Clinical trial results:
A Phase III Prospective, Two-Cohort Non-Randomized, Multi-Centre, Multinational, Open-Label Study to Assess the Safety of Assisted- and Self-Administered Subcutaneous Trastuzumab as Therapy in Patients With Operable HER2-Positive Early Breast Cancer (SafeHER)

Summary

EudraCT number	2011-005328-17
Trial protocol	IE CZ DE ES FR HU PT GB NO IT GR LT PL SI SK FI BG NL SE
Global end of trial date	

Results information

Result version number	v1
This version publication date	22 March 2017
First version publication date	22 March 2017

Trial information

Trial identification

Sponsor protocol code	MO28048

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01566721
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	10 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 March 2015
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

This multicenter, two-cohort, non-randomized, open-label study is designed to evaluate the safety and tolerability of assisted and self-administered subcutaneous (SC) Herceptin (trastuzumab) as adjuvant therapy in participants with early human epidermal growth factor receptor 2 (HER2)-positive breast cancer following tumor excision.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) guidelines according to the regulations and procedures described in the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 May 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Albania: 8
Country: Number of subjects enrolled	Algeria: 16
Country: Number of subjects enrolled	Argentina: 13
Country: Number of subjects enrolled	Australia: 54
Country: Number of subjects enrolled	Bosnia and Herzegovina: 5
Country: Number of subjects enrolled	Brazil: 31
Country: Number of subjects enrolled	Bulgaria: 16
Country: Number of subjects enrolled	Canada: 50
Country: Number of subjects enrolled	Chile: 25
Country: Number of subjects enrolled	Colombia: 6
Country: Number of subjects enrolled	Croatia: 7
Country: Number of subjects enrolled	Czech Republic: 68
Country: Number of subjects enrolled	Dominican Republic: 2
Country: Number of subjects enrolled	Ecuador: 13
Country: Number of subjects enrolled	Egypt: 34
Country: Number of subjects enrolled	El Salvador: 6
Country: Number of subjects enrolled	France: 224
Country: Number of subjects enrolled	Germany: 235
Country: Number of subjects enrolled	Greece: 64

Country: Number of subjects enrolled	Guatemala: 16
Country: Number of subjects enrolled	Hong Kong: 10
Country: Number of subjects enrolled	Hungary: 39
Country: Number of subjects enrolled	Indonesia: 61
Country: Number of subjects enrolled	Ireland: 26
Country: Number of subjects enrolled	Italy: 203
Country: Number of subjects enrolled	Korea, Republic of: 59
Country: Number of subjects enrolled	Lithuania: 12
Country: Number of subjects enrolled	Malaysia: 45
Country: Number of subjects enrolled	Mexico: 52
Country: Number of subjects enrolled	Morocco: 8
Country: Number of subjects enrolled	Netherlands: 81
Country: Number of subjects enrolled	New Zealand: 10
Country: Number of subjects enrolled	Norway: 29
Country: Number of subjects enrolled	Pakistan: 46
Country: Number of subjects enrolled	Panama: 8
Country: Number of subjects enrolled	Peru: 26
Country: Number of subjects enrolled	Philippines: 48
Country: Number of subjects enrolled	Poland: 48
Country: Number of subjects enrolled	Portugal: 26
Country: Number of subjects enrolled	Romania: 43
Country: Number of subjects enrolled	Russian Federation: 82
Country: Number of subjects enrolled	Saudi Arabia: 3
Country: Number of subjects enrolled	Serbia: 23
Country: Number of subjects enrolled	Singapore: 8
Country: Number of subjects enrolled	Slovakia: 19
Country: Number of subjects enrolled	Slovenia: 5
Country: Number of subjects enrolled	South Africa: 17
Country: Number of subjects enrolled	Spain: 161
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	Switzerland: 40
Country: Number of subjects enrolled	Taiwan: 32
Country: Number of subjects enrolled	Thailand: 28
Country: Number of subjects enrolled	Turkey: 47
Country: Number of subjects enrolled	Ukraine: 17
Country: Number of subjects enrolled	United Arab Emirates: 5
Country: Number of subjects enrolled	United Kingdom: 283
Country: Number of subjects enrolled	Uruguay: 3
Country: Number of subjects enrolled	Venezuela, Bolivarian Republic of: 5
Country: Number of subjects enrolled	Vietnam: 11
Worldwide total number of subjects	2577
EEA total number of subjects	1604

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	2090
From 65 to 84 years	483
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the 2984 participants screened, a total of 2577 participants were enrolled into the trial, and 2573 participants received at least one dose of study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A: SC Herceptin by Needle/Syringe

Arm description:

Participants received SC Herceptin by an assisted administration as 600 milligrams (mg) every 3 weeks for a total of 18 doses/cycles. Each dose of SC Herceptin was taken from a single-use vial and injected by needle/syringe.

Arm type	Experimental
Investigational medicinal product name	Herceptin
Investigational medicinal product code	
Other name	Trastuzumab
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Herceptin was given as 600 mg SC (into thigh) on Day 1 of each 3-week cycle for up to 18 cycles.

Arm title	Cohort B: SC Herceptin by Single-Use Injection Device (SID)

Arm description:

Participants received SC Herceptin as 600 mg every 3 weeks for a total of 18 doses/cycles. Each dose of SC Herceptin was administered from a pre-filled SID. The first administration was performed by a healthcare professional (HCP). Subsequent doses were self-administered by participants who were willing and judged competent by the HCP.

Arm type	Experimental
Investigational medicinal product name	Herceptin
Investigational medicinal product code	
Other name	Trastuzumab
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Herceptin was given as 600 mg SC (into thigh) on Day 1 of each 3-week cycle for up to 18 cycles.

Number of subjects in period 1	Cohort A: SC Herceptin by Needle/Syringe	Cohort B: SC Herceptin by Single-Use Injection Device (SID)
Started	1867	710
Received Treatment	1864	709
Completed	0	0
Not completed	1867	710
Consent withdrawn by subject	58	15
Death	6	3
Not specified	10	4
Disease progression/recurrence	123	28
Ongoing study	1649	659
Lost to follow-up	18	-
Withdrew prior to treatment	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A: SC Herceptin by Needle/Syringe
Reporting group description:	
Participants received SC Herceptin by an assisted administration as 600 milligrams (mg) every 3 weeks for a total of 18 doses/cycles. Each dose of SC Herceptin was taken from a single-use vial and injected by needle/syringe.	
Reporting group title	Cohort B: SC Herceptin by Single-Use Injection Device (SID)
Reporting group description:	
Participants received SC Herceptin as 600 mg every 3 weeks for a total of 18 doses/cycles. Each dose of SC Herceptin was administered from a pre-filled SID. The first administration was performed by a healthcare professional (HCP). Subsequent doses were self-administered by participants who were willing and judged competent by the HCP.	

Reporting group values	Cohort A: SC Herceptin by Needle/Syringe	Cohort B: SC Herceptin by Single-Use Injection Device (SID)	Total
Number of subjects	1867	710	2577
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	54	53	
standard deviation	± 12.01	± 11.32	-
Gender categorical			
Units: Subjects			
Female	1863	710	2573
Male	4	0	4

End points

End points reporting groups

Reporting group title	Cohort A: SC Herceptin by Needle/Syringe

Reporting group description:

Participants received SC Herceptin by an assisted administration as 600 milligrams (mg) every 3 weeks for a total of 18 doses/cycles. Each dose of SC Herceptin was taken from a single-use vial and injected by needle/syringe.

Reporting group title	Cohort B: SC Herceptin by Single-Use Injection Device (SID)

Reporting group description:

Participants received SC Herceptin as 600 mg every 3 weeks for a total of 18 doses/cycles. Each dose of SC Herceptin was administered from a pre-filled SID. The first administration was performed by a healthcare professional (HCP). Subsequent doses were self-administered by participants who were willing and judged competent by the HCP.

Subject analysis set title	Cohort B: SC Herceptin by SID (Self-Administered)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received SC Herceptin as 600 mg every 3 weeks for a total of 18 doses/cycles. Each dose of SC Herceptin was administered from a pre-filled SID. Dosing was either performed by self-administration or a qualified HCP. The present subgroup included only participants for whom SC Herceptin was given by self-administration.

Subject analysis set title	Cohort B: SC Herceptin by SID (HCP-Administered)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received SC Herceptin as 600 mg every 3 weeks for a total of 18 doses/cycles. Each dose of SC Herceptin was administered from a pre-filled SID. Dosing was either performed by self-administration or a qualified HCP. The present subgroup included only participants for whom SC Herceptin was administered by an HCP.

Subject analysis set title	Cohort A: SC Herceptin by Needle/Syringe (Intent-to-Treat)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received SC Herceptin by an assisted administration as 600 mg every 3 weeks for a total of 18 doses/cycles. Each dose of SC Herceptin was taken from a single-use vial and injected by needle/syringe. The Intent-to-Treat (ITT) Population included both treated and untreated participants.

Subject analysis set title	Cohort B: SC Herceptin by SID (Intent-to-Treat)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received SC Herceptin as 600 mg every 3 weeks for a total of 18 doses/cycles. Each dose of SC Herceptin was administered from a pre-filled SID. The first administration was performed by an HCP. Subsequent doses were self-administered by participants who were willing and judged competent by the HCP. The ITT Population included both treated and untreated participants.

Primary: Percentage of Participants With At Least 1 Adverse Event (AE) During the Treatment Period

End point title	Percentage of Participants With At Least 1 Adverse Event (AE) During the Treatment Period[1]

End point description:

Participants were planned to receive a total of 18 cycles of SC Herceptin. An AE was defined as any untoward medical occurrence in a participant administered SC Herceptin. Examples included unfavorable/unintended signs and symptoms, new or exacerbated disease, recurrence of intermittent condition, deterioration in laboratory value or other clinical test, or adverse procedure-related events. The percentage of participants with at least 1 AE during the treatment period (regardless of severity or seriousness) was reported. Safety Population: All enrolled participants who received at least one dose of study medication according to assigned treatment.

End point type	Primary

End point timeframe:

From Day 1 up to 19 cycles (cycle length 3 weeks) (approximately 1 year)

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: Study data were analyzed by descriptive summaries. No formal hypothesis testing was planned.

End point values	Cohort A: SC Herceptin by Needle/Syringe	Cohort B: SC Herceptin by Single-Use Injection Device (SID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1864	709		
Units: percentage of participants				
number (not applicable)	88.6	89		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With a Grade 3 or Higher AE During the Treatment Period

End point title	Percentage of Participants With a Grade 3 or Higher AE During the Treatment Period[2]

End point description:

Participants were planned to receive a total of 18 cycles of SC Herceptin. An AE was defined as any untoward medical occurrence in a participant administered SC Herceptin. Examples included unfavorable/unintended signs and symptoms, new or exacerbated disease, recurrence of intermittent condition, deterioration in laboratory value or other clinical test, or adverse procedure-related events. AEs were graded according to National Cancer Institute Common Terminology Criteria Version 4.0. Grade 3 AEs were those considered severe or medically significant but not immediately life-threatening. Grade 4 AEs were those considered life-threatening and/or for which urgent intervention was indicated. Grade 5 AEs were those resulting in death. The percentage of participants with a Grade 3 or higher (i.e., Grade 3 to 5) AE during the treatment period was reported. Safety Population.

End point type	Primary

End point timeframe:

From Day 1 up to 19 cycles (cycle length 3 weeks) (approximately 1 year)

Notes:

[2] - 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: Study data were analyzed by descriptive summaries. No formal hypothesis testing was planned.

End point values	Cohort A: SC Herceptin by Needle/Syringe	Cohort B: SC Herceptin by Single-Use Injection Device (SID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1864	709		
Units: percentage of participants				
number (confidence interval 95%)	24 (22.1 to 26)	21 (18.1 to 24.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Treatment Interruption Due to an AE

End point title	Percentage of Participants With Treatment Interruption Due to an AE[3]

End point description:

Participants were planned to receive a total of 18 cycles of SC Herceptin. An AE was defined as any untoward medical occurrence in a participant administered SC Herceptin. Examples included unfavorable/unintended signs and symptoms, new or exacerbated disease, recurrence of intermittent condition, deterioration in laboratory value or other clinical test, or adverse procedure-related events. The percentage of participants with SC Herceptin treatment interrupted to assess or treat AEs was reported. Safety Population.

End point type	Primary

End point timeframe:

From Day 1 up to 19 cycles (cycle length 3 weeks) (approximately 1 year)

Notes:

[3] - 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: Study data were analyzed by descriptive summaries. No formal hypothesis testing was planned.

End point values	Cohort A: SC Herceptin by Needle/Syringe	Cohort B: SC Herceptin by Single-Use Injection Device (SID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1864	709		
Units: percentage of participants				
number (not applicable)	9.8	10.4		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Herceptin Cycles Received

End point title	Number of Herceptin Cycles Received[4]

End point description:

Participants were planned to receive a total of 18 cycles of SC Herceptin. The median number of cycles actually received was reported. Safety Population. The endpoint also included an analysis of a subgroup of participants from Cohort B who received doses of self-administered SC Herceptin via SID.

End point type	Primary

End point timeframe:

From Day 1 up to 19 cycles (cycle length 3 weeks) (approximately 1 year)

Notes:

[4] - 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: Study data were analyzed by descriptive summaries. No formal hypothesis testing was planned.

End point values	Cohort A: SC Herceptin by Needle/Syringe	Cohort B: SC Herceptin by Single-Use Injection Device (SID)	Cohort B: SC Herceptin by SID (Self-Administered)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1864	709	550	
Units: cycles				
median (full range (min-max))	18 (1 to 19)	18 (1 to 18)	16 (1 to 17)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants by Total Number of Herceptin Cycles Received

End point title	Percentage of Participants by Total Number of Herceptin Cycles Received[5]

End point description:

Participants were planned to receive a total of 18 cycles of SC Herceptin. The percentage of participants was reported by the total number of cycles actually received. Because the data are presented non-cumulatively, this table reflects participant distribution by the highest number of cycles received. Safety Population. The endpoint also included an analysis of a subgroup of participants from Cohort B who received doses of self-administered SC Herceptin via SID.

End point type	Primary

End point timeframe:

From Day 1 up to 19 cycles (cycle length 3 weeks) (approximately 1 year)

Notes:

[5] - 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: Study data were analyzed by descriptive summaries. No formal hypothesis testing was planned.

End point values	Cohort A: SC Herceptin by Needle/Syringe	Cohort B: SC Herceptin by Single-Use Injection Device (SID)	Cohort B: SC Herceptin by SID (Self-Administered)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1864	709	550	
Units: percentage of participants				
number (not applicable)				
1 Cycle Received	1	0.8	2.7	
2 Cycles Received	0.5	0.4	1.3	
3 Cycles Received	0.5	0.1	1.1	
4 Cycles Received	1.2	0.7	1.6	
5 Cycles Received	0.8	0.6	1.3	
6 Cycles Received	0.5	0.1	1.6	
7 Cycles Received	0.7	0.8	2.2	
8 Cycles Received	0.9	0.3	2.2	
9 Cycles Received	0.2	0.6	1.8	
10 Cycles Received	0.3	0.1	1.5	
11 Cycles Received	0.4	0.3	3.5	
12 Cycles Received	0.9	0.8	2.5	
13 Cycles Received	0.2	0	4.9	

14 Cycles Received	0.5	0.6	6.9	
15 Cycles Received	0.5	0.4	10.7	
16 Cycles Received	0.6	0.3	21.6	
17 Cycles Received	1	1.1	32.5	
18 Cycles Received	89.2	91.8	0	
19 Cycles Received	0.2	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Received Concomitant Cancer Therapy

End point title	Percentage of Participants Who Received Concomitant Cancer Therapy[6]

End point description:

Concomitant cancer treatment included chemotherapy, radiotherapy, and hormone therapy administered during the study. The percentage of participants who received any of these concomitant therapies was reported. Safety Population.

End point type	Primary

End point timeframe:

From Baseline to data cutoff of 10 March 2015 (up to approximately 3 years)

Notes:

[6] - 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: Study data were analyzed by descriptive summaries. No formal hypothesis testing was planned.

End point values	Cohort A: SC Herceptin by Needle/Syringe	Cohort B: SC Herceptin by Single-Use Injection Device (SID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1864	709		
Units: percentage of participants				
number (not applicable)				
Chemotherapy	58.2	63.9		
Radiotherapy	51.3	48.5		
Hormone Therapy	53.5	50.4		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Received Concomitant Non-Cancer Therapy

End point title	Percentage of Participants Who Received Concomitant Non-Cancer Therapy[7]

End point description:

Concomitant non-cancer treatment included any pharmacologic interventions administered during the

study other than chemotherapy, radiotherapy, or hormone therapy. The percentage of participants who received any concomitant non-cancer therapies was reported. Safety Population.

End point type	Primary

End point timeframe:

From Baseline to data cutoff of 10 March 2015 (up to approximately 3 years)

Notes:

[7] - 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: Study data were analyzed by descriptive summaries. No formal hypothesis testing was planned.

End point values	Cohort A: SC Herceptin by Needle/Syringe	Cohort B: SC Herceptin by Single-Use Injection Device (SID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1864	709		
Units: percentage of participants				
number (not applicable)	89.1	89.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died by Data Cutoff of 10 March 2015

End point title	Percentage of Participants Who Died by Data Cutoff of 10 March 2015

End point description:

The percentage of participants who died from any cause was reported. ITT Population: All participants enrolled into the study regardless of whether treatment was received.

End point type	Secondary

End point timeframe:

From Baseline to time of event (maximum follow-up approximately 3 years as of data cutoff of 10 March 2015)

End point values	Cohort A: SC Herceptin by Needle/Syringe (Intent-to-Treat)	Cohort B: SC Herceptin by SID (Intent-to-Treat)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1867	710		
Units: percentage of participants				
number (not applicable)	1.5	0.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Item Response to SID Satisfaction Questionnaire

End point title	Percentage of Participants by Item Response to SID Satisfaction Questionnaire

End point description:

The SID satisfaction questionnaire was administered twice during study and asked participants to respond to five statements using a Likert scale from "Strongly Disagree" to "Strongly Agree". Questionnaire items were: "I felt comfortable injecting the study drug by myself" (Comfortable), "The SID was convenient and easy to use" (Easy to Use), "I am confident giving myself an injection in the thigh with the SID" (Confident), "Taking all things into account I find self-administration using the SID satisfactory" (Satisfactory), "If given the opportunity I would choose to continue self-injecting the study drug using the SID in the future" (Continue). Participants could select one response per questionnaire item. The percentage of participants was reported by response given for each item on the SID satisfaction questionnaire. Safety Population. Only those who self-administered were included. The number of participants who responded to the questionnaire item at each assessment (n) is shown.

End point type	Secondary

End point timeframe:

Cycle 4 (cycle length 3 weeks) and last safety follow-up (LSFU) (approximately 1 year)

End point values	Cohort B: SC Herceptin by SID (Self-Administered)			
Subject group type	Subject analysis set			
Number of subjects analysed	550			
Units: percentage of participants				
number (not applicable)				
Cycle 4: Comfortable, Strongly Disagree (n=514)	4.7			
Cycle 4: Comfortable, Disagree (n=514)	2.3			
Cycle 4: Comfortable, Unsure (n=514)	7.6			
Cycle 4: Comfortable, Agree (n=514)	41.6			
Cycle 4: Comfortable, Strongly Agree (n=514)	43.6			
Cycle 4: Comfortable, Response Missing (n=514)	0.2			
Cycle 4: Easy to Use, Strongly Disagree (n=514)	3.7			
Cycle 4: Easy to Use, Disagree (n=514)	0.6			
Cycle 4: Easy to Use, Unsure (n=514)	1.8			
Cycle 4: Easy to Use, Agree (n=514)	37.7			
Cycle 4: Easy to Use, Strongly Agree (n=514)	56			
Cycle 4: Easy to Use, Response Missing (n=514)	0.2			
Cycle 4: Confident, Strongly Disagree (n=514)	3.9			
Cycle 4: Confident, Disagree (n=514)	0.8			
Cycle 4: Confident, Unsure (n=514)	7.2			
Cycle 4: Confident, Agree (n=514)	42.8			
Cycle 4: Confident, Strongly Agree (n=514)	45.1			

Cycle 4: Confident, Response Missing (n=514)	0.2			
Cycle 4: Satisfactory, Strongly Disagree (n=514)	3.9			
Cycle 4: Satisfactory, Disagree (n=514)	0.6			
Cycle 4: Satisfactory, Unsure (n=514)	2.7			
Cycle 4: Satisfactory, Agree (n=514)	38.7			
Cycle 4: Satisfactory, Strongly Agree (n=514)	53.9			
Cycle 4: Satisfactory, Response Missing (n=514)	0.2			
Cycle 4: Continue, Strongly Disagree (n=514)	3.9			
Cycle 4: Continue, Disagree (n=514)	1.4			
Cycle 4: Continue, Unsure (n=514)	5.3			
Cycle 4: Continue, Agree (n=514)	33.5			
Cycle 4: Continue, Strongly Agree (n=514)	55.8			
Cycle 4: Continue, Response Missing (n=514)	0.2			
LSFU: Comfortable, Strongly Disagree (n=415)	3.6			
LSFU: Comfortable, Disagree (n=415)	3.1			
LSFU: Comfortable, Unsure (n=415)	5.3			
LSFU: Comfortable, Agree (n=415)	35.9			
LSFU: Comfortable, Strongly Agree (n=415)	51.8			
LSFU: Comfortable, Response Missing (n=415)	0.2			
LSFU: Easy to Use, Strongly Disagree (n=415)	3.9			
LSFU: Easy to Use, Disagree (n=415)	1			
LSFU: Easy to Use, Unsure (n=415)	1.7			
LSFU: Easy to Use, Agree (n=415)	34.9			
LSFU: Easy to Use, Strongly Agree (n=415)	58.6			
LSFU: Easy to Use, Response Missing (n=415)	0			
LSFU: Confident, Strongly Disagree (n=415)	4.6			
LSFU: Confident, Disagree (n=415)	1.2			
LSFU: Confident, Unsure (n=415)	4.3			
LSFU: Confident, Agree (n=415)	33.3			
LSFU: Confident, Strongly Agree (n=415)	56.6			
LSFU: Confident, Response Missing (n=415)	0			
LSFU: Satisfactory, Strongly Disagree (n=415)	4.3			
LSFU: Satisfactory, Disagree (n=415)	1.2			
LSFU: Satisfactory, Unsure (n=415)	2.2			
LSFU: Satisfactory, Agree (n=415)	30.8			
LSFU: Satisfactory, Strongly Agree (n=415)	61.2			
LSFU: Satisfactory, Response Missing (n=415)	0.2			
LSFU: Continue, Strongly Disagree (n=415)	4.6			

LSFU: Continue, Disagree (n=415)	1.2			
LSFU: Continue, Unsure (n=415)	2.9			
LSFU: Continue, Agree (n=415)	28.2			
LSFU: Continue, Strongly Agree (n=415)	63.1			
LSFU: Continue, Response Missing (n=415)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 up to 19 cycles (approximately 1 year)

Adverse event reporting additional description:

Safety Population. Three AEs with onset during treatment resulted in eventual death and are captured under the respective AE terms in Cohort A as fatal events. One of these deaths occurred during treatment and is captured in "Number of deaths (all causes)" for Cohort A. The remaining 2 deaths occurred in follow-up and are excluded from this count.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Cohort A: SC Herceptin by Needle/Syringe

Reporting group description:

Participants received SC Herceptin by an assisted administration as 600 mg every 3 weeks for a total of 18 doses/cycles. Each dose of SC Herceptin was taken from a single-use vial and injected by needle/syringe.

Reporting group title	Cohort B: SC Herceptin by Single-Use Injection Device (SID)

Reporting group description:

Participants received SC Herceptin as 600 mg every 3 weeks for a total of 18 doses/cycles. Each dose of SC Herceptin was administered from a pre-filled SID. The first administration was performed by an HCP. Subsequent doses were self-administered by participants who were willing and judged competent by the HCP.

Serious adverse events	Cohort A: SC Herceptin by Needle/Syringe	Cohort B: SC Herceptin by Single-Use Injection Device (SID)	
Total subjects affected by serious adverse events			
subjects affected / exposed	242 / 1864 (12.98%)	84 / 709 (11.85%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	1 / 1864 (0.05%)	2 / 709 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign pancreatic neoplasm			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Borderline serous tumour of ovary			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian fibroma			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			

subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Schwannoma			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid adenoma			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 1864 (0.05%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial stenosis			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			

subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (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 / 1864 (0.05%)	0 / 709 (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			
Pyrexia			
subjects affected / exposed	11 / 1864 (0.59%)	7 / 709 (0.99%)	
occurrences causally related to treatment / all	0 / 12	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device breakage			
subjects affected / exposed	1 / 1864 (0.05%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 1864 (0.05%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			

subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Device defective			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (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 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			

subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 1864 (0.00%)	2 / 709 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast fibrosis			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hypertrophy			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postmenopausal haemorrhage			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (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 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 1864 (0.05%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 1864 (0.00%)	2 / 709 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Painful respiration			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleurisy			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 1864 (0.05%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	3 / 1864 (0.16%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

White blood cell count decreased			
subjects affected / exposed	1 / 1864 (0.05%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood urea increased			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Radiation pneumonitis			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (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 / 1864 (0.05%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fibula fracture			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture displacement			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			

subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic arthropathy			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	10 / 1864 (0.54%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	9 / 10	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			

subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 1864 (0.05%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 1864 (0.05%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			

subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 1864 (0.05%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid sinus syndrome			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			

subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (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	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tension headache			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (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			
Febrile neutropenia			
subjects affected / exposed	39 / 1864 (2.09%)	14 / 709 (1.97%)	
occurrences causally related to treatment / all	5 / 39	1 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	9 / 1864 (0.48%)	6 / 709 (0.85%)	
occurrences causally related to treatment / all	0 / 11	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	2 / 1864 (0.11%)	2 / 709 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	3 / 1864 (0.16%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thymus enlargement			

subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniere's disease			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 1864 (0.43%)	4 / 709 (0.56%)	
occurrences causally related to treatment / all	0 / 9	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	5 / 1864 (0.27%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	3 / 1864 (0.16%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 1864 (0.05%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal discomfort			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal polyp			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			

subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 1864 (0.11%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis bullous			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema nodosum			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			

subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient acantholytic dermatosis			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthritis			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (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 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Neutropenic sepsis			
subjects affected / exposed	9 / 1864 (0.48%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	1 / 9	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Device related infection			
subjects affected / exposed	6 / 1864 (0.32%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 1864 (0.27%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	3 / 1864 (0.16%)	2 / 709 (0.28%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	3 / 1864 (0.16%)	2 / 709 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	4 / 1864 (0.21%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	3 / 1864 (0.16%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	4 / 1864 (0.21%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 1864 (0.11%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 1864 (0.11%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (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	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (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	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 1864 (0.05%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess of external auditory meatus			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendiceal abscess			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bartholin's abscess			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (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	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			

subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal sepsis			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lobar pneumonia			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node tuberculosis			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningoencephalitis bacterial			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			

subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (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	1 / 1864 (0.05%)	0 / 709 (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			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (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	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			

subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal infection			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 1864 (0.00%)	1 / 709 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	2 / 1864 (0.11%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (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 / 1864 (0.05%)	0 / 709 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 1864 (0.05%)	0 / 709 (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	Cohort A: SC Herceptin by Needle/Syringe	Cohort B: SC Herceptin by Single-Use Injection Device (SID)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1499 / 1864 (80.42%)	576 / 709 (81.24%)	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	80 / 1864 (4.29%)	36 / 709 (5.08%)	
occurrences (all)	85	43	
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	161 / 1864 (8.64%)	68 / 709 (9.59%)	
occurrences (all)	172	78	
Vascular disorders			
Hot flush			
subjects affected / exposed	164 / 1864 (8.80%)	72 / 709 (10.16%)	
occurrences (all)	179	77	
Hypertension			
subjects affected / exposed	142 / 1864 (7.62%)	35 / 709 (4.94%)	
occurrences (all)	183	50	
Nervous system disorders			
Headache			
subjects affected / exposed	228 / 1864 (12.23%)	73 / 709 (10.30%)	
occurrences (all)	344	89	
Neuropathy peripheral			
subjects affected / exposed	140 / 1864 (7.51%)	56 / 709 (7.90%)	
occurrences (all)	164	65	
Paraesthesia			
subjects affected / exposed	112 / 1864 (6.01%)	70 / 709 (9.87%)	
occurrences (all)	130	87	

Dizziness			
subjects affected / exposed	111 / 1864 (5.95%)	32 / 709 (4.51%)	
occurrences (all)	143	35	
Peripheral sensory neuropathy			
subjects affected / exposed	94 / 1864 (5.04%)	21 / 709 (2.96%)	
occurrences (all)	102	25	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	381 / 1864 (20.44%)	132 / 709 (18.62%)	
occurrences (all)	496	168	
Asthenia			
subjects affected / exposed	221 / 1864 (11.86%)	85 / 709 (11.99%)	
occurrences (all)	327	107	
Pyrexia			
subjects affected / exposed	185 / 1864 (9.92%)	55 / 709 (7.76%)	
occurrences (all)	231	67	
Oedema peripheral			
subjects affected / exposed	160 / 1864 (8.58%)	45 / 709 (6.35%)	
occurrences (all)	185	49	
Injection site erythema			
subjects affected / exposed	128 / 1864 (6.87%)	52 / 709 (7.33%)	
occurrences (all)	326	124	
Mucosal inflammation			
subjects affected / exposed	105 / 1864 (5.63%)	53 / 709 (7.48%)	
occurrences (all)	126	64	
Injection site pain			
subjects affected / exposed	117 / 1864 (6.28%)	37 / 709 (5.22%)	
occurrences (all)	190	107	
Injection site reaction			
subjects affected / exposed	101 / 1864 (5.42%)	36 / 709 (5.08%)	
occurrences (all)	279	58	
Pain			
subjects affected / exposed	63 / 1864 (3.38%)	36 / 709 (5.08%)	
occurrences (all)	70	41	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	130 / 1864 (6.97%)	43 / 709 (6.06%)	
occurrences (all)	159	53	
Neutropenia			
subjects affected / exposed	101 / 1864 (5.42%)	36 / 709 (5.08%)	
occurrences (all)	156	45	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	380 / 1864 (20.39%)	130 / 709 (18.34%)	
occurrences (all)	540	184	
Nausea			
subjects affected / exposed	274 / 1864 (14.70%)	102 / 709 (14.39%)	
occurrences (all)	362	133	
Constipation			
subjects affected / exposed	153 / 1864 (8.21%)	62 / 709 (8.74%)	
occurrences (all)	200	73	
Vomiting			
subjects affected / exposed	129 / 1864 (6.92%)	38 / 709 (5.36%)	
occurrences (all)	160	45	
Stomatitis			
subjects affected / exposed	116 / 1864 (6.22%)	42 / 709 (5.92%)	
occurrences (all)	140	47	
Abdominal pain			
subjects affected / exposed	87 / 1864 (4.67%)	36 / 709 (5.08%)	
occurrences (all)	104	45	
Dyspepsia			
subjects affected / exposed	69 / 1864 (3.70%)	44 / 709 (6.21%)	
occurrences (all)	80	50	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	190 / 1864 (10.19%)	56 / 709 (7.90%)	
occurrences (all)	223	59	
Dyspnoea			
subjects affected / exposed	115 / 1864 (6.17%)	47 / 709 (6.63%)	
occurrences (all)	126	49	

Epistaxis			
subjects affected / exposed	109 / 1864 (5.85%)	30 / 709 (4.23%)	
occurrences (all)	135	35	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	177 / 1864 (9.50%)	74 / 709 (10.44%)	
occurrences (all)	251	113	
Erythema			
subjects affected / exposed	156 / 1864 (8.37%)	74 / 709 (10.44%)	
occurrences (all)	223	86	
Alopecia			
subjects affected / exposed	163 / 1864 (8.74%)	49 / 709 (6.91%)	
occurrences (all)	170	50	
Pruritus			
subjects affected / exposed	115 / 1864 (6.17%)	35 / 709 (4.94%)	
occurrences (all)	136	40	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	108 / 1864 (5.79%)	50 / 709 (7.05%)	
occurrences (all)	125	52	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	362 / 1864 (19.42%)	133 / 709 (18.76%)	
occurrences (all)	471	160	
Myalgia			
subjects affected / exposed	260 / 1864 (13.95%)	84 / 709 (11.85%)	
occurrences (all)	349	107	
Pain in extremity			
subjects affected / exposed	194 / 1864 (10.41%)	49 / 709 (6.91%)	
occurrences (all)	248	63	
Back pain			
subjects affected / exposed	114 / 1864 (6.12%)	42 / 709 (5.92%)	
occurrences (all)	136	44	
Musculoskeletal pain			

subjects affected / exposed	89 / 1864 (4.77%)	36 / 709 (5.08%)	
occurrences (all)	107	40	
Bone pain			
subjects affected / exposed	70 / 1864 (3.76%)	40 / 709 (5.64%)	
occurrences (all)	80	53	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	146 / 1864 (7.83%)	58 / 709 (8.18%)	
occurrences (all)	190	79	
Upper respiratory tract infection			
subjects affected / exposed	113 / 1864 (6.06%)	21 / 709 (2.96%)	
occurrences (all)	132	25	
Urinary tract infection			
subjects affected / exposed	94 / 1864 (5.04%)	32 / 709 (4.51%)	
occurrences (all)	114	43	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2012	The amendment allowed participants to be treated with SC Herceptin according to indication and to allow a sub-population of participants to be enrolled to provide complementary safety data for regulatory purposes. The duration of treatment-free follow-up was extended from a minimum of 2 years to a minimum of 5 years, and the AE reporting timeframe was revised.
18 March 2013	The protocol was amended to clarify the timeframe for AE reporting as well as the definition of "treatment period". Participants were also allowed the opportunity to self-administer SC Herceptin via SID at the discretion and supervision of the HCP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported