



Clinical trial results:

A Multicenter Open-Label Extension Study to Assess Long-Term Safety of PF-00547659 in Subjects With Crohn's Disease (OPERA II)

Summary

| | |
|--------------------------|---|
| EudraCT number | 2010-024638-48 |
| Trial protocol | SK BE SE AT PT DE NO NL ES PL BG Outside EU/EEA |
| Global end of trial date | 27 July 2016 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 11 August 2017 |
| First version publication date | 11 August 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | A7281007 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01298492 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Shire |
| Sponsor organisation address | 300 Shire Way, Lexington, MA, United States, 02421 |
| Public contact | Study Physician, Shire, 1 866-842-5335, |
| Scientific contact | Study Physician, Shire, 1 866-842-5335, |

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 | 27 July 2016 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 27 July 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to monitor the safety and tolerability of PF-00547659 during long-term treatment.

Protection of trial subjects:

This study was conducted in accordance with current applicable regulations, International Council for Harmonisation (ICH) of Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 22 July 2011 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 6 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Austria: 17 |
| Country: Number of subjects enrolled | Belgium: 25 |
| Country: Number of subjects enrolled | Canada: 7 |
| Country: Number of subjects enrolled | France: 18 |
| Country: Number of subjects enrolled | Germany: 24 |
| Country: Number of subjects enrolled | Japan: 8 |
| Country: Number of subjects enrolled | Korea, Republic of: 9 |
| Country: Number of subjects enrolled | Netherlands: 36 |
| Country: Number of subjects enrolled | Norway: 5 |
| Country: Number of subjects enrolled | Poland: 13 |
| Country: Number of subjects enrolled | Serbia: 14 |
| Country: Number of subjects enrolled | Slovakia: 8 |
| Country: Number of subjects enrolled | South Africa: 4 |
| Country: Number of subjects enrolled | Spain: 8 |
| Country: Number of subjects enrolled | United States: 72 |
| Worldwide total number of subjects | 268 |
| EEA total number of subjects | 154 |

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) | 265 |
| From 65 to 84 years | 3 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 81 centers in Austria, Belgium, Canada, France, Germany, Japan, Netherlands, Norway, Poland, Republic of Korea, Serbia, Slovakia, South Africa, Spain and United States between 22 July 2011 (first subject first visit) and 27 July 2016 (last subject last visit).

Pre-assignment

Screening details:

A total of 268 subjects (225 subjects from Feeder Study A7281006 [NCT01276509] and 43 subjects from Feeder Study A7281008 [NCT01387594]) were enrolled and overall 149 subjects completed the study.

Period 1

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

Arms

| | |
|-----------|-------------------|
| Arm title | PF-00547659 75 mg |
|-----------|-------------------|

Arm description:

Subjects received PF-00547659 75 mg subcutaneous injection once in every 4 weeks through Week 72. One time dose escalation to 225 mg subcutaneous injection was allowed after 8 weeks of the study for the subjects who experienced clinical deterioration or unacceptably low level of response to study drug. One time dose de-escalation to 22.5 mg subcutaneous injection due to intolerance or AEs was also allowed after the investigator carefully assessed the status of the subject.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Product 1 |
| Investigational medicinal product code | PF-00547659 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received PF-00547659 75 mg subcutaneous injection once in every 4 weeks through Week 72. One time dose escalation to 225 mg subcutaneous injection was allowed after 8 weeks of the study for the subjects who experienced clinical deterioration or unacceptably low level of response to study drug. One time dose de-escalation to 22.5 mg subcutaneous injection due to intolerance or AEs was also allowed after the investigator carefully assessed the status of the subject.

| | |
|---------------------------------------|-------------------|
| Number of subjects in period 1 | PF-00547659 75 mg |
| Started | 268 |
| Completed | 149 |
| Not completed | 119 |
| Adverse event, serious fatal | 2 |
| Withdrawn Due to Pregnancy | 1 |
| Consent withdrawn by subject | 47 |
| Insufficient Clinical Response | 22 |
| Unspecified | 7 |

| | |
|--|----|
| Lost to follow-up | 12 |
| Adverse Event (Related to Study Drug) | 8 |
| Adverse Event(Not Related to Study Drug) | 18 |
| Protocol deviation | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | PF-00547659 75 mg |
|-----------------------|-------------------|

Reporting group description:

Subjects received PF-00547659 75 mg subcutaneous injection once in every 4 weeks through Week 72. One time dose escalation to 225 mg subcutaneous injection was allowed after 8 weeks of the study for the subjects who experienced clinical deterioration or unacceptably low level of response to study drug. One time dose de-escalation to 22.5 mg subcutaneous injection due to intolerance or AEs was also allowed after the investigator carefully assessed the status of the subject.

| Reporting group values | PF-00547659 75 mg | Total | |
|---|-------------------|-------|--|
| Number of subjects | 268 | 268 | |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 36.5 ± 11.7 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 151 | 151 | |
| Male | 117 | 117 | |

End points

End points reporting groups

| | |
|---|-------------------|
| Reporting group title | PF-00547659 75 mg |
| Reporting group description: | |
| Subjects received PF-00547659 75 mg subcutaneous injection once in every 4 weeks through Week 72. One time dose escalation to 225 mg subcutaneous injection was allowed after 8 weeks of the study for the subjects who experienced clinical deterioration or unacceptably low level of response to study drug. One time dose de-escalation to 22.5 mg subcutaneous injection due to intolerance or AEs was also allowed after the investigator carefully assessed the status of the subject. | |

Primary: Number of Subjects with On-Treatment Adverse Events (AEs), AEs Led to Withdrawal, and Serious Adverse Events (SAEs)

| | |
|-----------------|--|
| End point title | Number of Subjects with On-Treatment Adverse Events (AEs), AEs Led to Withdrawal, and Serious Adverse Events (SAEs) ^[1] |
|-----------------|--|

End point description:

AEs included adverse drug reactions, illnesses with onset during the study, exacerbation of previous illnesses, clinically significant changes in physical examination findings and abnormal objective test findings (electrocardiogram (ECG), laboratory). An SAE was defined as any AE at any dose that resulted in death; was life threatening (immediate risk of death); required in-subject hospitalization or prolongation of existing hospitalization; resulted in a persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions); or resulted in congenital anomaly/birth defect. The modified intent-to-treat (mITT) population included all enrolled subjects who received at least 1 dose of investigational product was analysed for this end point.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From start of study treatment up to Week 72 (Treatment Period)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

| | | | | |
|-------------------------------------|----------------------|--|--|--|
| End point values | PF-00547659 75 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 268 | | | |
| Units: subject | | | | |
| Subjects With AEs | 249 | | | |
| Subjects With AEs Led to Withdrawal | 53 | | | |
| Subjects With SAEs | 80 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Positive Anti-Drug (PF-00547659) Antibodies

| | |
|-----------------|---|
| End point title | Number of Subjects with Positive Anti-Drug (PF-00547659) Antibodies |
|-----------------|---|

End point description:

Positive Anti-Drug Antibodies (ADA) result was defined as ADA titre value greater than or equal to (\geq) 4.64 at at least one of the time points. The modified intent-to-treat (mITT) population included all

enrolled subjects who received at least 1 dose of investigational product was analysed for this end point.

| | |
|------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Week 96 | |

| | | | | |
|-----------------------------|----------------------|--|--|--|
| End point values | PF-00547659 75 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 268 | | | |
| Units: subject | | | | |
| Subjects | 63 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Trough Concentrations of PF-00547659 Versus Time

| | |
|--|--|
| End point title | Serum Trough Concentrations of PF-00547659 Versus Time |
| End point description: | |
| Serum trough concentrations of PF-00547659 were analyzed using population Pharmacokinetic (PK) methodology. The PK population included all enrolled subjects who received at least 1 dose of investigational product and had data on at least 1 PK concentration was analysed for this end point. Here "n" represents the number of subjects evaluable for this end point. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 4,8,12,16,20,24,28,32,36,40,44,48,52,56,60,64,68,72,76,80,84,88,92,96 | |

| | | | | |
|--|----------------------|--|--|--|
| End point values | PF-00547659 75 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 260 | | | |
| Units: nanogram per milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=226) | 6673 (± 6634.2) | | | |
| Week 8 (n=222) | 6064 (± 4455.3) | | | |
| Week 12 (n=201) | 8040 (± 6293.1) | | | |
| Week 16 (n=188) | 9563 (± 7285.4) | | | |
| Week 20 (n=186) | 10400 (± 8438.6) | | | |
| Week 24 (n=172) | 10450 (± 7934.6) | | | |
| Week 28 (n=162) | 10780 (± 9211) | | | |

| | | | | |
|-----------------|------------------|--|--|--|
| Week 32 (n=165) | 11920 (± 10675) | | | |
| Week 36 (n=164) | 12460 (± 9717.1) | | | |
| Week 40 (n=152) | 12570 (± 10077) | | | |
| Week 44 (n=149) | 12960 (± 10999) | | | |
| Week 48 (n=148) | 13170 (± 11108) | | | |
| Week 52 (n=144) | 13560 (± 11388) | | | |
| Week 56 (n=134) | 13930 (± 11191) | | | |
| Week 60 (n=131) | 14130 (± 11095) | | | |
| Week 64 (n=127) | 14360 (± 11290) | | | |
| Week 68 (n=120) | 14990 (± 12883) | | | |
| Week 72 (n=114) | 13910 (± 10554) | | | |
| Week 76 (n=173) | 10520 (± 10082) | | | |
| Week 80 (n=170) | 3555 (± 5339.8) | | | |
| Week 84 (n=149) | 1129 (± 2634.7) | | | |
| Week 88 (n=145) | 403.8 (± 1522.6) | | | |
| Week 92 (n=136) | 154.2 (± 1001.9) | | | |
| Week 96 (n=145) | 54.73 (± 487.07) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Start of Study Treatment up to Safety Follow up (Week 96)

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | PF-00547659 75 mg |
|-----------------------|-------------------|

Reporting group description:

Subjects received PF-00547659 75 mg subcutaneous injection once in every 4 weeks through Week 72. One time dose escalation to 225 mg subcutaneous injection was allowed after 8 weeks of the study for the subjects who experienced clinical deterioration or unacceptably low level of response to study drug. One time dose de-escalation to 22.5 mg subcutaneous injection due to intolerance or AEs was also allowed after the investigator carefully assessed the status of the subject.

| Serious adverse events | PF-00547659 75 mg | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 118 / 268 (44.03%) | | |
| number of deaths (all causes) | 2 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon cancer | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Renal cancer | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Benign breast lump removal | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 268 (0.75%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Female genital tract fistula | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Menorrhagia | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Perineal fistula | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia aspiration | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Investigations | | | |
| Blood creatine phosphokinase mm increased | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematocrit decreased | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Anastomotic leak | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fracture | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal stoma complication | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Humerus fracture | | | |
| subjects affected / exposed | 2 / 268 (0.75%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Postoperative ileus | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Stomal hernia | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound dehiscence | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 268 (0.75%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intracranial venous sinus thrombosis | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal hernia obstructive | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 268 (1.12%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anal fistula | | | |
| subjects affected / exposed | 7 / 268 (2.61%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anal stenosis | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Crohn's disease | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 44 / 268 (16.42%) | | |
| occurrences causally related to treatment / all | 1 / 51 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Duodenitis | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterocutaneous fistula | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ileal stenosis | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ileus | | | |
| subjects affected / exposed | 4 / 268 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal fistula | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 2 / 268 (0.75%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Large intestinal obstruction | | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Large intestinal stenosis | | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Melaena | | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nausea | | | | |
| subjects affected / exposed | 3 / 268 (1.12%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatitis | | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatitis acute | | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small intestinal obstruction | | | | |
| subjects affected / exposed | 4 / 268 (1.49%) | | | |
| occurrences causally related to treatment / all | 0 / 11 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vomiting | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 3 / 268 (1.12%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 2 / 268 (0.75%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic cyst | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Pyoderma gangrenosum | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Bladder dysfunction | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 2 / 268 (0.75%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Ureterolithiasis | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinoma | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Adrenocortical insufficiency acute | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arthritis | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arthritis enteropathic | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|------------------|--|--|
| Spinal column stenosis | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 2 / 268 (0.75%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal wall abscess | | | |
| subjects affected / exposed | 2 / 268 (0.75%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abscess intestinal | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abscess neck | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anal abscess | | | |
| subjects affected / exposed | 10 / 268 (3.73%) | | |
| occurrences causally related to treatment / all | 1 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 3 / 268 (1.12%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device related infection | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 3 / 268 (1.12%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Liver abscess | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvic abscess | | | |
| subjects affected / exposed | 2 / 268 (0.75%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Perirectal abscess | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonitis | | | |
| subjects affected / exposed | 3 / 268 (1.12%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 268 (1.49%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Postoperative abscess | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rotavirus infection | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Splenic abscess | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vulval abscess | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Fluid retention | | | |
| subjects affected / exposed | 1 / 268 (0.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| | | | |
|---|--------------------|--|--|
| Non-serious adverse events | PF-00547659 75 mg | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 206 / 268 (76.87%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 35 / 268 (13.06%) | | |
| occurrences (all) | 45 | | |
| General disorders and administration | | | |

| | | | |
|---|-------------------|--|--|
| site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 15 / 268 (5.60%) | | |
| occurrences (all) | 20 | | |
| Fatigue | | | |
| subjects affected / exposed | 20 / 268 (7.46%) | | |
| occurrences (all) | 23 | | |
| Pyrexia | | | |
| subjects affected / exposed | 27 / 268 (10.07%) | | |
| occurrences (all) | 36 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 49 / 268 (18.28%) | | |
| occurrences (all) | 59 | | |
| Anal fissure | | | |
| subjects affected / exposed | 14 / 268 (5.22%) | | |
| occurrences (all) | 14 | | |
| Aphthous ulcer | | | |
| subjects affected / exposed | 14 / 268 (5.22%) | | |
| occurrences (all) | 18 | | |
| Crohn's disease | | | |
| subjects affected / exposed | 79 / 268 (29.48%) | | |
| occurrences (all) | 111 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 24 / 268 (8.96%) | | |
| occurrences (all) | 38 | | |
| Nausea | | | |
| subjects affected / exposed | 32 / 268 (11.94%) | | |
| occurrences (all) | 44 | | |
| Vomiting | | | |
| subjects affected / exposed | 23 / 268 (8.58%) | | |
| occurrences (all) | 34 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 83 / 268 (30.97%) | | |
| occurrences (all) | 113 | | |

| | | | |
|---|-------------------------|--|--|
| Back pain subjects affected / exposed occurrences (all) | 28 / 268 (10.45%) 30 | | |
| Infections and infestations | | | |
| Anal abscess subjects affected / exposed occurrences (all) | 14 / 268 (5.22%) 16 | | |
| Bronchitis subjects affected / exposed occurrences (all) | 20 / 268 (7.46%) 26 | | |
| Gastroenteritis subjects affected / exposed occurrences (all) | 19 / 268 (7.09%) 22 | | |
| Influenza subjects affected / exposed occurrences (all) | 18 / 268 (6.72%) 19 | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 54 / 268 (20.15%) 93 | | |
| Pharyngitis subjects affected / exposed occurrences (all) | 15 / 268 (5.60%) 18 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 20 / 268 (7.46%) 25 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 19 / 268 (7.09%) 28 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 15 February 2011 | Subjects were required to discontinue concomitant immunosuppressants prior to entering the open-label extension (OLE) study; interim analysis was added to study with statistical analysis modified accordingly. |
| 17 May 2011 | Included addition of footnotes to the Schedule of Activities to clarify which procedures would be carried forward from A7281006 (2010-023437-30) and A7281008 (2011-001443-74) Week 12 and not repeated. Addition of risk-benefit section; creation of section on Dosing to better describe the dose escalation and dose discontinuation criteria; update to reporting period for AEs; update of injection site monitoring instructions. |
| 18 July 2011 | Title of study updated; clarification to baseline procedures section and also other study visits in the Study Procedures section to specify that repeat NTproBNP, echocardiogram, and cardiology consultation should be performed for specified elevations in NTproBNP and that data were to be reviewed if applicable. |
| 23 April 2012 | Updates to protocol summary, study design, study design schematic, early withdrawal from OLE treatment for responders that relapse, minor administrative changes/corrections. |
| 25 June 2012 | Addition of Schedule of Activities for subjects enrolled in Japan and estimation of PK parameters for subjects enrolled in Japan. |
| 01 August 2012 | Addition of Appendix 8: Appendix 8 consisted of a version of the protocol to be implemented in Japan to accommodate specific requirements from the Pharmaceuticals and Medical Devices Agency. |
| 19 February 2013 | Revision of interim analysis section for clarification and revisions to PK analysis section and exploratory pharmacodynamics analysis section; revision to Data Monitoring Committee to indicate that the interim analysis results would be reviewed by the Data Monitoring Committee; added units from International System of Units for NTproBNP levels; addition of Simple Endoscopic Score for Crohn's Disease (SES-CD). |
| 09 December 2015 | Removal of 18-month telephone call follow-up period and corresponding updates to protocol sections where applicable; addition of note for clarification of baseline for neurological assessments where applicable; and updates where applicable to be consistent with Pfizer standards. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported