Clinical trial results:
A Phase 3 Randomized, Double-Blind Study of PF-05280014 Plus Paclitaxel Versus Trastuzumab Plus Paclitaxel for the First-Line Treatment of Patients with HER2-Positive Metastatic Breast Cancer

Summary

EudraCT number	2013-001352-34
Trial protocol	CZ HU ES PT PL GR LV SK
Global end of trial date	

Results information

Result version number	v1
This version publication date	14 October 2017
First version publication date	14 October 2017

Trial information

Trial identification

Sponsor protocol code	B3271002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01989676
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.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	16 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 August 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the objective response rate (ORR) in patients with metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer who received PF-05280014 in combination with paclitaxel to those who received trastuzumab EU in combination with paclitaxel.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), the Declaration of Helsinki (World Medical Association 1996 and 2008), and in compliance with all International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed; in particular, those affording greater protection to the safety of study participants.

Background therapy:

Paclitaxel administered during the study (considered as background therapy) was the branded or generic product available in the local region.

Evidence for comparator: -

Actual start date of recruitment	24 February 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 5
Country: Number of subjects enrolled	Brazil: 17
Country: Number of subjects enrolled	Chile: 15
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	India: 39
Country: Number of subjects enrolled	Japan: 32
Country: Number of subjects enrolled	Korea, Republic of: 36
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Peru: 8
Country: Number of subjects enrolled	Philippines: 68
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	Portugal: 3

Country: Number of subjects enrolled	Romania: 15
Country: Number of subjects enrolled	Russian Federation: 199
Country: Number of subjects enrolled	Serbia: 4
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	South Africa: 36
Country: Number of subjects enrolled	Thailand: 9
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	Ukraine: 160
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	702
EEA total number of subjects	58

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	575
From 65 to 84 years	126
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 707 subjects were randomized to the study. Of these, 5 patients were randomized but did not receive study drug.

Pre-assignment

Screening details:

Participants who fulfilled the inclusion/exclusion criteria were randomly assigned to 1 of the 2 treatments of this study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PF-05280014

Arm description:

Participants with human epidermal growth factor receptor 2 (HER2)-positive breast cancer received PF-05280014 in combination with paclitaxel.

Arm type	Experimental
Investigational medicinal product name	PF-05280014
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

PF-05280014 was administered on Days 1, 8, 15 and 22 of each 28-day cycle intravenously followed by paclitaxel on Days 1, 8, and 15 of each 28-day cycle until at least Week 33 of the study. The first infusion of PF-05280014 was 4 mg/kg over 90 minutes on Cycle 1 Day 1. Subsequent weekly infusions of PF-05280014 were 2 mg/kg over 30 to 90 minutes. Paclitaxel was administered at a dose of 80 mg/m^2 over 60 minutes. Following completion of the paclitaxel administration period and beginning no earlier than Week 33 of the study, the PF-05280014 regimen could be changed at the discretion of the investigator to every 3 weeks at a dose of 6 mg/kg infused over 30 to 90 minutes depending on tolerability.

Arm title	Trastuzumab-EU

Arm description:

Participants with HER2-positive breast cancer received trastuzumab-EU in combination with paclitaxel.

Arm type	Active comparator
Investigational medicinal product name	Trastuzumab-EU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Trastuzumab-EU was administered on Days 1, 8, 15 and 22 of each 28-day cycle intravenously followed by paclitaxel on Days 1, 8, and 15 of each 28-day cycle until at least Week 33 of the study. The first infusion of trastuzumab-EU was 4 mg/kg over 90 minutes on Cycle 1 Day 1. Subsequent weekly infusions of trastuzumab-EU were 2 mg/kg over 30 to 90 minutes. Paclitaxel was administered at a dose of 80 mg/m^2 over 60 minutes. Following completion of the paclitaxel administration period and beginning no earlier than Week 33 of the study, the trastuzuamab-EU regimen could be changed at the

discretion of the investigator to every 3 weeks at a dose of 6 mg/kg infused over 30 to 90 minutes depending on tolerability.

Number of subjects in period 1	PF-05280014	Trastuzumab-EU
Started	349	353
Completed	11	6
Not completed	338	347
Discontinued	59	68
Ongoing at data cutoff	279	279

Baseline characteristics

Reporting groups	
Reporting group title	PF-05280014
Reporting group description:	
Participants with human epidermal growth factor receptor 2 (HER2)-positive breast cancer received PF-05280014 in combination with paclitaxel.	
Reporting group title	Trastuzumab-EU
Reporting group description:	
Participants with HER2-positive breast cancer received trastuzumab-EU in combination with paclitaxel.	

Reporting group values	PF-05280014	Trastuzumab-EU	Total
Number of subjects	349	353	702
Age Categorical Units: Subjects			
<18	0	0	0
18 to 64	283	292	575
65 to 84	66	60	126
≥85	0	1	1
Age continuous Units: years			
arithmetic mean	54	54.1	
standard deviation	± 10.9	± 10.9	-
Gender, Male/Female Units: Subjects			
Female	349	353	702
Male	0	0	0

End points

End points reporting groups

Reporting group title	PF-05280014

Reporting group description:

Participants with human epidermal growth factor receptor 2 (HER2)-positive breast cancer received PF-05280014 in combination with paclitaxel.

Reporting group title	Trastuzumab-EU

Reporting group description:

Participants with HER2-positive breast cancer received trastuzumab-EU in combination with paclitaxel.

Subject analysis set title	PF-05280014
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants with human epidermal growth factor receptor 2 (HER2)-positive breast cancer received PF-05280014 on Days 1, 8, 15 and 22 of each 28-day cycle followed by paclitaxel on Days 1, 8 and 15 of each 28-day cycle both as intravenous (IV) infusions until at least Week 33 of the study. The first infusion of PF-05280014 was 4 mg/kg over 90 minutes on Cycle 1 Day 1. Subsequent weekly infusions of PF-05280014 were 2 mg/kg over 30 to 90 minutes. Paclitaxel was administered at a dose of 80 mg/m^2 over 60 minutes. Following completion of the paclitaxel administration period and beginning no earlier than Week 33 of the study, the PF-05280014 could be changed at the discretion of the investigator to every 3 weeks at a dose of 6 mg/kg infused over 30 to 90 minutes depending on tolerability.

Subject analysis set title	Trastuzumab-EU
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants with HER2-positive breast cancer received trastuzumab-EU on Days 1, 8, 15 and 22 of each 28-day cycle followed by paclitaxel on Days 1, 8 and 15 of each 28-day cycle both as IV infusions until at least Week 33 of the study. The first infusion of trastuzumab-EU was 4 mg/kg over 90 minutes on Cycle 1 Day 1. Subsequent weekly infusions of trastuzumab-EU were 2 mg/kg over 30 to 90 minutes. Paclitaxel was administered at a dose of 80 mg/m^2 over 60 minutes. Following completion of the paclitaxel administration period and beginning no earlier than Week 33 of the study, the trastuzuamab-EU could be changed at the discretion of the investigator to every 3 weeks at a dose of 6 mg/kg infused over 30 to 90 minutes depending on tolerability.

Primary: Objective Response Rate (ORR) Derived from Central Radiology Assessments: ITT Population

End point title	Objective Response Rate (ORR) Derived from Central Radiology Assessments: ITT Population

End point description:

ORR was defined as the percentage of participants who achieved complete response (CR, complete disappearance of all target lesions with the exception of nodal disease; all target nodes must have decreased to normal size [short axis <10 mm]) or partial response (PR, ≥30% decrease from Baseline of the sum of diameters of all target measurable lesions; the short diameter was used in the sum for target nodes, while the longest diameter was used in the sum for all other target lesions) by Week 25 of the study and confirmed on a follow-up assessment (Week 33±14 days), based on the assessments of the central radiology review in accordance with RECIST 1.1.

End point type	Primary

End point timeframe:

From the date of randomization until the cutoff date of 24 August 2016 when all participants had either completed the Week 33 tumor assessment or discontinued study drug earlier than the Week 33 visit.

End point values	PF-05280014	Trastuzumab-EU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	352	355		
Units: Percentage of participants				
number (confidence interval 95%)	62.5 (57.2 to 67.6)	66.5 (61.3 to 71.4)		

Statistical analyses

Statistical analysis title	Analysis of ORR
Statistical analysis description:	
RR and associated 95% CI are unstratified and based on the Miettinen and Nurminen method.	
Comparison groups	Trastuzumab-EU v PF-05280014
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk ratio (RR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.842
upper limit	1.049

Secondary: One-year Progression-Free Survival (PFS) Rate Derived from Central Radiology Assessments: ITT Population

End point title	One-year Progression-Free Survival (PFS) Rate Derived from Central Radiology Assessments: ITT Population
End point description:	
One (1)-year PFS rate was analyzed based on the time from date of randomization to first documentation of progressive disease (PD), or death due to any cause in the absence of documented PD, based on the assessments of the central radiology review in accordance with RECIST 1.1. The 95% CI for the median time to event was based on the Brookmeyer and Crowley method. The 95% CI for the hazard ratio was based on the Cox's proportional hazards model. 9999 = not estimable, there were insufficient events to estimate the upper bound of the 95% CI.	
End point type	Secondary
End point timeframe:	
From the date of randomization until 378 days post-randomization as of the cutoff date of 24 August 2016.	

End point values	PF-05280014	Trastuzumab-EU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	352	355		
Units: Months				
median (confidence interval 95%)	12.16 (11.89 to 13.4)	12.22 (11.83 to 9999)		

Statistical analyses

Statistical analysis title	Analysis of PFS
Comparison groups	PF-05280014 v Trastuzumab-EU
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.691 [1]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.37

Notes:

[1] - 1-sided p-value from the log-rank test stratified by Prior Trastuzumab Exposure (Yes/No) and Estrogen Receptor (ER) Status (ER positive vs. ER negative)

Secondary: Duration of Response (DOR) per Central Radiology Assessments: ITT Population

End point title	Duration of Response (DOR) per Central Radiology Assessments: ITT Population

End point description:

DOR was defined as the time from date of the first documentation of objective tumor response (CR or PR) to the first documentation of PD, or to death due to any cause in the absence of documented PD, based on the assessments of the central radiology review in accordance with RECIST 1.1. The 95% CI for the median time to event was based on the Brookmeyer and Crowley method. The 95% CI for the hazard ratio was based on the Cox's proportional hazards model. 9999 = not estimable, there were insufficient events to estimate the value of median and 95% CI for the PF-05280014 group and insufficient events to estimate the upper bound of the 95% CI for the Trastuzumab-EU group.

End point type	Secondary

End point timeframe:

From the date of randomization until 378 days post-randomization as of the cutoff date of 24 August 2016.

End point values	PF-05280014	Trastuzumab-EU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	352	355		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	10.61 (10.22 to 9999)		

Statistical analyses

Statistical analysis title	Analysis of DOR
Comparison groups	PF-05280014 v Trastuzumab-EU
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.661 [2]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.56

Notes:

[2] - 1-sided p-value from the log-rank test stratified by Prior Trastuzumab Exposure (Yes/No) and Estrogen Receptor (ER) Status (ER positive vs.
ER negative).

Secondary: One-year Survival Rate: ITT Population

End point title	One-year Survival Rate: ITT Population

End point description:

One-year survival rate was analyzed based on the time from date of randomization to the date of death due to any cause while the participant was on the study. The 95% CI for the median time to event was based on the Brookmeyer and Crowley method. The 95% CI for the hazard ratio was based on the Cox's proportional hazards model. 9999 = not estimable, there were insufficient events to estimate the values.

End point type	Secondary

End point timeframe:

From the date of randomization until 378 days post-randomization as of the cutoff date of 24 August 2016.

End point values	PF-05280014	Trastuzumab-EU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	352	355		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

Statistical analysis title	Analysis of 1-year Survival Rate
Comparison groups	PF-05280014 v Trastuzumab-EU
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.581 [3]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.669
upper limit	1.642

Notes:

[3] - 1-sided p-value from the log-rank test stratified by prior trastuzumab exposure (Yes/No) and ER status (ER positive versus ER negative)

Secondary: Serum Peak (1 Hour Post End of Infusion) Concentration of PF-05280014 at Selected Cycles: Pharmacokinetics (PK) Population

End point title	Serum Peak (1 Hour Post End of Infusion) Concentration of PF-05280014 at Selected Cycles: Pharmacokinetics (PK) Population[4]

End point description:

Human PK serum samples were analyzed for concentrations of PF-05280014 using a validated, sensitive, and specific enzyme-linked immuno-sorbent assay (ELISA).

End point type	Secondary

End point timeframe:

Available peak PK concentration data collected at Cycle 1, Day 1 and Cycle 5, Day 1 as of the data cutoff date of 24 August 2016

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Quantification of trastuzumab concentrations was not part of the planned analyses.

End point values	PF-05280014			
Subject group type	Reporting group			
Number of subjects analysed	349			
Units: µg/mL				
median (full range (min-max))				
Cycle 1 Day 1 (N=267, NALQ=260)	90.5 (0 to 246)			
Cycle 5 Day 1 (N=205, NALQ=204)	95.6 (0 to 435)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Peak (1 Hour Post End of Infusion) Concentration of Trastuzumab-EU at Selected Cycles: PK Population

End point title	Serum Peak (1 Hour Post End of Infusion) Concentration of Trastuzumab-EU at Selected Cycles: PK Population[5]

End point description:

Human PK serum samples were analyzed for concentrations of trastuzumab-EU using a validated, sensitive, and specific ELISA.

End point type	Secondary

End point timeframe:

Available peak PK concentration data collected at Cycle 1, Day 1 and Cycle 5, Day 1 as of the data cutoff date of 24 August 2016

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Quantification of trastuzumab concentrations was not part of the planned analyses.

End point values	Trastuzumab-EU			
Subject group type	Reporting group			
Number of subjects analysed	353			
Units: µg/mL				
median (full range (min-max))				
Cycle 1 Day 1 (N=259, NALQ=255)	90.8 (0 to 273)			
Cycle 5 Day 1 (N=220, NALQ=220)	94.35 (8.96 to 353)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Trough (Pre-dose) Concentration of PF-05280014 at Selected Cycles: PK Population

End point title	Serum Trough (Pre-dose) Concentration of PF-05280014 at Selected Cycles: PK Population[6]

End point description:

Human PK serum samples were analyzed for concentrations of PF-05280014 using a validated, sensitive, and specific ELISA.

End point type	Secondary

End point timeframe:

Available trough concentrations collected from Cycle 1, Day 1 to Cycle 17, Day 1 as of the data cutoff date of 24 August 2016, except the EOT visit and unplanned records.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Quantification of trastuzumab concentrations was not part of the planned analyses.

End point values	PF-05280014			
Subject group type	Reporting group			
Number of subjects analysed	349			
Units: µg/mL				
median (full range (min-max))				
Cycle 1 Day 1 (N=349, NALQ=17)	0 (0 to 123)			
Cycle 1 Day 8 (N= 339, NALQ=334)	27.9 (0 to 91.5)			
Cycle 3 Day 1 (N=309, NALQ=307)	48.2 (0 to 110)			
Cycle 4 Day 1 (N=304, NALQ=303)	53.5 (0 to 150)			
Cycle 5 Day 1 (N=289, NALQ=288)	57 (0 to 182)			
Cycle 5 Day 8 (N=277, NALQ=277)	57.4 (9.85 to 174)			
Cycle 7 Day 1 (N=266, NALQ=264)	60.8 (0 to 152)			
Cycle 8 Day 1 (N=255, NALQ=254)	62.2 (0 to 140)			
Cycle 11 Day 1 (N=212, NALQ=209)	54.4 (0 to 148)			
Cycle 14 Day 1 (N=153, NALQ=152)	50.9 (0 to 169)			
Cycle 17 Day 1 (N=106, NALQ=105)	49.15 (0 to 131)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Trough (Pre-dose) Concentration Trastuzumab-EU at Selected Cycles: PK Population

End point title	Serum Trough (Pre-dose) Concentration Trastuzumab-EU at Selected Cycles: PK Population[7]

End point description:

Human PK serum samples were analyzed for concentrations of trastuzumab-EU using a validated, sensitive, and specific ELISA.

End point type	Secondary

End point timeframe:

Available trough concentrations collected from Cycle 1, Day 1 to Cycle 17, Day 1 as of the data cutoff date of 24 August 2016, except the EOT visit and unplanned records.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Quantification of trastuzumab concentrations was not part of the planned analyses.

End point values	Trastuzumab-EU			
Subject group type	Reporting group			
Number of subjects analysed	353			
Units: µg/mL				
median (full range (min-max))				
Cycle 1 Day 1 (N=348, NALQ=17)	0 (0 to 98)			

Cycle 1 Day 8 (N=340, NALQ=339)	29.8 (0 to 101)			
Cycle 3 Day 1 (N=319, NALQ=319)	50.4 (1.74 to 171)			
Cycle 4 Day 1 (N=316, NALQ=312)	54.35 (0 to 148)			
Cycle 5 Day 1 (N=303, NALQ=302)	60 (0 to 244)			
Cycle 5 Day 8 (N=287, NALQ=287)	61.2 (4.64 to 150)			
Cycle 7 Day 1 (N=275, NALQ=275)	62.9 (1.93 to 340)			
Cycle 8 Day 1 (N=261, NALQ=261)	65.6 (0.69 to 155)			
Cycle 11 Day 1 (N=215, NALQ=215)	58.7 (1.52 to 251)			
Cycle 14 Day 1 (N=142, NALQ=142)	55.1 (4.68 to 187)			
Cycle 17 Day 1 (N=101, NALQ=101)	50.6 (15 to 126)			

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-Drug Antibodies (ADA) Incidence: Safety Population

End point title	Anti-Drug Antibodies (ADA) Incidence: Safety Population

End point description:

Two sensitive, specific, and semi-quantitative electrochemiluminescent (ECL) immunoassays, 1 for detecting antibodies against PF-05280014 and the other for detecting antibodies against trastuzumab, were used to analyze ADA samples. Serum samples were first screened for ADA. Any samples that were positive in the screening assay were further analyzed to confirm the positive result and determine the antibody titers. All samples were taken prior to dosing. The number of participants with a positive sample (titer≥1.0) is provided.

End point type	Secondary

End point timeframe:

Available data from Baseline through Cycle 17, Day 1 as of the data cutoff date of 24 August 2016, except the EOT visit and unplanned records.

End point values	PF-05280014	Trastuzumab-EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	349	353		
Units: Not Applicable				
Cycle 1 Day 1 (Prior to treatment) (n=349, 350)	30	14		
Cycle 3 Day 1 (n=308, 321)	0	0		
Cycle 5 Day 1 (n=287, 303)	0	0		
Cycle 8 Day 1 (n=253, 263)	0	0		
Cycle 11 Day 1 (n=218, 222)	0	0		
Cycle 14 Day 1 (n=160, 147)	0	0		
Cycle 17 Day 1 (n=107, 105)	0	1		
Overall (Post-treatment) (n=323, 331)	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Neutralizing Antibodies (NAb) Incidence at Cycle 1 Day 1 Prior to Treatment: Safety Population

End point title	Neutralizing Antibodies (NAb) Incidence at Cycle 1 Day 1 Prior to Treatment: Safety Population

End point description:

Human serum samples testing positive for the presence of ADA (anti-PF-05280014 or anti-trastuzumab-EU) were analyzed for the presence or absence of NAb (neutralizing anti-PF-05280014 or neutralizing anti-trastuzumab-EU antibodies) following a tiered approach using screening and titer determination. All samples at baseline (prior to treatment) or post-treatment were taken prior to dosing. All participants with the exception of 1 participant in the trastuzumab-EU group tested negative for ADA (titer <1.00) from Cycle 1, Day 1 post-treatment through Cycle 17, Day 1. The corresponding NAb result for this Cycle 17, Day 1 ADA positive sample was not yet available; thus, not reported. The number of participants at Baseline (prior to treatment) with a positive NAb sample (titer≥1.48) is provided.

End point type	Secondary

End point timeframe:

Available data from Baseline to Cycle 17, Day 1 as of the data cutoff date of 24 August 2016, except the EOT visit and unplanned records.

End point values	PF-05280014	Trastuzumab-EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	348	350		
Units: Not Applicable	16	8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) and serious AEs (SAEs) were reported from the time the participant had taken at least 1 dose of study drug and the time of informed consent, respectively, through 70 days after the last dose of study drug.

Adverse event reporting additional description:

Incidence of treatment emergent AEs/SAEs was comparable across treatment groups, and defined as AEs occurring from first dose of study drug (or any pre-existing event that worsened in severity after dosing) through 70 days after the last dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Trastuzumab-EU

Reporting group description:

Participants with HER2-positive breast cancer received trastuzumab-EU on Days 1, 8, 15 and 22 of each 28-day cycle followed by paclitaxel on Days 1, 8 and 15 of each 28-day cycle both as IV infusions until at least Week 33 of the study. The first infusion of trastuzumab-EU was 4 mg/kg over 90 minutes on Cycle 1 Day 1. Subsequent weekly infusions of trastuzumab-EU were 2 mg/kg over 30 to 90 minutes. Paclitaxel was administered at a dose of 80 mg/m^2 over 60 minutes. Following completion of the paclitaxel administration period and beginning no earlier than Week 33 of the study, the trastuzuamab-EU could be changed at the discretion of the investigator to every 3 weeks at a dose of 6 mg/kg infused over 30 to 90 minutes depending on tolerability.

Reporting group title	PF-05280014

Reporting group description:

Participants with HER2-positive breast cancer received PF-05280014 on Days 1, 8, 15 and 22 of each 28-day cycle followed by paclitaxel on Days 1, 8 and 15 of each 28-day cycle both as IV infusions until at least Week 33 of the study. The first infusion of PF-05280014 was 4 mg/kg over 90 minutes on Cycle 1 Day 1. Subsequent weekly infusions of PF-05280014 were 2 mg/kg over 30 to 90 minutes. Paclitaxel was administered at a dose of 80 mg/m^2 over 60 minutes. Following completion of the paclitaxel administration period and beginning no earlier than Week 33 of the study, the PF-05280014 could be changed at the discretion of the investigator to every 3 weeks at a dose of 6 mg/kg infused over 30 to 90 minutes depending on tolerability.

Serious adverse events	Trastuzumab-EU	PF-05280014	
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 353 (15.30%)	51 / 349 (14.61%)	
number of deaths (all causes)	24	16	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	0 / 353 (0.00%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian germ cell teratoma benign			

subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Uterine leiomyoma			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 353 (0.00%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertension			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Cyst rupture			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Death			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Disease progression			
subjects affected / exposed	12 / 353 (3.40%)	12 / 349 (3.44%)	
occurrences causally related to treatment / all	0 / 12	0 / 12	
deaths causally related to treatment / all	0 / 12	0 / 12	
Fatigue			
subjects affected / exposed	1 / 353 (0.28%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 353 (0.85%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	2 / 353 (0.57%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Uterine prolapse			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
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			
Acute respiratory failure			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alveolitis allergic			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 353 (0.57%)	5 / 349 (1.43%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary oedema			
subjects affected / exposed	0 / 353 (0.00%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	2 / 353 (0.57%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 353 (0.28%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			

subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 353 (0.28%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 353 (0.00%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 353 (0.85%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	2 / 2	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 353 (0.00%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pericardial effusion			

subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Intracranial venous sinus thrombosis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 353 (0.57%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 353 (0.00%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 353 (0.28%)	3 / 349 (0.86%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 353 (0.28%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	1 / 353 (0.28%)	3 / 349 (0.86%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 353 (0.28%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Macular degeneration			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 353 (0.28%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Small intestinal obstruction			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
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			
Angioedema			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis contact			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 353 (0.28%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (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	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			

subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	4 / 353 (1.13%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			

subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 353 (0.85%)	4 / 349 (1.15%)	
occurrences causally related to treatment / all	1 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 353 (0.57%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Staphylococcal sepsis			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (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	2 / 353 (0.57%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 353 (0.00%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	0 / 353 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 353 (0.00%)	4 / 349 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 353 (0.28%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Trastuzumab-EU	PF-05280014	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	331 / 353 (93.77%)	327 / 349 (93.70%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	41 / 353 (11.61%)	29 / 349 (8.31%)	
occurrences (all)	100	38	
Aspartate aminotransferase			

increased			
subjects affected / exposed	26 / 353 (7.37%)	25 / 349 (7.16%)	
occurrences (all)	69	25	
Blood alkaline phosphatase increased			
subjects affected / exposed	24 / 353 (6.80%)	16 / 349 (4.58%)	
occurrences (all)	36	20	
Ejection fraction decreased			
subjects affected / exposed	34 / 353 (9.63%)	30 / 349 (8.60%)	
occurrences (all)	44	39	
Weight increased			
subjects affected / exposed	20 / 353 (5.67%)	15 / 349 (4.30%)	
occurrences (all)	27	20	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	29 / 353 (8.22%)	33 / 349 (9.46%)	
occurrences (all)	44	53	
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 353 (7.37%)	34 / 349 (9.74%)	
occurrences (all)	53	58	
Nervous system disorders			
Dizziness			
subjects affected / exposed	15 / 353 (4.25%)	30 / 349 (8.60%)	
occurrences (all)	21	42	
Headache			
subjects affected / exposed	51 / 353 (14.45%)	40 / 349 (11.46%)	
occurrences (all)	60	52	
Neuropathy peripheral			
subjects affected / exposed	33 / 353 (9.35%)	29 / 349 (8.31%)	
occurrences (all)	48	42	
Peripheral sensory neuropathy			
subjects affected / exposed	83 / 353 (23.51%)	93 / 349 (26.65%)	
occurrences (all)	139	168	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	129 / 353 (36.54%)	117 / 349 (33.52%)	
occurrences (all)	406	299	
Leukopenia			
subjects affected / exposed	40 / 353 (11.33%)	33 / 349 (9.46%)	
occurrences (all)	103	109	
Neutropenia			
subjects affected / exposed	90 / 353 (25.50%)	95 / 349 (27.22%)	
occurrences (all)	251	282	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	43 / 353 (12.18%)	50 / 349 (14.33%)	
occurrences (all)	53	57	
Fatigue			
subjects affected / exposed	49 / 353 (13.88%)	42 / 349 (12.03%)	
occurrences (all)	80	71	
Oedema peripheral			
subjects affected / exposed	41 / 353 (11.61%)	23 / 349 (6.59%)	
occurrences (all)	59	29	
Pyrexia			
subjects affected / exposed	26 / 353 (7.37%)	39 / 349 (11.17%)	
occurrences (all)	49	55	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	28 / 353 (7.93%)	11 / 349 (3.15%)	
occurrences (all)	38	17	
Constipation			
subjects affected / exposed	26 / 353 (7.37%)	20 / 349 (5.73%)	
occurrences (all)	43	21	
Diarrhoea			
subjects affected / exposed	65 / 353 (18.41%)	56 / 349 (16.05%)	
occurrences (all)	116	96	
Nausea			
subjects affected / exposed	63 / 353 (17.85%)	54 / 349 (15.47%)	
occurrences (all)	134	160	
Stomatitis			

subjects affected / exposed	12 / 353 (3.40%)	23 / 349 (6.59%)	
occurrences (all)	20	28	
Vomiting			
subjects affected / exposed	24 / 353 (6.80%)	26 / 349 (7.45%)	
occurrences (all)	33	38	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	29 / 353 (8.22%)	29 / 349 (8.31%)	
occurrences (all)	39	41	
Dyspnoea			
subjects affected / exposed	18 / 353 (5.10%)	19 / 349 (5.44%)	
occurrences (all)	20	29	
Epistaxis			
subjects affected / exposed	22 / 353 (6.23%)	15 / 349 (4.30%)	
occurrences (all)	29	21	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	184 / 353 (52.12%)	189 / 349 (54.15%)	
occurrences (all)	249	243	
Pruritus			
subjects affected / exposed	18 / 353 (5.10%)	11 / 349 (3.15%)	
occurrences (all)	20	14	
Rash			
subjects affected / exposed	24 / 353 (6.80%)	24 / 349 (6.88%)	
occurrences (all)	30	34	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	35 / 353 (9.92%)	39 / 349 (11.17%)	
occurrences (all)	56	70	
Back pain			
subjects affected / exposed	29 / 353 (8.22%)	13 / 349 (3.72%)	
occurrences (all)	36	17	
Bone pain			
subjects affected / exposed	12 / 353 (3.40%)	19 / 349 (5.44%)	
occurrences (all)	18	25	
Myalgia			

subjects affected / exposed	33 / 353 (9.35%)	21 / 349 (6.02%)	
occurrences (all)	75	33	
Pain in extremity			
subjects affected / exposed	19 / 353 (5.38%)	19 / 349 (5.44%)	
occurrences (all)	34	26	
Infections and infestations			
Respiratory tract infection viral			
subjects affected / exposed	11 / 353 (3.12%)	20 / 349 (5.73%)	
occurrences (all)	13	27	
Upper respiratory tract infection			
subjects affected / exposed	40 / 353 (11.33%)	30 / 349 (8.60%)	
occurrences (all)	68	41	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	15 / 353 (4.25%)	21 / 349 (6.02%)	
occurrences (all)	17	25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2013	This amendment was implemented in response to recommendations made by regulatory agencies during reviews performed prior to Health Authority, Institutional Review Board or Independent Ethics Committee submissions; no patients had been screened or randomized at the time of the amendment.
10 July 2014	This amendment was implemented due to feedback from a retrospective review by Parexel Informatics of randomized patients to determine if they had measurable disease (following investigator assessment), and subsequent to feedback from regulatory agencies.
27 September 2016	This amendment was implemented to update the study design to end patient treatment after the completion of Week 53 visit assessments, following communication with regulatory agencies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported