

**Clinical trial results:****A Multicenter Randomized Phase II Study to Compare the Combination Trastuzumab and Capecitabine, With or Without Pertuzumab, in Patients with HER2-Positive Metastatic Breast Cancer That Have Progressed After One Line of Trastuzumab-Based Therapy in the Metastatic Setting (PHEREXA)****Summary**

EudraCT number	2008-006801-17
Trial protocol	AT ES DE CZ EE HU GB IT FR BE NL
Global end of trial date	

**Results information**

Result version number	v1
This version publication date	02 September 2016
First version publication date	02 September 2016

**Trial information****Trial identification**

Sponsor protocol code	MO22324
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01026142
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
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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	29 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 May 2015
Global end of trial reached?	No

Notes:

## General information about the trial

Main objective of the trial:

To compare progression-free survival (PFS) between the two treatment arms based on assessments by an independent review facility (IRF).

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice. All subjects signed an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 January 2010
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	Argentina: 7
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 23
Country: Number of subjects enrolled	Brazil: 13
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Croatia: 7
Country: Number of subjects enrolled	Czech Republic: 22
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Germany: 34
Country: Number of subjects enrolled	Hong Kong: 16
Country: Number of subjects enrolled	Hungary: 42
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Peru: 15
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Romania: 14
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Korea, Republic of: 38
Country: Number of subjects enrolled	Spain: 70
Country: Number of subjects enrolled	Thailand: 5
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	United Kingdom: 35

Worldwide total number of subjects	446
EEA total number of subjects	331

Notes:

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**Subjects enrolled per age group**

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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)	366
From 65 to 84 years	80
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Study included females with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) with progression during or following 1 line of trastuzumab-based therapy in metastatic setting. 452 participants randomized to 1 of 2 treatment arms (Arm A, n = 224) or (Arm B, n = 228). 6 participants did not receive treatment.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Capecitabine + Trastuzumab
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

In Cycle 1, every 3 weeks: the first dose of capecitabine should be administered in the evening of Day 1 and the last dose in the morning of Day 15. 1250 mg/m<sup>2</sup> twice daily (morning and evening, equivalent to 2500 mg/m<sup>2</sup> total daily dose) for 14 days followed by 7-day rest.

In Cycle 2 and subsequent cycles, every 3 weeks: 1250 mg/m<sup>2</sup> twice daily (morning and evening, equivalent to 2500 mg/m<sup>2</sup> total daily dose) for 14 days followed by 7-day rest.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use, Parenteral use

Dosage and administration details:

In Cycle 1, every 3 weeks, beginning on Day 1: 8 mg/kg intravenous (IV) loading dose over 90 min followed by a 60-min observation period. If the first infusion of trastuzumab is tolerated without infusion-associated AEs (fever and/or chills), the second and subsequent infusions may be delivered over 30 minutes.

In Cycle 2 and subsequent cycles, every 3 weeks, beginning on Day 1: 6 mg/kg IV over 90 min followed by a 30- to 60-min observation period. If the first infusion of trastuzumab is tolerated without infusion-associated AEs (fever and/or chills), the second and subsequent infusions may be delivered over 30 minutes.

<b>Arm title</b>	Capecitabine + Trastuzumab + Pertuzumab
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Arm description: -

Arm type	Experimental
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Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

In Cycle 1, every 3 weeks: On Day 2, 1000 mg/m<sup>2</sup> twice daily (morning and evening, equivalent to 2000 mg/m<sup>2</sup> total daily dose) for 14 days followed by 7-day rest. In Cycle 1, the first dose of capecitabine should be administered in the morning of Day 2 and the last dose in the evening of Day 15.

In Cycle 2 and subsequent cycles, every 3 weeks: On Day 1, 1000 mg/m<sup>2</sup> twice daily (morning and evening, equivalent to 2000 mg/m<sup>2</sup> total daily dose) for 14 days followed by 7-day rest.

If the administration of the three study drugs is well tolerated during the first cycle, starting from Cycle 2, the first dose of capecitabine should be administered in the evening of Day 1 and the last dose in the morning of Day 15.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Parenteral use , Intravenous use

Dosage and administration details:

In Cycle 1, every 3 weeks: On Day 2, 8 mg/kg IV over 90 min followed by a 60-min observation period. If the first infusion of trastuzumab is tolerated without infusion-associated AEs (fever and/or chills), the second and subsequent infusions may be delivered over 30 minutes.

In Cycle 2 and subsequent cycles, every 3 weeks: On Day 1, after pertuzumab observation 6 mg/kg IV over 90 min followed by a 30-to 60-min observation period. If the first infusion of trastuzumab and pertuzumab is tolerated without infusion-associated AEs (fever and/or chills), the second and subsequent infusions may be delivered over 30 minutes.

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In Cycle 1, every 3 weeks: On Day 1, 840 mg IV loading dose over 60 min followed by a 60-min observation period.

In Cycle 2 and subsequent cycles, every 3 weeks: On Day 1, 420 mg IV over 60 min followed by a 30-to 60-min observation period. If the participant misses a dose of pertuzumab for one cycle (i.e., the two sequential administration times are 6 weeks or more apart), a re-loading dose of pertuzumab (840 mg) should be given. If re-loading is required for a given cycle, the three study therapies should be given on the same schedule as Cycle 1 (i.e., pertuzumab on Day 1 and trastuzumab and capecitabine on Day 2). Subsequent maintenance pertuzumab doses of 420 mg will then be given every 3 weeks, starting 3 weeks later.

Number of subjects in period 1	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab
Started	218	228
Completed	64	82
Not completed	154	146
On Treatment	15	25
Death	114	98

Withdrawn consent or lost to survival follow-up	25	23
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## Baseline characteristics

### Reporting groups

Reporting group title	Capecitabine + Trastuzumab
Reporting group description: -	
Reporting group title	Capecitabine + Trastuzumab + Pertuzumab
Reporting group description: -	

Reporting group values	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab	Total
Number of subjects	218	228	446
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	55.1 ± 10.1	53 ± 11.21	-
Gender categorical Units: Subjects			
Female	218	228	446
Male	0	0	0

## End points

### End points reporting groups

Reporting group title	Capecitabine + Trastuzumab
Reporting group description: -	
Reporting group title	Capecitabine + Trastuzumab + Pertuzumab
Reporting group description: -	
Subject analysis set title	Capecitabine + Trastuzumab
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients were randomized to receive Capecitabine + Trastuzumab in 3-week cycles.	
Subject analysis set title	Capecitabine + Trastuzumab + Pertuzumab
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients were randomized to receive Capecitabine + Trastuzumab + Pertuzumab in 3-week cycles.	

### Primary: Progression Free Survival (PFS) - Independent Assessment

End point title	Progression Free Survival (PFS) - Independent Assessment
End point description:	
Progression Free Survival is defined as the time from randomization to the first documented disease progression, (PD) as determined by IRF using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, or death from any cause, whichever occurs first.	
End point type	Primary
End point timeframe:	
Tumor Assessment every 9 weeks until week 27, then every 12 weeks thereafter	

End point values	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224	228		
Units: Months				
median (confidence interval 95%)	9 (8 to 10)	11.1 (9 to 13)		

### Statistical analyses

Statistical analysis title	IRF-Assessed Progression-Free Survival (PFS)
Comparison groups	Capecitabine + Trastuzumab v Capecitabine + Trastuzumab + Pertuzumab
Number of subjects included in analysis	452
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0731
Method	Kaplan-Meier
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.02

### Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
<p>Overall Survival (OS) was defined as the time from the date of randomization to the date of death from any cause. An interim analysis of OS was performed at the time of the analysis of the primary endpoint, Independent Review Facility (IRF)-assessed Progression-Free Survival (PFS), with type 1 error control. The final OS analysis will take place at the end of study when 67% of patients have died (approximately 300 deaths). Analysis methods at this time will be the same as those described for the primary endpoint. Prior to the data analysis cut-off, it will be ensured that all patients who are in survival follow-up have been contacted as recently as possible within the last 3 months to confirm current survival status.</p>	
End point type	Secondary
End point timeframe:	
Timeframe was from randomization until death from any cause	

End point values	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224	228		
Units: Months				
median (confidence interval 95%)	28.1 (22 to 35)	36.1 (31 to 39)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS) Based on a 2-year Truncated Analysis

End point title	Overall Survival (OS) Based on a 2-year Truncated Analysis
End point description:	
<p>Overall Survival is defined as the time from the date of randomization to the date of death from any cause, with censoring of all events and follow-up beyond the end of the second year.</p>	
End point type	Secondary
End point timeframe:	
Timeframe is from randomization until death from any cause	

<b>End point values</b>	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224	228		
Units: Percentage				
number (confidence interval 95%)	54.5 (47.56 to 61.49)	74.6 (68.7 to 80.48)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Investigator Assessment Progression-Free Survival (PFS)

End point title	Investigator Assessment Progression-Free Survival (PFS)
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End point description:

Investigator Assessment Progression-Free Survival (PFS) was defined as the time from randomization to the first documented progressive disease, as determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) v1.0, or death from any cause, whichever occurred first.

End point type	Secondary
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End point timeframe:

Tumor Assessment every 9 weeks until week 27, then every 12 weeks thereafter

<b>End point values</b>	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224	228		
Units: Months				
median (confidence interval 95%)	9 (8 to 12)	11.8 (9 to 14)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Progression (TTP) Based Upon IRF Assessment

End point title	Time to Progression (TTP) Based Upon IRF Assessment
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End point description:

Time to Progression (TTP) was defined as time between randomization and the first occurrence of progressive disease.

End point type	Secondary
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End point timeframe:

Tumor Assessment every 9 weeks until week 27, then every 12 weeks thereafter

<b>End point values</b>	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224	228		
Units: Weeks				
median (confidence interval 95%)	39 (35 to 44)	50.6 (39 to 62)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Treatment Failure (TTF)

End point title	Time to Treatment Failure (TTF)
End point description:	
Time to Treatment Failure (TTF) was defined as time between randomization and date of disease progression based on IRF assessments, death, or withdrawal of treatment due to adverse events, withdrawn informed consent, refusal of treatment/failure to cooperate, or failure to return, whichever occurred first. Based upon Independent Review Facility (IRF) assessment.	
End point type	Secondary
End point timeframe:	
Tumor Assessment every 9 weeks until week 27, then every 12 weeks thereafter	

<b>End point values</b>	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224	228		
Units: Weeks				
median (confidence interval 95%)	39 (34 to 44)	50.9 (39 to 62)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Objective Response Rate (ORR)

End point title	Overall Objective Response Rate (ORR)
End point description:	
Overall Objective Response Rate is based upon investigator and Independent Review Facility (IRF) assessments. Objective Response Rate (ORR) was defined as the percentage of patients with a confirmed complete response (CR) or partial response (PR) among those who had measurable disease at baseline. Patients without a post-baseline tumor assessment were considered to be non-responders.	
End point type	Secondary

End point timeframe:

Tumor Assessment every 9 weeks until week 27, then every 12 weeks thereafter

<b>End point values</b>	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	164	163		
Units: Percentage				
number (not applicable)				
Complete Response (CR) - IRF Assessment	0	1.8		
Partial Response (PR) - IRF Assessment	32.9	38.7		
Complete Response (CR) - Investigator Assessed	1.2	6.7		
Partial Response (PR) - Investigator Assessed	36	38		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)
End point description:	Clinical Benefit Rate is based upon Independent Review Facility (IRF) assessments; defined as the percentage of patients with a complete response (CR), partial response (PR), or stable disease for at least 8 cycles or 6 months.
End point type	Secondary
End point timeframe:	Tumor Assessment every 9 weeks until week 27, then every 12 weeks thereafter

<b>End point values</b>	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	121	145		
Units: Percentage				
number (confidence interval 95%)	54 (47.3 to 60.7)	63.6 (57 to 69.8)		

### Statistical analyses

No statistical analyses for this end point

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### Secondary: Duration of Objective Response

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End point title	Duration of Objective Response
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End point description:

Duration of Objective Response was defined for the subpopulation of responders as time from first Independent Review Facility (IRF)-assessed complete response (CR) or partial response (PR) to subsequent first documented, IRF-confirmed evidence of disease progression. Only patients with an objective response were included in the analysis of duration of objective response.

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End point type	Secondary
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End point timeframe:

Tumor Assessment every 9 weeks until week 27, then every 12 weeks thereafter

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End point values	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	66		
Units: Weeks				
median (confidence interval 95%)	30 (21 to 42)	51.6 (42 to 57)		

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded and reported during the study and up to two years after the last dose of the study drug was received.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

### Reporting groups

Reporting group title	Capecitabine + Trastuzumab
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Reporting group description:

Safety data were analyzed and compared between the two arms using standard methods and based on the safety population. The safety analysis population includes all patients who receive any amount of study drug summarized by treatment actually received.

Reporting group title	Capecitabine + Trastuzumab + Pertuzumab
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Reporting group description:

Safety data were analyzed and compared between the two arms using standard methods and based on the safety population. The safety analysis population includes all patients who receive any amount of study drug summarized by treatment actually received.

<b>Serious adverse events</b>	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 218 (23.85%)	56 / 228 (24.56%)	
number of deaths (all causes)	114	98	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute promyelocytic leukaemia			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			

subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Vascular disorders</b>			
Vena cava thrombosis			
subjects affected / exposed	1 / 218 (0.46%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (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 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>General disorders and administration site conditions</b>			
General physical health deterioration			
subjects affected / exposed	2 / 218 (0.92%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	2 / 218 (0.92%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Thrombosis in device			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	4 / 218 (1.83%)	3 / 228 (1.32%)	
occurrences causally related to treatment / all	0 / 4	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thrombosis			
subjects affected / exposed	0 / 218 (0.00%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Investigations</b>			
Blood sodium decreased			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Injury, poisoning and procedural complications</b>			
Femur fracture			
subjects affected / exposed	2 / 218 (0.92%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 218 (0.00%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acetabulum fracture			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone fissure			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fracture			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (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 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (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 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial rupture			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Left ventricular dysfunction			
subjects affected / exposed	3 / 218 (1.38%)	10 / 228 (4.39%)	
occurrences causally related to treatment / all	3 / 3	9 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 218 (0.00%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriospasm coronary			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Supraventricular extrasystoles			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 218 (0.92%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	1 / 218 (0.46%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Hemiparesis</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Ischaemic stroke</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Sciatica</b>			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Secondary cerebellar degeneration</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Status epilepticus</b>			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Subarachnoid haemorrhage</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
<b>Blood and lymphatic system disorders</b>			
<b>Febrile neutropenia</b>			
subjects affected / exposed	2 / 218 (0.92%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Neutropenia</b>			

subjects affected / exposed	2 / 218 (0.92%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Anaemia</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Thrombocytopenia</b>			
subjects affected / exposed	1 / 218 (0.46%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pancytopenia</b>			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Eye disorders</b>			
<b>Retinal detachment</b>			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastrointestinal disorders</b>			
<b>Diarrhoea</b>			
subjects affected / exposed	6 / 218 (2.75%)	8 / 228 (3.51%)	
occurrences causally related to treatment / all	6 / 6	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Nausea</b>			
subjects affected / exposed	2 / 218 (0.92%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Vomiting</b>			
subjects affected / exposed	2 / 218 (0.92%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Abdominal hernia</b>			

subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Colitis</b>			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Diverticulum</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Dysphagia</b>			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastric perforation</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastric ulcer</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Ileus</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Subileus</b>			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Hepatobiliary disorders</b>			
Cholecystitis			

subjects affected / exposed	1 / 218 (0.46%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1 / 218 (0.46%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Ureteric stenosis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (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			
Back pain			
subjects affected / exposed	0 / 218 (0.00%)	2 / 228 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			

subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Osteitis</b>			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Osteonecrosis</b>			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pain in extremity</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
<b>Sepsis</b>			
subjects affected / exposed	2 / 218 (0.92%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Appendicitis</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Bacteraemia</b>			
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Bronchopneumonia</b>			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Catheter site infection</b>			

subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cellulitis		
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Clostridium difficile colitis		
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Device related infection		
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis		
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Phlebitis infective		
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia		
subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary tuberculosis		
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory tract infection		

subjects affected / exposed	1 / 218 (0.46%)	0 / 228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 218 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Capecitabine + Trastuzumab	Capecitabine + Trastuzumab + Pertuzumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	209 / 218 (95.87%)	216 / 228 (94.74%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 218 (6.42%)	18 / 228 (7.89%)	
occurrences (all)	18	18	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	51 / 218 (23.39%)	47 / 228 (20.61%)	
occurrences (all)	87	77	
Fatigue			
subjects affected / exposed	39 / 218 (17.89%)	44 / 228 (19.30%)	
occurrences (all)	59	61	
Mucosal inflammation			
subjects affected / exposed	27 / 218 (12.39%)	29 / 228 (12.72%)	
occurrences (all)	36	42	
Pyrexia			

subjects affected / exposed occurrences (all)	20 / 218 (9.17%) 24	29 / 228 (12.72%) 40	
Oedema peripheral subjects affected / exposed occurrences (all)	13 / 218 (5.96%) 13	17 / 228 (7.46%) 18	
Chest pain subjects affected / exposed occurrences (all)	12 / 218 (5.50%) 15	9 / 228 (3.95%) 11	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	22 / 218 (10.09%) 27	28 / 228 (12.28%) 36	
Dyspnoea subjects affected / exposed occurrences (all)	24 / 218 (11.01%) 28	19 / 228 (8.33%) 23	
Epistaxis subjects affected / exposed occurrences (all)	9 / 218 (4.13%) 9	12 / 228 (5.26%) 14	
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	12 / 218 (5.50%) 17	23 / 228 (10.09%) 27	
Investigations			
Weight decreased subjects affected / exposed occurrences (all)	13 / 218 (5.96%) 14	19 / 228 (8.33%) 20	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	11 / 218 (5.05%) 15	16 / 228 (7.02%) 24	
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	8 / 218 (3.67%) 11	17 / 228 (7.46%) 23	
Cardiac disorders			
Left ventricular dysfunction subjects affected / exposed occurrences (all)	5 / 218 (2.29%) 5	12 / 228 (5.26%) 14	

Nervous system disorders			
Headache			
subjects affected / exposed	39 / 218 (17.89%)	39 / 228 (17.11%)	
occurrences (all)	61	51	
Dizziness			
subjects affected / exposed	21 / 218 (9.63%)	24 / 228 (10.53%)	
occurrences (all)	28	26	
Neuropathy peripheral			
subjects affected / exposed	14 / 218 (6.42%)	15 / 228 (6.58%)	
occurrences (all)	17	16	
Paraesthesia			
subjects affected / exposed	13 / 218 (5.96%)	8 / 228 (3.51%)	
occurrences (all)	15	8	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	38 / 218 (17.43%)	28 / 228 (12.28%)	
occurrences (all)	88	72	
Anaemia			
subjects affected / exposed	17 / 218 (7.80%)	19 / 228 (8.33%)	
occurrences (all)	23	26	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	13 / 218 (5.96%)	6 / 228 (2.63%)	
occurrences (all)	17	8	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	127 / 218 (58.26%)	157 / 228 (68.86%)	
occurrences (all)	274	431	
Nausea			
subjects affected / exposed	97 / 218 (44.50%)	88 / 228 (38.60%)	
occurrences (all)	152	128	
Vomiting			
subjects affected / exposed	45 / 218 (20.64%)	37 / 228 (16.23%)	
occurrences (all)	56	57	
Stomatitis			
subjects affected / exposed	32 / 218 (14.68%)	41 / 228 (17.98%)	
occurrences (all)	39	56	

Abdominal pain subjects affected / exposed occurrences (all)	30 / 218 (13.76%) 36	28 / 228 (12.28%) 48	
Abdominal pain upper subjects affected / exposed occurrences (all)	24 / 218 (11.01%) 31	29 / 228 (12.72%) 44	
Dyspepsia subjects affected / exposed occurrences (all)	21 / 218 (9.63%) 22	24 / 228 (10.53%) 33	
Constipation subjects affected / exposed occurrences (all)	20 / 218 (9.17%) 26	18 / 228 (7.89%) 22	
<b>Skin and subcutaneous tissue disorders</b>			
Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all)	158 / 218 (72.48%) 240	128 / 228 (56.14%) 176	
Rash subjects affected / exposed occurrences (all)	11 / 218 (5.05%) 12	33 / 228 (14.47%) 40	
Pruritus subjects affected / exposed occurrences (all)	7 / 218 (3.21%) 7	21 / 228 (9.21%) 29	
Dry skin subjects affected / exposed occurrences (all)	9 / 218 (4.13%) 10	15 / 228 (6.58%) 16	
Nail disorder subjects affected / exposed occurrences (all)	8 / 218 (3.67%) 8	14 / 228 (6.14%) 15	
Alopecia subjects affected / exposed occurrences (all)	11 / 218 (5.05%) 12	6 / 228 (2.63%) 6	
<b>Musculoskeletal and connective tissue disorders</b>			
Pain in extremity subjects affected / exposed occurrences (all)	15 / 218 (6.88%) 24	26 / 228 (11.40%) 30	
Arthralgia			

subjects affected / exposed occurrences (all)	17 / 218 (7.80%) 18	21 / 228 (9.21%) 27	
Back pain subjects affected / exposed occurrences (all)	17 / 218 (7.80%) 21	18 / 228 (7.89%) 21	
Muscle spasms subjects affected / exposed occurrences (all)	12 / 218 (5.50%) 20	17 / 228 (7.46%) 21	
Bone pain subjects affected / exposed occurrences (all)	12 / 218 (5.50%) 16	8 / 228 (3.51%) 9	
Myalgia subjects affected / exposed occurrences (all)	6 / 218 (2.75%) 8	12 / 228 (5.26%) 19	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	4 / 218 (1.83%) 6	12 / 228 (5.26%) 13	
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	14 / 218 (6.42%) 17	26 / 228 (11.40%) 33	
Urinary tract infection subjects affected / exposed occurrences (all)	16 / 218 (7.34%) 16	20 / 228 (8.77%) 27	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	9 / 218 (4.13%) 10	19 / 228 (8.33%) 44	
Paronychia subjects affected / exposed occurrences (all)	11 / 218 (5.05%) 15	15 / 228 (6.58%) 16	
Influenza subjects affected / exposed occurrences (all)	4 / 218 (1.83%) 5	12 / 228 (5.26%) 12	
Metabolism and nutrition disorders Decreased appetite			

subjects affected / exposed	28 / 218 (12.84%)	36 / 228 (15.79%)
occurrences (all)	43	43
Hypokalaemia		
subjects affected / exposed	13 / 218 (5.96%)	28 / 228 (12.28%)
occurrences (all)	19	40

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported