)				
AEs Grade ≥ 3 for hepatic events	6.9	12.2		
AEs Grade ≥ 3 for allergic reactions	2.3	1.1		
AEs Grade ≥ 3 for thrombocytopenia	3.7	36.5		
AEs Grade ≥ 3 for hemorrhage events	2.3	1.7		
AEs Grade ≥ 3 related to trastuzumab emtansine	18.4	48.6		
Pneumonitis of all grades	1.0	2.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adverse Events of Special Interest (AESIs)

End point title	Percentage of Participants with Adverse Events of Special Interest (AESIs)
End point description: AESIs included: 1) Potential drug-induced liver injury, which included any potential case of drug-induced liver injury as, assessed by laboratory criteria for Hy's law (AST and/or ALT elevations that were $>3 \times$ ULN, Concurrent elevation of total bilirubin $>2 \times$ ULN (or clinical jaundice if total bilirubin measures were not available), except in participants with documented Gilbert's syndrome. Those with Gilbert's syndrome, elevation of direct bilirubin $>2 \times$ ULN was used instead. 2) Suspected transmission of an infectious agent by study drug was defined as any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic. A transmission of an infectious agent suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a medicinal product. The safety population included all participants who had received at least 1 dose of study medication.	
End point type	Secondary
End point timeframe: Baseline up to approximately 7 years	

End point values	Trastuzumab Emtansine (All Participants)	Trastuzumab Emtansine (Asian Participants)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2002	181		
Units: Percentage of Participants				
number (not applicable)				
Potential drug-induced liver injury	1.2	1.1		
Suspected transmission of an infectious agent	0.2	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival According to Response Evaluation for Solid Tumors (RECIST) Version (v) 1.1 As Per Investigator Assessment

End point title	Progression-Free Survival According to Response Evaluation for Solid Tumors (RECIST) Version (v) 1.1 As Per Investigator Assessment
-----------------	---

End point description:

Progression free survival is defined as the time (in months) between the date of first dose and the date of disease progression or death from any cause. Progressive disease (PD) is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 millimeters (mm). Intent to Treat (ITT) population included all participants enrolled in the study.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline up to disease progression or death due to any cause, whichever occurs first (assessed every 12 weeks during treatment period thereafter 28-42 days after the last dose or every 3-6 months up to approximately 7 years)

End point values	Trastuzumab Emtansine (All Participants)	Trastuzumab Emtansine (Asian Participants)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2003	182		
Units: months				
median (confidence interval 95%)	6.8 (5.8 to 7.6)	5.7 (5.5 to 7.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
End point description: Overall survival is defined as time to death, which is the time from the date of dosing until the date of death, regardless of the cause of death. ITT Population included all participants enrolled in the study. The value of 9999999 means that the CI has no upper limit.	
End point type	Secondary
End point timeframe: Baseline until death (up to approximately 7 years)	

End point values	Trastuzumab Emtansine (All Participants)	Trastuzumab Emtansine (Asian Participants)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2003	182		
Units: months				
median (confidence interval 95%)	27.2 (25.5 to 28.7)	29.5 (21.1 to 9999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Best Overall Response (Complete Response [CR] or Partial Response [PR]) According to RECIST v 1.1 As Per Investigator Assessment

End point title	Percentage of Participants with Best Overall Response (Complete Response [CR] or Partial Response [PR]) According to RECIST v 1.1 As Per Investigator Assessment
End point description: Best Overall Response reported here is the Best confirmed Overall Response. To be assigned a status of PR or CR, i.e., to be a responder, changes in tumor measurements had to be confirmed by repeat assessments that had to be performed no less than 4 weeks after the criteria for response were first met, i.e., subjects needed to have two consecutive assessments of PR or CR. CR: disappearance of all target lesions. PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. ITT population included all participants enrolled in the study. Only participants with measurable disease were included in the analysis.	
End point type	Secondary
End point timeframe: Baseline up to disease progression or death due to any cause, whichever occurs first (assessed every 12 weeks during treatment period thereafter 28-42 days after the last dose or every 3-6 months up to approximately 7 years)	

End point values	Trastuzumab Emtansine (All Participants)	Trastuzumab Emtansine (Asian Participants)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1613	169		
Units: Percentage of Participants				
number (confidence interval 95%)	29.3 (27.1 to 31.6)	29.6 (22.8 to 37.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Clinical Benefit (CR or PR or Stable Disease [SD]) According to RECIST v 1.1

End point title	Percentage of Participants with Clinical Benefit (CR or PR or Stable Disease [SD]) According to RECIST v 1.1
-----------------	--

End point description:

Clinical Benefit was defined as CR plus PR plus SD. CR: disappearance of all target lesions. PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. SD: neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD. ITT population included all participants enrolled in the study. Only participants with measurable disease were included in the analysis.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline up to disease progression or death due to any cause, whichever occurs first (assessed every 12 weeks during treatment period thereafter 28-42 days after the last dose or every 3-6 months up to approximately 47 months)

End point values	Trastuzumab Emtansine (All Participants)	Trastuzumab Emtansine (Asian Participants)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1613	169		
Units: Percentage of Participants				
number (confidence interval 95%)	47.1 (44.7 to 49.6)	39.6 (32.2 to 47.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) According to RECIST v 1.1

End point title	Duration of Response (DOR) According to RECIST v 1.1
-----------------	--

End point description:

DOR is defined as the period from the date of initial confirmed PR or CR (whichever occurs first) until the date of PD or death from any cause. CR: disappearance of all target lesions. PR: At least a 30%

decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 millimeters (mm). ITT population included all participants enrolled in the study. Only participants with measurable disease were included in the analysis.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline up to disease progression or death due to any cause, whichever occurs first (assessed every 12 weeks during treatment period thereafter 28-42 days after the last dose or every 3-6 months up to approximately 47 months)

End point values	Trastuzumab Emtansine (All Participants)	Trastuzumab Emtansine (Asian Participants)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1613	169		
Units: months				
median (confidence interval 95%)	13.8 (12.2 to 15.0)	14.2 (11.1 to 24.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response According to RECIST v 1.1

End point title	Time to Response According to RECIST v 1.1
-----------------	--

End point description:

Time to Response is defined as the time from first dose to first documentation of confirmed PR or CR (whichever occurs first). CR: disappearance of all target lesions. PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. ITT population included all participants enrolled in the study. Only responders were included in the analysis. The value of 9999999 means that the CI has no upper limit.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline up to disease progression or death due to any cause, whichever occurs first (assessed every 12 weeks during treatment period thereafter 28-42 days after the last dose or every 3-6 months up to approximately 47 months)

End point values	Trastuzumab Emtansine (All Participants)	Trastuzumab Emtansine (Asian Participants)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	473	50		
Units: months				
median (confidence interval 95%)	22.3 (11.8 to 38.2)	8.3 (5.7 to 9999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Hospital Visits

End point title	Number of Hospital Visits
-----------------	---------------------------

End point description:

The number of hospital visits were recorded to evaluate the resource expenditures while participants were on study treatment.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline up to approximately 7 years

End point values	Trastuzumab Emtansine (All Participants)	Trastuzumab Emtansine (Asian Participants)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2002	181		
Units: Number of Hospital Visits				
arithmetic mean (standard deviation)	2.7 ($\pm$ 2.78)	2.1 ($\pm$ 1.70)		

Statistical analyses

No statistical analyses for this end point

Secondary: Type of Hospital Visits

End point title	Type of Hospital Visits
-----------------	-------------------------

End point description:

The type of hospital visits (intensive care unit (ICU) versus other) were recorded to evaluate the resource expenditures while participants were on study treatment. The number of participants with at least one ICU visit are based on the number of participants with at least one hospital visit, in each group.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline up to approximately 7 years

End point values	Trastuzumab Emtansine (All Participants)	Trastuzumab Emtansine (Asian Participants)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2002	181		
Units: Participants				
number (not applicable)				
Other Hospital Visit	558	33		
ICU Visit	39	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to approximately 7 years

Adverse event reporting additional description:

The analysis of AEs focused on treatment-emergent AEs (TEAEs) which were AEs that occurred on the day of or after first administration of study drug.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	22.1
--------------------	------

Reporting groups

Reporting group title	Trastuzumab Emtansine (All Participants)
-----------------------	--

Reporting group description:

This cohort (Cohort 1) enrolled all participants with HER2 positive, unresectable, LABC or mBC who had received prior anti-HER2 and chemotherapy treatment and had progressed on or after the most recent treatment for LABC or mBC, or within 6 months of completing adjuvant therapy. Participants received trastuzumab emtansine every 3 weeks until unacceptable toxicity, withdrawal of consent, or disease progression.

Reporting group title	Trastuzumab Emtansine (Asian Participants)
-----------------------	--

Reporting group description:

This cohort (Cohort 2) enrolled Asian race participants with HER2-positive, unresectable, LABC or mBC who had received prior anti-HER2 and chemotherapy treatment and had progressed on or after the most recent treatment for LABC or mBC, or within 6 months of completing adjuvant therapy. Participants received trastuzumab emtansine every 3 weeks until unacceptable toxicity, withdrawal of consent, or disease progression.

Serious adverse events	Trastuzumab Emtansine (All Participants)	Trastuzumab Emtansine (Asian Participants)	
Total subjects affected by serious adverse events			
subjects affected / exposed	427 / 2002 (21.33%)	36 / 181 (19.89%)	
number of deaths (all causes)	1072	77	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BENIGN NEOPLASM			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

BREAST CANCER METASTATIC			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CANCER PAIN			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT MELANOMA			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENINGIOMA			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTASES TO BONE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTATIC UTERINE CANCER			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
NAEVUS HAEMORRHAGE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SARCOMA			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN NEOPLASM BLEEDING			

subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
CIRCULATORY COLLAPSE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLISM			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
HAEMATOMA			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENA CAVA THROMBOSIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENOUS THROMBOSIS LIMB			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

BREAST CONSERVING SURGERY			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SCAR EXCISION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CATHETER SITE ERYTHEMA			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHILLS			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEATH			
subjects affected / exposed	5 / 2002 (0.25%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 0	
FATIGUE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	4 / 2002 (0.20%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

HYPERTHERMIA			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMPLANT SITE DEHISCENCE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLAMMATION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALAISE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTIPLE ORGAN DYSFUNCTION SYNDROME			
subjects affected / exposed	3 / 2002 (0.15%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
PYREXIA			
subjects affected / exposed	13 / 2002 (0.65%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	30 / 42	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUDDEN DEATH			
subjects affected / exposed	0 / 2002 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			

ALLERGIC OEDEMA			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERSENSITIVITY			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
CYSTOCELE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
METRORRHAGIA			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UTERINE HAEMORRHAGE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UTERINE POLYP			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VAGINAL HAEMORRHAGE			
subjects affected / exposed	1 / 2002 (0.05%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE PULMONARY OEDEMA			

subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPIRATION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASTHMATIC CRISIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOKING			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
DYSPNOEA			
subjects affected / exposed	7 / 2002 (0.35%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	6 / 24	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
EPISTAXIS			
subjects affected / exposed	7 / 2002 (0.35%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	3 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOPTYSIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	4 / 2002 (0.20%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PLEURAL EFFUSION			

subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURITIC PAIN			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
subjects affected / exposed	6 / 2002 (0.30%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	4 / 6	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
PNEUMOTHORAX			
subjects affected / exposed	5 / 2002 (0.25%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY ALVEOLAR HAEMORRHAGE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PULMONARY FIBROSIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PULMONARY OEDEMA			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY DISTRESS			

subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	1 / 2002 (0.05%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
RESPIRATORY TRACT HAEMORRHAGE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SLEEP APNOEA SYNDROME			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
AGITATION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANXIETY			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COMPLETED SUICIDE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CONFUSIONAL STATE			
subjects affected / exposed	4 / 2002 (0.20%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEPRESSION			

subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HALLUCINATION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
DEVICE BREAKAGE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE EXTRUSION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE LOOSENING			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
AMYLASE INCREASED			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	2 / 2002 (0.10%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ECG SIGNS OF MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC ENZYME INCREASED			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIVER FUNCTION TEST ABNORMAL			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIVER FUNCTION TEST INCREASED			
subjects affected / exposed	0 / 2002 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLATELET COUNT DECREASED			
subjects affected / exposed	2 / 2002 (0.10%)	8 / 181 (4.42%)	
occurrences causally related to treatment / all	2 / 2	12 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSAMINASES INCREASED			

subjects affected / exposed	0 / 2002 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
ANASTOMOTIC ULCER			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANKLE FRACTURE			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FALL			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL NECK FRACTURE			
subjects affected / exposed	4 / 2002 (0.20%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR FRACTURE			
subjects affected / exposed	8 / 2002 (0.40%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FOREARM FRACTURE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAND FRACTURE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEAD INJURY			

subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIP FRACTURE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMERUS FRACTURE			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFUSION RELATED REACTION			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTENTIONAL OVERDOSE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUMBAR VERTEBRAL FRACTURE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PELVIC FRACTURE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIATION NECROSIS			

subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
RIB FRACTURE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ROAD TRAFFIC ACCIDENT			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
SKELETAL INJURY			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPLENIC INJURY			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBDURAL HAEMATOMA			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THERMAL BURN			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER LIMB FRACTURE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WRIST FRACTURE			

subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	3 / 2002 (0.15%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANGINA PECTORIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CARDIAC FAILURE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC TAMPONADE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PALPITATIONS			
subjects affected / exposed	1 / 2002 (0.05%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERICARDIAL EFFUSION			

subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
APHASIA			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATAXIA			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRAIN OEDEMA			
subjects affected / exposed	6 / 2002 (0.30%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	2 / 7	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
CENTRAL NERVOUS SYSTEM NECROSIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	4 / 2002 (0.20%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	4 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL ISCHAEMIA			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			

subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIZZINESS			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPILEPSY			
subjects affected / exposed	8 / 2002 (0.40%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 15	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	2 / 6	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
HAEMORRHAGIC STROKE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEADACHE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEMIPARESIS			
subjects affected / exposed	5 / 2002 (0.25%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IIIRD NERVE PARESIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEUKOENCEPHALOPATHY			

subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MIGRAINE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MOTOR DYSFUNCTION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NERVOUS SYSTEM DISORDER			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARTIAL SEIZURES			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PRESYNCOPE			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SCIATICA			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEIZURE			
subjects affected / exposed	7 / 2002 (0.35%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 11	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			

subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOCAL CORD PARALYSIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	13 / 2002 (0.65%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	8 / 14	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE MARROW FAILURE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DISSEMINATED INTRAVASCULAR COAGULATION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	11 / 2002 (0.55%)	10 / 181 (5.52%)	
occurrences causally related to treatment / all	11 / 11	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye disorders			
BLINDNESS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CATARACT			
subjects affected / exposed	0 / 2002 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RETINAL VEIN THROMBOSIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN			
subjects affected / exposed	4 / 2002 (0.20%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	2 / 12	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAL FISSURE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAL HAEMORRHAGE			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

ASCITES			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	3 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	4 / 2002 (0.20%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL ULCER			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL ULCER HAEMORRHAGE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPHAGIA			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ANTRAL VASCULAR ECTASIA			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC HAEMORRHAGE			

subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	2 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ULCER			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS EROSIIVE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRODUODENAL ULCER			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	6 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GINGIVAL BLEEDING			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GLOSSITIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL OBSTRUCTION			

subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 2002 (0.05%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MELAENA			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	4 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	5 / 2002 (0.25%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	5 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL FISTULA			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL VARICES HAEMORRHAGE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS ACUTE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIODONTAL DISEASE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROCTALGIA			

subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL HAEMORRHAGE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STOMATITIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBILEUS			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOOTH LOSS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	3 / 2002 (0.15%)	2 / 181 (1.10%)	
occurrences causally related to treatment / all	2 / 6	4 / 6	
deaths causally related to treatment / all	0 / 2	0 / 0	
VOMITING			

subjects affected / exposed	17 / 2002 (0.85%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	10 / 19	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLESTASIS			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DRUG-INDUCED LIVER INJURY			
subjects affected / exposed	1 / 2002 (0.05%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 3	0 / 0	
HEPATIC FAILURE			
subjects affected / exposed	5 / 2002 (0.25%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	2 / 10	0 / 0	
deaths causally related to treatment / all	0 / 6	0 / 0	
HEPATIC FUNCTION ABNORMAL			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
HEPATIC PAIN			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATOTOXICITY			
subjects affected / exposed	7 / 2002 (0.35%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	10 / 14	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
JAUNDICE			

subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NODULAR REGENERATIVE HYPERPLASIA			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NON-CIRRHOTIC PORTAL HYPERTENSION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PORTAL HYPERTENSION			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
SPIDER NAEVUS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
HAEMATURIA			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEPHROLITHIASIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

RENAL COLIC			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	4 / 2002 (0.20%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
RENAL INJURY			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT OBSTRUCTION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
ADRENAL INSUFFICIENCY			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTHYROIDISM			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACK PAIN			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

BONE LESION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE PAIN			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATOMA MUSCLE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
KYPHOSIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MOBILITY DECREASED			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEONECROSIS OF JAW			

subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN IN EXTREMITY			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PATHOLOGICAL FRACTURE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL PAIN			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYSTEMIC LUPUS ERYTHEMATOSUS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ABSCCESS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACINETOBACTER INFECTION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTHRITIS INFECTIVE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERAEEMIA			

subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERIAL INFECTION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERIAL SEPSIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRAIN ABSCESS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST CELLULITIS			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CATHETER SITE INFECTION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	8 / 2002 (0.40%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE COLITIS			

subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTITIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DENGUE HAEMORRHAGIC FEVER			
subjects affected / exposed	0 / 2002 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
subjects affected / exposed	6 / 2002 (0.30%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENCEPHALITIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENDOCARDITIS			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed	4 / 2002 (0.20%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS NOROVIRUS			

subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS VIRAL			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL VIRAL INFECTION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIOUS PLEURAL EFFUSION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
INFECTIVE EXACERBATION OF BRONCHIECTASIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERVERTEBRAL DISCITIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
KLEBSIELLA BACTERAEMIA			

subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LISTERIOSIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIVER ABSCESS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	9 / 2002 (0.45%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MASTITIS			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENINGITIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OTITIS MEDIA			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERITONITIS			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
PHARYNGITIS			

subjects affected / exposed	1 / 2002 (0.05%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOCOCCAL INFECTION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	22 / 2002 (1.10%)	8 / 181 (4.42%)	
occurrences causally related to treatment / all	2 / 23	3 / 8	
deaths causally related to treatment / all	0 / 2	0 / 1	
PNEUMONIA STREPTOCOCCAL			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA VIRAL			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS ACUTE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS CHRONIC			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			

subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION VIRAL			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	9 / 2002 (0.45%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 9	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
SEPTIC SHOCK			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN INFECTION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SOFT TISSUE INFECTION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL BACTERAEMIA			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL SEPSIS			

subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STREPTOCOCCAL INFECTION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRACHEOBRONCHITIS			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	11 / 2002 (0.55%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 12	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULAR DEVICE INFECTION			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL INFECTION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VULVAL ABSCESS			

subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	2 / 2002 (0.10%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FAILURE TO THRIVE			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
HYPERCALCAEMIA			
subjects affected / exposed	3 / 2002 (0.15%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERURICAEMIA			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOGLYCAEMIA			
subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
subjects affected / exposed	1 / 2002 (0.05%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			

subjects affected / exposed	1 / 2002 (0.05%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Trastuzumab Emtansine (All Participants)	Trastuzumab Emtansine (Asian Participants)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1734 / 2002 (86.61%)	170 / 181 (93.92%)	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	86 / 2002 (4.30%)	58 / 181 (32.04%)	
occurrences (all)	100	133	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	136 / 2002 (6.79%)	77 / 181 (42.54%)	
occurrences (all)	156	143	
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	52 / 2002 (2.60%)	14 / 181 (7.73%)	
occurrences (all)	52	16	
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	89 / 2002 (4.45%)	30 / 181 (16.57%)	
occurrences (all)	171	85	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	84 / 2002 (4.20%)	21 / 181 (11.60%)	
occurrences (all)	94	31	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	36 / 2002 (1.80%)	20 / 181 (11.05%)	
occurrences (all)	58	84	
PLATELET COUNT DECREASED			
subjects affected / exposed	91 / 2002 (4.55%)	55 / 181 (30.39%)	
occurrences (all)	124	191	
TRANSAMINASES INCREASED			

subjects affected / exposed occurrences (all)	27 / 2002 (1.35%) 28	18 / 181 (9.94%) 39	
WEIGHT DECREASED subjects affected / exposed occurrences (all)	106 / 2002 (5.29%) 109	8 / 181 (4.42%) 8	
WHITE BLOOD CELL COUNT DECREASED subjects affected / exposed occurrences (all)	11 / 2002 (0.55%) 13	20 / 181 (11.05%) 85	
Vascular disorders HYPERTENSION subjects affected / exposed occurrences (all)	96 / 2002 (4.80%) 113	12 / 181 (6.63%) 17	
Nervous system disorders DIZZINESS subjects affected / exposed occurrences (all)	117 / 2002 (5.84%) 137	11 / 181 (6.08%) 17	
HEADACHE subjects affected / exposed occurrences (all)	454 / 2002 (22.68%) 650	19 / 181 (10.50%) 32	
PARAESTHESIA subjects affected / exposed occurrences (all)	128 / 2002 (6.39%) 139	4 / 181 (2.21%) 5	
PERIPHERAL SENSORY NEUROPATHY subjects affected / exposed occurrences (all)	113 / 2002 (5.64%) 132	0 / 181 (0.00%) 0	
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all)	173 / 2002 (8.64%) 231	27 / 181 (14.92%) 49	
LEUKOPENIA subjects affected / exposed occurrences (all)	19 / 2002 (0.95%) 23	15 / 181 (8.29%) 69	
NEUTROPENIA subjects affected / exposed occurrences (all)	79 / 2002 (3.95%) 151	17 / 181 (9.39%) 72	
THROMBOCYTOPENIA			

subjects affected / exposed occurrences (all)	165 / 2002 (8.24%) 257	47 / 181 (25.97%) 157	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	491 / 2002 (24.53%)	18 / 181 (9.94%)	
occurrences (all)	828	44	
FATIGUE			
subjects affected / exposed	556 / 2002 (27.77%)	12 / 181 (6.63%)	
occurrences (all)	846	17	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	107 / 2002 (5.34%)	3 / 181 (1.66%)	
occurrences (all)	161	3	
OEDEMA PERIPHERAL			
subjects affected / exposed	102 / 2002 (5.09%)	6 / 181 (3.31%)	
occurrences (all)	115	10	
PAIN			
subjects affected / exposed	85 / 2002 (4.25%)	10 / 181 (5.52%)	
occurrences (all)	92	11	
PYREXIA			
subjects affected / exposed	339 / 2002 (16.93%)	47 / 181 (25.97%)	
occurrences (all)	1599	243	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	139 / 2002 (6.94%)	6 / 181 (3.31%)	
occurrences (all)	182	8	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	135 / 2002 (6.74%)	5 / 181 (2.76%)	
occurrences (all)	163	5	
CONSTIPATION			
subjects affected / exposed	394 / 2002 (19.68%)	10 / 181 (5.52%)	
occurrences (all)	568	38	
DIARRHOEA			
subjects affected / exposed	252 / 2002 (12.59%)	9 / 181 (4.97%)	
occurrences (all)	376	9	
DRY MOUTH			

subjects affected / exposed	283 / 2002 (14.14%)	7 / 181 (3.87%)	
occurrences (all)	303	13	
GINGIVAL BLEEDING			
subjects affected / exposed	83 / 2002 (4.15%)	14 / 181 (7.73%)	
occurrences (all)	96	19	
NAUSEA			
subjects affected / exposed	651 / 2002 (32.52%)	28 / 181 (15.47%)	
occurrences (all)	1204	45	
STOMATITIS			
subjects affected / exposed	160 / 2002 (7.99%)	4 / 181 (2.21%)	
occurrences (all)	213	6	
VOMITING			
subjects affected / exposed	294 / 2002 (14.69%)	17 / 181 (9.39%)	
occurrences (all)	408	24	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	220 / 2002 (10.99%)	23 / 181 (12.71%)	
occurrences (all)	256	28	
DYSPNOEA			
subjects affected / exposed	211 / 2002 (10.54%)	2 / 181 (1.10%)	
occurrences (all)	705	6	
EPISTAXIS			
subjects affected / exposed	402 / 2002 (20.08%)	30 / 181 (16.57%)	
occurrences (all)	669	43	
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	118 / 2002 (5.89%)	11 / 181 (6.08%)	
occurrences (all)	134	13	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	265 / 2002 (13.24%)	6 / 181 (3.31%)	
occurrences (all)	349	7	
BACK PAIN			

subjects affected / exposed	199 / 2002 (9.94%)	5 / 181 (2.76%)	
occurrences (all)	226	5	
MUSCLE SPASMS			
subjects affected / exposed	124 / 2002 (6.19%)	1 / 181 (0.55%)	
occurrences (all)	154	1	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	135 / 2002 (6.74%)	3 / 181 (1.66%)	
occurrences (all)	150	3	
MYALGIA			
subjects affected / exposed	205 / 2002 (10.24%)	8 / 181 (4.42%)	
occurrences (all)	279	11	
PAIN IN EXTREMITY			
subjects affected / exposed	148 / 2002 (7.39%)	3 / 181 (1.66%)	
occurrences (all)	169	3	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	136 / 2002 (6.79%)	8 / 181 (4.42%)	
occurrences (all)	195	13	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	80 / 2002 (4.00%)	14 / 181 (7.73%)	
occurrences (all)	107	18	
URINARY TRACT INFECTION			
subjects affected / exposed	157 / 2002 (7.84%)	4 / 181 (2.21%)	
occurrences (all)	230	4	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	320 / 2002 (15.98%)	16 / 181 (8.84%)	
occurrences (all)	398	23	
HYPOALBUMINAEMIA			
subjects affected / exposed	13 / 2002 (0.65%)	11 / 181 (6.08%)	
occurrences (all)	13	14	
HYPOKALAEMIA			
subjects affected / exposed	73 / 2002 (3.65%)	19 / 181 (10.50%)	
occurrences (all)	91	37	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2012	This amendment included treatment discontinuation in participants who were diagnosed with pneumonitis; clarification that prospective HER2 analysis was not needed and that results from earlier immunohistochemistry/in-situ hybridization (IHC/ISH) assessments were acceptable; the Eastern Cooperative Oncology Group (ECOG) performance status table in Appendix 4 was amended to include Grade 0 and scale wording for grade 4 status.
11 February 2013	The reasons for this amendment include adjusting the target population definition to provide further clarification to investigators; inclusion criteria number 17 was updated to provide further clarification to investigator of the trastuzumab emtansine components and prevent possible participant hypersensitivity reaction; inclusion of the OS results of the Phase III Study TDM4370g (EMILIA); a subgroup analysis of >75 versus ≤ 75 years of age was added to be in line with other studies and Health Authority guidance; Safety data review by the independent Data Monitoring Committee (iDMC) after enrollment of approximately 50 participants was an interim safety analysis.
20 May 2013	In this amendment, the sample size was increased from 1000 to 2000 participants to further understand the trastuzumab emtansine safety profile.
29 January 2014	This amendment presented the inclusion of an additional cohort (Cohort 2) to further explore the higher incidence of thrombocytopenia in the Asian population. This cohort only recruited participants of Asian race.
18 July 2019	This protocol amendment included a clarification about post-trial access to the extension study; clarifications regarding traditional Chinese medicines was added; language was updated to reflect the revised pregnancy and post-study AE reporting.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported