# 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<br>Units: Subjects | | | |
| <18 | 0 | 0 | 0 |
| 18 to 64 | 283 | 292 | 575 |
| 65 to 84 | 66 | 60 | 126 |
| ≥85 | 0 | 1 | 1 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 54 | 54.1 | |
| standard deviation | ± 10.9 | ± 10.9 | - |
| Gender, Male/Female<br>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