Clinical trial results:
A Phase 3 Randomised, Double-Blind Study of PF-05280014 Plus Paclitaxel Versus Trastuzumab Plus Paclitaxel for the First-Line Treatment of Subjects 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	27 June 2020

Results information

Result version number	v2 (current)
This version publication date	23 June 2021
First version publication date	14 October 2017
Version creation reason	

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 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 8007181021, 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	Final
Date of interim/final analysis	05 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

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	1 Years
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	Czechia: 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 randomised to the study. Of these, 5 subjects were randomised but did not receive the study drug.

Pre-assignment

Screening details:

Subjects 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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	PF-05280014

Arm description:

Subjects 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 the end 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.

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:

Subjects 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 the end 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.

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	234	217
Not completed	115	136
Adverse event, serious fatal	52	60
No longer willing to participate in study	26	25
Unspecified	1	2
Lost to follow-up	8	18
Subjects terminated from study by Sponsor	26	30
Protocol deviation	2	1

Baseline characteristics

Reporting groups

Reporting group title	PF-05280014

Reporting group description:

Subjects 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 the end 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.

Reporting group title	Trastuzumab-EU

Reporting group description:

Subjects 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 the end 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 values	PF-05280014	Trastuzumab-EU	Total
Number of subjects	349	353	702
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	283	292	575
From 65-84 years	66	60	126
85 years and over	0	1	1
Age continuous Units: years			
arithmetic mean	54.0	54.1	
standard deviation	± 10.9	± 10.9	-
Sex: Female, Male Units: Subjects			
Female	349	353	702
Male	0	0	0

End points

End points reporting groups

Reporting group title	PF-05280014

Reporting group description:

Subjects 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 the end 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.

Reporting group title	Trastuzumab-EU

Reporting group description:

Subjects 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 the end 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.

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

Subject analysis set description:

Subjects 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 the end 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:

Subjects 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 the end 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 subjects 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 (SOD) 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. The ITT population was defined as all subjects who were randomised to study drug.

End point type	Primary

End point timeframe:

From the date of randomisation until all subjects 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 subjects				
number (confidence interval 95%)	62.5 (57.2 to 67.6)	66.5 (61.3 to 71.4)		

Statistical analyses

Statistical analysis title	PF-05280014 versus Trastuzumab-EU

Statistical analysis description:

Risk Ratio and associated 95% confidence interval (CI) are unstratified and based on the Miettinen and Nurminen method.

Comparison groups	PF-05280014 v Trastuzumab-EU
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Risk ratio (RR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.842
upper limit	1.049

Notes:

[1] - The hypothesis to be tested in this study was that the risk ratio of ORR of PF-05280014 versus that of trastuzumab-EU by Week 25 (+/-14 days) was within a pre-specified margin of 0.80 to 1.25.

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-year PFS rate was analysed based on the time from date of randomisation to first documentation of progressive disease (PD), or death due to any cause in the absence of documented PD, based on assessments of central radiology review in accordance with RECIST 1.1. PD was defined for target disease as at least a 20% increase in sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in sum was observed during therapy) with a minimum absolute increase of 5 mm. For non-target disease PD: unequivocal progression of pre-existing lesions and if overall tumor burden increased sufficiently to merit discontinuation of therapy; appearance of any new unequivocal malignant lesion was also considered PD. The 95% CI for median time to event was based on Brookmeyer and Crowley method. The ITT population was defined as all subjects who were randomised to study drug. 99999=there are insufficient events to estimate the upper bound of the 95% CI.

End point type	Secondary

End point timeframe:

From the date of randomisation until 378 days post-randomisation

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 (11.93 to 12.48)	12.06 (11.79 to 99999)		

Statistical analyses

Statistical analysis title	PF-05280014 versus Trastuzumab-EU

Statistical analysis description:

The 95% CI for the hazard ratio was based on the Cox's proportional hazard model.

Comparison groups	PF-05280014 v Trastuzumab-EU
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.505 [2]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.26

Notes:

[2] - 1-sided log-rank test was used to compare the PFS distribution between the two treatment groups and was 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:time from first documentation of OR(CR or PR) to first documentation of PD/death due to any cause, based on central radiology review.Per RECIST v1.1, CR:complete disappearance of all target (T) lesions with exception of nodal disease; all T nodes reduced in short axis <10 mm. PR: >=30% decrease from baseline of SOD of T lesions; short diameter used in sum for T nodes, longest diameter used in sum for other T lesions. PD for T disease:at least 20% increase in SOD of T lesions above smallest sum observed with minimum absolute increase of 5 mm. For non-T disease:unequivocal progression of pre-existing lesions and if overall tumor burden increased sufficiently to merit discontinuation of therapy; appearance of any new unequivocal malignant lesion was also considered PD. 95% CI for median time to event based on Brookmeyer and Crowley method. ITT population was analysed. "N"=subjects evaluable for this endpoint. 99999=there are insufficient events to estimate upper bound of 95% CI.

End point type	Secondary

End point timeframe:

From the date of randomisation until 378 days post-randomisation

End point values	PF-05280014	Trastuzumab-EU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224	238		
Units: months				
median (confidence interval 95%)	11.27 (10.41 to 11.27)	10.58 (10.22 to 99999)		

Statistical analyses

Statistical analysis title	PF-05280014 versus Trastuzumab-EU

Statistical analysis description:

The 95% CI for the hazard ratio was based on the Cox's proportional hazard model.

Comparison groups	PF-05280014 v Trastuzumab-EU
Number of subjects included in analysis	462
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.304 [3]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.27

Notes:

[3] - 1-sided log-rank test was used to compare the DOR distribution between the two treatment groups and was stratified by prior trastuzumab exposure (Yes/No) and ER status (ER positive vs. ER negative).

Secondary: Overall Survival: ITT Population

End point title	Overall Survival: ITT Population

End point description:

Overall survival was analysed based on the time from date of randomisation to the date of death due to any cause. Subjects last known to be alive were censored on the date of last contact. The 95% CI for the median time to event was based on the Brookmeyer and Crowley Method. The ITT population was defined as all subjects who were randomised to study drug. Here, 99999 signifies that there are insufficient events to estimate the median survival and the 95% CI.

End point type	Secondary

End point timeframe:

From the date of randomisation until end of study (approximately 6 years)

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%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	PF-05280014 versus Trastuzumab-EU

Statistical analysis description:

The 95% CI for the hazard ratio was based on the Cox's proportional hazard model.

Comparison groups	PF-05280014 v Trastuzumab-EU
Number of subjects included in analysis	707
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.339 [4]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.929
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.656
upper limit	1.316

Notes:

[4] - 1-sided log-rank test was used to compare the OS distribution between the two treatment groups and was stratified by prior trastuzumab exposure (Yes/No) and ER status (ER positive vs. ER negative).

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[5]

End point description:

Human PK serum samples were analysed for concentrations of PF-05280014 using a validated, sensitive, and specific ELISA. PK population. "n"=subjects evaluable at specified time points only. Here, 99999 signifies that the Cycle 17 Day 1 (C17D1) samples summarised previously at PCD (Week 33) fell outside of cut-off used for final analysis (Week 53), to limit data for up to 1-year post randomisation, which was more conservative from previous Week 33 analysis. While comparing data between Week 33 and Week 53, there was a significant drop off in number of samples summarised at C17D1 and was down to zero for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose on Day 1 of Cycles 1, 3, 4, 5, 7, 8, 11, 14, 17 and Day 8 of Cycles 1 and 5

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: No statistical analysis was performed for this endpoint

End point values	PF-05280014			
Subject group type	Reporting group			
Number of subjects analysed	349			
Units: mcg/mL				
median (full range (min-max))				
Cycle 1 Day 1 (n= 349)	0.00 (0.00 to 123)			
Cycle 1 Day 8 (n= 339)	27.90 (0.00 to 91.5)			
Cycle 3 Day 1 (n= 309)	48.20 (0.00 to 110)			
Cycle 4 Day 1 (n= 304)	53.50 (0.00 to 150)			
Cycle 5 Day 1 (n= 288)	57.00 (0.00 to 182)			
Cycle 5 Day 8 (n= 277)	57.40 (9.85 to 174)			
Cycle 7 Day 1 (n= 265)	60.50 (0.00 to 152)			
Cycle 8 Day 1 (n= 256)	62.25 (0.00 to 140)			
Cycle 11 Day 1 (n= 220)	54.65 (0.00 to 148)			
Cycle 14 Day 1 (n= 188)	50.70 (0.00 to 189)			
Cycle 17 Day 1 (n= 0)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Peak Concentration of PF-05280014 at Selected Cycles: Pharmacokinetics (PK) Population

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

End point description:

Human PK serum samples were analysed for concentrations of PF-05280014 using a validated, sensitive, and specific enzyme-linked immunosorbent assay (ELISA). PK population was used for analysis, included all subjects who received PF-05280014 or trastuzumab-EU and had no major protocol deviations that influenced PK assessments, and had at least 1 post dose concentration measurement. Here "number analysed (n)" signifies subjects evaluable at specified time points only.

End point type	Secondary

End point timeframe:

1 hour post end of infusion on Day 1 of Cycles 1 and 5

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: No statistical analysis was performed for this endpoint

End point values	PF-05280014			
Subject group type	Reporting group			
Number of subjects analysed	349			
Units: mcg/mL				
median (full range (min-max))				
Cycle 1 Day 1 (n= 278)	89.85 (0.00 to 246)			
Cycle 5 Day 1 (n= 204)	95.70 (0.00 to 435)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Peak Concentration of Trastuzumab-EU at Selected Cycles: PK Population

End point title	Serum Peak Concentration of Trastuzumab-EU at Selected Cycles: PK Population[7]

End point description:

Human PK serum samples were analysed for concentrations of trastuzumab-EU using a validated, sensitive, and specific ELISA. PK population was used for analysis, included all subjects who received PF-05280014 or trastuzumab-EU and had no major protocol deviations that influenced PK assessments, and had at least 1 post dose concentration measurement. Here "n" signifies subjects evaluable at specified time points only.

End point type	Secondary

End point timeframe:

1 hour post end of infusion on Day 1 of Cycles 1 and 5

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: No statistical analysis was performed for this endpoint

End point values	Trastuzumab-EU			
Subject group type	Reporting group			
Number of subjects analysed	353			
Units: mcg/mL				
median (full range (min-max))				
Cycle 1 Day 1 (n= 267)	89.70 (0.00 to 273)			
Cycle 5 Day 1 (n= 221)	94.40 (8.96 to 353)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Serum Trough (Pre-dose) Concentration of Trastuzumab-EU at

	Selected Cycles: PK Population[8]

End point description:

Human PK serum samples were analysed for concentrations of trastuzumab-EU using a validated, sensitive, and specific ELISA. PK population was used for analysis, included all subjects who received PF-05280014 or trastuzumab-EU and had no major protocol deviations that influenced PK assessments, and had at least 1 post dose concentration measurement. Here "n" signifies subjects evaluable at specified time points only.

End point type	Secondary

End point timeframe:

Pre-dose on Day 1 of Cycles 1, 3, 4, 5, 7, 8, 11, 14, 17 and Day 8 of Cycles 1 and 5

Notes:

[8] - 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: No statistical analysis was performed for this endpoint

End point values	Trastuzumab-EU			
Subject group type	Reporting group			
Number of subjects analysed	353			
Units: mcg/mL				
median (full range (min-max))				
Cycle 1 Day 1 (n= 349)	0.00 (0.00 to 98.0)			
Cycle 1 Day 8 (n= 340)	29.80 (0.00 to 101)			
Cycle 3 Day 1 (n= 319)	50.40 (1.74 to 171)			
Cycle 4 Day 1 (n= 316)	54.35 (0.00 to 148)			
Cycle 5 Day 1 (n= 303)	60.00 (0.00 to 244)			
Cycle 5 Day 8 (n= 287)	61.20 (4.64 to 150)			
Cycle 7 Day 1 (n= 276)	63.00 (1.93 to 340)			
Cycle 8 Day 1 (n= 262)	65.55 (0.690 to 155)			
Cycle 11 Day 1 (n= 223)	57.50 (1.52 to 251)			
Cycle 14 Day 1 (n= 173)	54.60 (0.00 to 187)			
Cycle 17 Day 1 (n= 1)	45.10 (45.1 to 45.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Positive Anti-Drug Antibodies (ADA) Sample: Safety Population

End point title	Number of Subjects With Positive Anti-Drug Antibodies (ADA) Sample: 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 analyse ADA samples. Serum samples were first screened for ADA. Any samples that were

positive in the screening assay were further analysed to confirm the positive result and determine the antibody titers. All samples were taken prior to dosing. The number of subjects with a positive sample (titer >=1.0) is provided. Safety population was used for analysis, included all subjects who received at least 1 dose of study drug. Here "n" signifies subjects evaluable at specified time points only. Here, 99999 signifies subjects were not tested for anti-drug antibodies.

End point type	Secondary

End point timeframe:

Pre-dose on Day 1 of Cycles 1, 3, 5, 8, 11, 14, 17

End point values	PF-05280014	Trastuzumab-EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	349	353		
Units: subjects				
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= 255, 263)	0	0		
Cycle 11 Day 1 (n= 223, 224)	0	0		
Cycle 14 Day 1 (n= 192, 175)	0	0		
Cycle 17 Day 1 (n= 0, 1)	99999	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Positive Neutralising Antibodies (Nab) Prior to Treatment: Safety Population

End point title	Number of Subjects With Positive Neutralising Antibodies (Nab) 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 analysed for the presence or absence of NAb (neutralising anti-PF-05280014 or neutralising anti-trastuzumab-EU antibodies) following a tiered approach using screening and titer determination. The number of subjects at baseline (prior to treatment) with a positive NAb sample (titer >=1.48) is provided. Safety population was used for analysis, included all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (prior to treatment)

End point values	PF-05280014	Trastuzumab-EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	349	350		
Units: subjects	20	9		

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) which occurred from the time the subject 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 (maximum up to 328 weeks)

Adverse event reporting additional description:

The total number of deaths occurred during study are reported for all randomised subjects, not only for treated subjects, and included deaths which occurred beyond 70 days post last study drug dose (i.e. beyond 328 weeks). SAEs, Non-SAEs: safety population (all subjects who received at least 1 dose of study drug).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	PF-05280014

Reporting group description:

Subjects 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 the end 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.

Reporting group title	Trastuzumab-EU

Reporting group description:

Subjects 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 the end 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.

Serious adverse events	PF-05280014	Trastuzumab-EU	
Total subjects affected by serious adverse events			
subjects affected / exposed	67 / 349 (19.20%)	69 / 353 (19.55%)	
number of deaths (all causes)	52	60	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	2 / 349 (0.57%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ovarian germ cell teratoma benign			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngeal neoplasm benign			
subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression	Additional description: Preferred term coding updates were made at different times for the 2 databases collecting adverse events. After reconciliation acceptable discrepancies between preferred terms were permitted.		
subjects affected / exposed	2 / 349 (0.57%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 4	
Vascular disorders			

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

Disease progression			
subjects affected / exposed	15 / 349 (4.30%)	16 / 353 (4.53%)	
occurrences causally related to treatment / all	0 / 15	0 / 16	
deaths causally related to treatment / all	0 / 12	0 / 11	
Pyrexia			
subjects affected / exposed	0 / 349 (0.00%)	4 / 353 (1.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	0 / 349 (0.00%)	2 / 353 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

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

subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 349 (0.29%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 349 (0.29%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 349 (0.57%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 349 (0.29%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			

subjects affected / exposed	0 / 349 (0.00%)	4 / 353 (1.13%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	2 / 2	
Cardiac failure acute			
subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 349 (0.57%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myocardial infarction			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Ischaemic stroke			

subjects affected / exposed	1 / 349 (0.29%)	3 / 353 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	3 / 349 (0.86%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral venous sinus thrombosis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 349 (0.86%)	2 / 353 (0.57%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Neutropenia			
subjects affected / exposed	3 / 349 (0.86%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	1 / 349 (0.29%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 349 (0.29%)	1 / 353 (0.28%)	
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	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Macular degeneration			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 349 (0.29%)	1 / 353 (0.28%)	
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	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspepsia			
subjects affected / exposed	0 / 349 (0.00%)	2 / 353 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Small intestinal obstruction			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
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	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis contact			
subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin disorder			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 349 (0.29%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyroiditis subacute			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (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	2 / 349 (0.57%)	4 / 353 (1.13%)	
occurrences causally related to treatment / all	1 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
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	1 / 349 (0.29%)	0 / 353 (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	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (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	6 / 349 (1.72%)	3 / 353 (0.85%)	
occurrences causally related to treatment / all	2 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 349 (0.57%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sepsis			
subjects affected / exposed	0 / 349 (0.00%)	2 / 353 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Staphylococcal sepsis			
subjects affected / exposed	0 / 349 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 349 (0.86%)	2 / 353 (0.57%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	1 / 349 (0.29%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

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

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

Non-serious adverse events	PF-05280014	Trastuzumab-EU	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	337 / 349 (96.56%)	334 / 353 (94.62%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	42 / 349 (12.03%)	45 / 353 (12.75%)	
occurrences (all)	59	114	
Aspartate aminotransferase increased			

subjects affected / exposed	36 / 349 (10.32%)	31 / 353 (8.78%)	
occurrences (all)	41	85	
Blood alkaline phosphatase increased			
subjects affected / exposed	28 / 349 (8.02%)	26 / 353 (7.37%)	
occurrences (all)	42	51	
Ejection fraction decreased			
subjects affected / exposed	49 / 349 (14.04%)	45 / 353 (12.75%)	
occurrences (all)	61	61	
Weight increased			
subjects affected / exposed	20 / 349 (5.73%)	22 / 353 (6.23%)	
occurrences (all)	32	32	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	33 / 349 (9.46%)	31 / 353 (8.78%)	
occurrences (all)	53	44	
Vascular disorders			
Hypertension			
subjects affected / exposed	40 / 349 (11.46%)	33 / 353 (9.35%)	
occurrences (all)	67	61	
Nervous system disorders			
Dizziness			
subjects affected / exposed	38 / 349 (10.89%)	30 / 353 (8.50%)	
occurrences (all)	53	38	
Headache			
subjects affected / exposed	53 / 349 (15.19%)	73 / 353 (20.68%)	
occurrences (all)	76	89	
Neuropathy peripheral			
subjects affected / exposed	33 / 349 (9.46%)	34 / 353 (9.63%)	
occurrences (all)	47	54	
Peripheral sensory neuropathy			
subjects affected / exposed	93 / 349 (26.65%)	85 / 353 (24.08%)	
occurrences (all)	186	153	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	122 / 349 (34.96%)	134 / 353 (37.96%)	
occurrences (all)	341	474	

Leukopenia			
subjects affected / exposed	36 / 349 (10.32%)	45 / 353 (12.75%)	
occurrences (all)	114	121	
Neutropenia			
subjects affected / exposed	97 / 349 (27.79%)	94 / 353 (26.63%)	
occurrences (all)	308	283	
Thrombocytopenia			
subjects affected / exposed	18 / 349 (5.16%)	12 / 353 (3.40%)	
occurrences (all)	36	20	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	53 / 349 (15.19%)	46 / 353 (13.03%)	
occurrences (all)	63	61	
Fatigue			
subjects affected / exposed	46 / 349 (13.18%)	51 / 353 (14.45%)	
occurrences (all)	80	82	
Oedema peripheral			
subjects affected / exposed	27 / 349 (7.74%)	45 / 353 (12.75%)	
occurrences (all)	35	67	
Pyrexia			
subjects affected / exposed	41 / 349 (11.75%)	29 / 353 (8.22%)	
occurrences (all)	63	54	
Chills			
subjects affected / exposed	17 / 349 (4.87%)	18 / 353 (5.10%)	
occurrences (all)	17	21	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	14 / 349 (4.01%)	32 / 353 (9.07%)	
occurrences (all)	20	43	
Constipation			
subjects affected / exposed	24 / 349 (6.88%)	31 / 353 (8.78%)	
occurrences (all)	26	49	
Diarrhoea			
subjects affected / exposed	61 / 349 (17.48%)	65 / 353 (18.41%)	
occurrences (all)	104	119	
Nausea			

subjects affected / exposed	58 / 349 (16.62%)	70 / 353 (19.83%)	
occurrences (all)	168	145	
Stomatitis			
subjects affected / exposed	23 / 349 (6.59%)	13 / 353 (3.68%)	
occurrences (all)	31	21	
Vomiting			
subjects affected / exposed	28 / 349 (8.02%)	26 / 353 (7.37%)	
occurrences (all)	40	39	
Dyspepsia			
subjects affected / exposed	16 / 349 (4.58%)	18 / 353 (5.10%)	
occurrences (all)	22	27	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	33 / 349 (9.46%)	32 / 353 (9.07%)	
occurrences (all)	48	49	
Dyspnoea			
subjects affected / exposed	20 / 349 (5.73%)	22 / 353 (6.23%)	
occurrences (all)	30	25	
Epistaxis			
subjects affected / exposed	15 / 349 (4.30%)	23 / 353 (6.52%)	
occurrences (all)	21	31	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	189 / 349 (54.15%)	186 / 353 (52.69%)	
occurrences (all)	251	259	
Pruritus			
subjects affected / exposed	12 / 349 (3.44%)	23 / 353 (6.52%)	
occurrences (all)	21	31	
Rash			
subjects affected / exposed	26 / 349 (7.45%)	26 / 353 (7.37%)	
occurrences (all)	46	33	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	44 / 349 (12.61%)	38 / 353 (10.76%)	
occurrences (all)	79	62	
Back pain			

subjects affected / exposed	18 / 349 (5.16%)	33 / 353 (9.35%)	
occurrences (all)	23	47	
Bone pain			
subjects affected / exposed	20 / 349 (5.73%)	14 / 353 (3.97%)	
occurrences (all)	27	20	
Myalgia			
subjects affected / exposed	26 / 349 (7.45%)	35 / 353 (9.92%)	
occurrences (all)	43	84	
Pain in extremity			
subjects affected / exposed	22 / 349 (6.30%)	24 / 353 (6.80%)	
occurrences (all)	30	40	
Infections and infestations			
Respiratory tract infection viral			
subjects affected / exposed	23 / 349 (6.59%)	13 / 353 (3.68%)	
occurrences (all)	34	16	
Upper respiratory tract infection			
subjects affected / exposed	36 / 349 (10.32%)	46 / 353 (13.03%)	
occurrences (all)	55	94	
Nasopharyngitis			
subjects affected / exposed	21 / 349 (6.02%)	19 / 353 (5.38%)	
occurrences (all)	34	38	
Urinary tract infection			
subjects affected / exposed	5 / 349 (1.43%)	19 / 353 (5.38%)	
occurrences (all)	7	24	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	23 / 349 (6.59%)	21 / 353 (5.95%)	
occurrences (all)	28	23	

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 subjects had been screened or randomised at the time of the amendment.
10 July 2014	This amendment was implemented due to feedback from a retrospective review by Parexel Informatics of randomised subjects 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 subject treatment after the completion of Week 53 visit assessments, following communication with regulatory agencies.
16 March 2017	This amendment was implemented to update the study design to delineate two treatment periods to allow for continued treatment beyond Week 53, but with limited protocol required assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported