



Clinical trial results:

A PHASE II TRIAL OF PF-04856884 (CVX-060), A SELECTIVE ANGIOPOIETIN-2 (ANG-2) INHIBITOR IN COMBINATION WITH AG-013736 (AXITINIB) IN PATIENTS WITH PREVIOUSLY TREATED METASTATIC RENAL CELL CARCINOMA

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2011-002190-33 |
| Trial protocol | ES IT CZ DE GB AT FI |
| Global end of trial date | 27 March 2014 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 05 April 2016 |
| First version publication date | 08 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | B1131004 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01441414 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Pfizer, Inc. |
| Sponsor organisation address | 235 East 42nd Street, New York, , United States, NY 10017 |
| Public contact | Clinical Trials.gov Call Center, Pfizer Inc., 001 800 7181021, ClinicalTrials.govCallCenter@pfizer.com |
| Scientific contact | Clinical Trials.gov Call Center, Pfizer Inc., 001 800 7181021, ClinicalTrials.govCallCenter@pfizer.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 24 October 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 March 2014 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

Part I: To confirm that the combination of PF-04856884 and AG-013736 is safe and tolerable at the doses to be used in Part II of the study.

Part II: To document clinical activity of the combination of PF-04856884 and AG-013736 or AG-013736 alone as measured by PFS in adult patients with previously treated Metastatic Renal Cell Cancer (mRCC).

Protection of trial subjects:

Palliative and supportive care for disease related symptoms was available per local standard of care for all patients on this study. Low dose oral steroids (defined as <5 mg per day prednisone or equivalent), short course of oral steroids (defined as <5 consecutive days of therapy) or topical or inhaled steroids at any dose may have been taken during the study. No other chemotherapy, hormonal therapy, radiotherapy, or experimental anticancer medications were permitted while the patient was on study; patients on luteinizing hormone releasing hormone (LHRH) analogs may have been maintained on treatment. Any disease progression requiring other forms of specific anticancer therapy were cause for discontinuation from study drug.

Background therapy:

- Part I: Have received 1-3 prior systemic regimens for treatment of mRCC.
- Part II: Evidence of disease progression following 1 prior regimen administered as 1st line therapy for mRCC. The prior regimen must have contained one of the following:
- VEGFR 2 TKI such as (but not limited to) pazopanib, sunitinib, tivozanib, or sorafenib;
- Other anti VEGF compounds, such as bevacizumab.

As of 06 November 2012, based upon the safety findings from Part I of the study, Pfizer decided not to open patient enrolment onto Part II of the study.

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 21 October 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Czech Republic: 1 |
| Country: Number of subjects enrolled | United States: 17 |
| Worldwide total number of subjects | 18 |
| EEA total number of subjects | 1 |

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) | 10 |
| From 65 to 84 years | 8 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This multicenter, open-label study consisted of a safety lead in stage (Part I) followed by a randomized Phase 2 stage (Part II). A total of 18 participants were screened and assigned to treatment in Part I, with 3 participants completing Part I of the study. At the completion of Part I, all 18 participants had discontinued combined treatment.

Pre-assignment

Screening details:

During Part I, 3 to 4 participants were initially treated with the study drug combination in 28-day cycles. If no participants experienced Cycle 1 dose limiting toxicities (DLTs), another 6 to 9 participants were treated at this dose level. Part II of the study was to be initiated if Cycle 1 DLTs were observed in <33% in at least 12 participants.

Pre-assignment period milestones

| | |
|------------------------------|----|
| Number of subjects started | 18 |
| Number of subjects completed | 18 |

Period 1

| | |
|------------------------------|--|
| Period 1 title | PF-04856884 + AG-013736 (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|-------------------------|
| Arm title | PF-04856884 + AG-013736 |
|-----------|-------------------------|

Arm description:

Participants in Part I received PF-04856884 15 mg/kg/week and AG-013736 5 mg twice a day. Following the decision of 06 November 2012 not to continue with Part II of the study, any participant remaining in Part I continued to receive PF-04856884 at a reduced dose of 10 mg/kg/week in combination with AG-013736 (5 mg twice a week) or AG-013736 alone (5 mg twice a week).

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | PF 04856884 and AG 013736 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion, Tablet |
| Routes of administration | Oral use, Intravenous use |

Dosage and administration details:

Study treatment began within 3 days of registering the patient for Part I.

PF 04856884: During Cycle 1, this was given as a 60 minute infusion. After the first cycle, the infusion duration was reduced to 30 minutes for all subsequent cycles. AG 013736: This was taken orally with or without food. Twice daily doses were approximately 12 hours apart and at approximately the same times each day. For patients enrolled in Part I, the morning dose coincided with the timing of the start of the infusion at all visits with post dose sampling.

Patients in Part I received PF 04856884 15 mg/kg/week and AG 013736 5 mg BID. Following the decision of 06 November 2012, any patient remaining in Part I continued to receive PF 04856884 at a reduced dose of 10 mg/kg/week in combination with AG 013736 (5 mg BID) or AG 013736 alone (5 mg BID).

| Number of subjects in period 1 | PF-04856884 + AG-013736 |
|---------------------------------------|-------------------------|
| Started | 18 |
| Completed | 3 |
| Not completed | 15 |
| Participant died | 9 |
| Study terminated by sponsor | 2 |
| Other reasons | 3 |
| Participant refused further follow-up | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | PF-04856884 + AG-013736 |
|-----------------------|-------------------------|

Reporting group description:

Participants in Part I received PF-04856884 15 mg/kg/week and AG-013736 5 mg twice a day. Following the decision of 06 November 2012 not to continue with Part II of the study, any participant remaining in Part I continued to receive PF-04856884 at a reduced dose of 10 mg/kg/week in combination with AG-013736 (5 mg twice a week) or AG-013736 alone (5 mg twice a week).

| Reporting group values | PF-04856884 + AG-013736 | Total | |
|--|-------------------------|-------|--|
| Number of subjects | 18 | 18 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| < 18 | 0 | 0 | |
| 18-44 | 2 | 2 | |
| 45-64 | 8 | 8 | |
| 65 years and over | 8 | 8 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 63.2 | | |
| standard deviation | ± 10.9 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 4 | 4 | |
| Male | 14 | 14 | |

End points

End points reporting groups

| | |
|---|---------------------------------|
| Reporting group title | PF-04856884 + AG-013736 |
| Reporting group description: Participants in Part I received PF-04856884 15 mg/kg/week and AG-013736 5 mg twice a day. Following the decision of 06 November 2012 not to continue with Part II of the study, any participant remaining in Part I continued to receive PF-04856884 at a reduced dose of 10 mg/kg/week in combination with AG-013736 (5 mg twice a week) or AG-013736 alone (5 mg twice a week). | |
| Subject analysis set title | All-causality CTCAE Grade 3 |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Incidence and severity of all-causality CTCAE Grade 3 TEAEs are presented. Participants with multiple occurrences of an AE within a category were counted once within the category. | |
| Subject analysis set title | All-causality CTCAE Grade 4 |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Incidence and severity of all-causality CTCAE Grade 4 TEAEs are presented. Participants with multiple occurrences of an AE within a category were counted once within the category. | |
| Subject analysis set title | All-causality CTCAE Grade 5 |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Incidence and severity of all-causality CTCAE Grade 5 TEAEs are presented. Participants with multiple occurrences of an AE within a category were counted once within the category. | |
| Subject analysis set title | Treatment-related CTCAE Grade 3 |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Incidence and severity of treatment-related CTCAE Grade 3 TEAEs are presented. Participants with multiple occurrences of an AE within a category were counted once within the category. | |
| Subject analysis set title | Treatment-related CTCAE Grade 4 |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Incidence and severity of treatment-related CTCAE Grade 4 TEAEs are presented. Participants with multiple occurrences of an AE within a category were counted once within the category. | |
| Subject analysis set title | Treatment related CTCAE Grade 5 |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Incidence and severity of all-causality CTCAE Grade 5 TEAEs are presented. Participants with multiple occurrences of an AE within a category were counted once within the category. | |
| Subject analysis set title | All-causality CTCAE Grade 2 |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Number of participants who had serious TEAEs (all-causality) of CTCAE Grade 2 TEAEs are presented | |

Primary: Number of Participants With non-serious Adverse Events (AEs) in Part I (Reported in ≥ 2 of the participants)

| | |
|--|--|
| End point title | Number of Participants With non-serious Adverse Events (AEs) in Part I (Reported in ≥ 2 of the participants) ^[1] |
| End point description: Incidence and severity of all treatment-emergent AEs (TEAEs) of both all-causality and treatment-related are presented by preferred term (PT) categorized according to Common Terminology Criteria for Adverse Events (CTCAE) grades reported in ≥ 2 participants (for any PT). Participants in Part I received PF-04856884 15 mg/kg/week and AG-013736 5 mg twice daily. Following the decision on 06 November 2012 not to continue with Part II of the study, any participant remaining in Part I continued to receive PF-04856884 at a reduced dose of 10 mg/kg/week in combination with AG-013736 (5 mg twice a week) | |

or AG-013736 alone (5 mg twice a week). Where a TEAE-PT is already included under all-causality TEAEs, the treatment-related TEAE-PTs are presented as "0"; and where less than 2 participants experienced treatment-related TEAE, the data is presented as "0" in the following table.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| 4 months | |

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: Statistical analysis was not required by the statistical analysis plan (SAP) for this endpoint.

| End point values | All-causality CTCAE Grade 3 | All-causality CTCAE Grade 4 | All-causality CTCAE Grade 5 | Treatment- related CTCAE Grade 3 |
|-----------------------------------|--------------------------------|--------------------------------|--------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 18 | 18 | 18 | 18 |
| Units: participants | | | | |
| Anaemia | 0 | 0 | 0 | 0 |
| Leukocytosis | 2 | 0 | 0 | 0 |
| Pericardial effusion | 0 | 1 | 0 | 0 |
| Hyperthyroidism | 0 | 0 | 0 | 0 |
| Hypothyroidism | 0 | 0 | 0 | 0 |
| Vision blurred | 0 | 0 | 0 | 0 |
| Abdominal pain | 1 | 0 | 0 | 0 |
| Constipation | 0 | 0 | 0 | 0 |
| Diarrhoea | 0 | 0 | 0 | 0 |
| Dry mouth | 0 | 0 | 0 | 0 |
| Gastritis | 0 | 0 | 0 | 0 |
| Nausea | 1 | 0 | 0 | 1 |
| Oral pain | 0 | 0 | 0 | 0 |
| Stomatitis | 0 | 0 | 0 | 0 |
| Toothache | 0 | 0 | 0 | 0 |
| Vomiting | 1 | 0 | 0 | 1 |
| Asthenia | 1 | 0 | 0 | 1 |
| Fatigue | 5 | 0 | 0 | 4 |
| Oedema peripheral | 0 | 0 | 0 | 0 |
| Pneumonia | 1 | 0 | 0 | 0 |
| Upper respiratory tract infection | 0 | 0 | 0 | 0 |
| Urinary tract infection | 1 | 0 | 0 | 0 |
| Blood creatinine increased | 0 | 0 | 0 | 0 |
| Weight decreased | 2 | 0 | 0 | 1 |
| Decreased appetite | 1 | 0 | 0 | 1 |
| Dehydration | 0 | 0 | 0 | 0 |
| Hypercalcaemia | 0 | 0 | 0 | 0 |
| Hypokalaemia | 1 | 0 | 0 | 0 |
| Hyponatraemia | 1 | 0 | 0 | 0 |
| Hypovolaemia | 0 | 0 | 0 | 0 |
| Arthralgia | 1 | 0 | 0 | 0 |
| Back pain | 1 | 0 | 0 | 0 |
| Muscle spasms | 0 | 0 | 0 | 0 |
| Muscular weakness | 0 | 0 | 0 | 0 |
| Myalgia | 0 | 0 | 0 | 0 |
| Cerebrovascular accident | 1 | 1 | 0 | 1 |

| | | | | |
|-----------------------------------|---|---|---|---|
| Dizziness | 0 | 0 | 0 | 0 |
| Headache | 1 | 0 | 0 | 1 |
| Migraine | 1 | 0 | 0 | 1 |
| Neuropathy peripheral | 1 | 0 | 0 | 0 |
| Depression | 1 | 0 | 0 | 0 |
| Insomnia | 1 | 0 | 0 | 1 |
| Proteinuria | 0 | 0 | 0 | 0 |
| Cough | 0 | 0 | 0 | 0 |
| Dysphonia | 0 | 0 | 0 | 0 |
| Dyspnoea | 1 | 0 | 0 | 0 |
| Hypoxia | 1 | 0 | 0 | 0 |
| Pleural effusion | 1 | 0 | 0 | 0 |
| Pulmonary embolism | 1 | 1 | 0 | 1 |
| Night sweats | 0 | 0 | 0 | 0 |
| Palmar-plantar erythrodysesthesia | 0 | 0 | 0 | 0 |
| Hot flush | 0 | 0 | 0 | 0 |
| Hypertension | 5 | 0 | 0 | 4 |
| Hypotension | 1 | 0 | 0 | 0 |

| End point values | Treatment-related CTCAE Grade 4 | Treatment related CTCAE Grade 5 | | |
|-----------------------------------|---------------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 18 | 18 | | |
| Units: participants | | | | |
| Anaemia | 0 | 0 | | |
| Leukocytosis | 0 | 0 | | |
| Pericardial effusion | 1 | 0 | | |
| Hyperthyroidism | 0 | 0 | | |
| Hypothyroidism | 0 | 0 | | |
| Vision blurred | 0 | 0 | | |
| Abdominal pain | 0 | 0 | | |
| Constipation | 0 | 0 | | |
| Diarrhoea | 0 | 0 | | |
| Dry mouth | 0 | 0 | | |
| Gastritis | 0 | 0 | | |
| Nausea | 0 | 0 | | |
| Oral pain | 0 | 0 | | |
| Stomatitis | 0 | 0 | | |
| Toothache | 0 | 0 | | |
| Vomiting | 0 | 0 | | |
| Asthenia | 0 | 0 | | |
| Fatigue | 0 | 0 | | |
| Oedema peripheral | 0 | 0 | | |
| Pneumonia | 0 | 0 | | |
| Upper respiratory tract infection | 0 | 0 | | |
| Urinary tract infection | 0 | 0 | | |
| Blood creatinine increased | 0 | 0 | | |
| Weight decreased | 0 | 0 | | |
| Decreased appetite | 0 | 0 | | |

| | | | | |
|-----------------------------------|---|---|--|--|
| Dehydration | 0 | 0 | | |
| Hypercalcaemia | 0 | 0 | | |
| Hypokalaemia | 0 | 0 | | |
| Hyponatraemia | 0 | 0 | | |
| Hypovolaemia | 0 | 0 | | |
| Arthralgia | 0 | 0 | | |
| Back pain | 0 | 0 | | |
| Muscle spasms | 0 | 0 | | |
| Muscular weakness | 0 | 0 | | |
| Myalgia | 0 | 0 | | |
| Cerebrovascular accident | 1 | 0 | | |
| Dizziness | 0 | 0 | | |
| Headache | 0 | 0 | | |
| Migraine | 0 | 0 | | |
| Neuropathy peripheral | 0 | 0 | | |
| Depression | 0 | 0 | | |
| Insomnia | 0 | 0 | | |
| Proteinuria | 0 | 0 | | |
| Cough | 0 | 0 | | |
| Dysphonia | 0 | 0 | | |
| Dyspnoea | 0 | 0 | | |
| Hypoxia | 0 | 0 | | |
| Pleural effusion | 0 | 0 | | |
| Pulmonary embolism | 1 | 0 | | |
| Night sweats | 0 | 0 | | |
| Palmar-plantar erythrodysesthesia | 0 | 0 | | |
| Hot flush | 0 | 0 | | |
| Hypertension | 0 | 0 | | |
| Hypotension | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Serious Adverse Events (SAEs) in Part I (Reported in ≥2 participants)

| | |
|-----------------|--|
| End point title | Number of Participants with Serious Adverse Events (SAEs) in Part I (Reported in ≥2 participants) ^[2] |
|-----------------|--|

End point description:

Incidence and severity of all-causality serious adverse events (SAEs) are presented by PT categorized according to Common Terminology Criteria for Adverse Events (CTCAE) grades. Participants in Part I received PF-04856884 15 mg/kg/week and AG-013736 5 mg twice daily. Following the decision on 06 November 2012 not to continue with Part II of the study, any participant remaining in Part I continued to receive PF-04856884 at a reduced dose of 10 mg/kg/week in combination with AG-013736 (5 mg twice a week) or AG-013736 alone (5 mg twice a week). Participants with treatment-related TEAE are coded as NA if they appear for the same preferred term under all-causality TEAE.

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

End point timeframe:

4 months

Notes:

[2] - 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: Statistical analysis was not required by the statistical analysis plan (SAP) for this endpoint.

| End point values | All-causality CTCAE Grade 3 | All-causality CTCAE Grade 4 | All-causality CTCAE Grade 5 | All-causality CTCAE Grade 2 |
|-----------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 18 | 18 | 18 | 18 |
| Units: participants | | | | |
| Pneumonia | 1 | 0 | 0 | 1 |
| Pleural effusion | 1 | 0 | 0 | 1 |
| Ileus | 0 | 0 | 0 | 1 |
| Abdominal pain | 1 | 0 | 0 | 0 |
| Ascites | 0 | 0 | 0 | 1 |
| Lung infection | 1 | 0 | 0 | 0 |
| Back pain | 1 | 0 | 0 | 0 |
| Musculoskeletal chest pain | 1 | 0 | 0 | 0 |
| Convulsion | 0 | 0 | 0 | 1 |
| Embolism | 0 | 0 | 0 | 1 |
| Hyponatraemia | 1 | 0 | 0 | 0 |
| Dyspnoea | 1 | 0 | 0 | 0 |
| Hypotension | 1 | 0 | 0 | 0 |
| Cerebrovascular accident | 1 | 1 | 0 | 0 |
| Migraine | 1 | 0 | 0 | 0 |
| Meningioma | 1 | 0 | 0 | 0 |
| Hypovolaemia | 0 | 0 | 0 | 1 |
| Pulmonary embolism | 1 | 1 | 0 | 0 |
| Pericardial effusion | 0 | 1 | 0 | 0 |
| Gastrointestinal disorder | 0 | 0 | 1 | 0 |
| Chest discomfort | 1 | 0 | 0 | 0 |
| Hypertension | 1 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Primary: Progression free survival (PFS) in adult participants with previously treated metastatic Renal Cell Cancer (mRCC) in Part II

| | |
|-----------------|---|
| End point title | Progression free survival (PFS) in adult participants with previously treated metastatic Renal Cell Cancer (mRCC) in Part II ^[3] |
|-----------------|---|

End point description:

PFS is defined as the time (in days) from date of randomization to first documentation of investigator assessed tumor progression or death, whichever comes first. Progression free survival was to be calculated as (first event date – the date of randomization +1).

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

End point timeframe:

3 years

Notes:

[3] - 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: Statistical analysis was not required by the statistical analysis plan (SAP) for this endpoint.

| | | | | |
|-----------------------------|-------------------------|--|--|--|
| End point values | PF-04856884 + AG-013736 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[4] | | | |
| Units: days | | | | |

Notes:

[4] - PFS in Part II was not assessed due to early termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with non-serious AEs and SAEs

| | |
|--|--|
| End point title | Number of Participants with non-serious AEs and SAEs |
| End point description: | |
| Incidence and severity of all-causality AEs and SAEs to be presented by PT categorized according to Common Terminology Criteria for Adverse Events (CTCAE) grades. Participants in Part I received PF-04856884 15 mg/kg/week and AG-013736 5 mg twice daily. Following the decision on 06 November 2012 not to continue with Part II of the study, any participant remaining in Part I continued to receive PF-04856884 at a reduced dose of 10 mg/kg/week in combination with AG-013736 (5 mg twice a week) or AG-013736 alone (5 mg twice a week). | |
| End point type | Secondary |
| End point timeframe: | |
| 3 years | |

| | | | | |
|-----------------------------|-------------------------|--|--|--|
| End point values | PF-04856884 + AG-013736 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[5] | | | |
| Units: participants | | | | |

Notes:

[5] - This endpoint was not assessed due to the early termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) in metastatic Renal Cell Cancer (mRCC) patients treated with PF-04856884 in combination with AG-013736 vs. AG-013736 alone

| | | | | |
|-----------------|--|--|--|--|
| End point title | Overall Response Rate (ORR) in metastatic Renal Cell Cancer (mRCC) patients treated with PF-04856884 in combination with AG-013736 vs. AG-013736 alone | | | |
|-----------------|--|--|--|--|

End point description:

ORR is defined as the proportion of participants with confirmed complete response (CR) or confirmed partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST), relative to all randomized participants as defined in the FA Set. Confirmed responses are those that persist on repeat

imaging study ≥ 4 weeks after initial documentation of response. Participants who do not have on-study radiographic tumor evaluation or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders (NR) in the assessment of ORR.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 4 months | |

| | | | | |
|-----------------------------------|-------------------------|--|--|--|
| End point values | PF-04856884 + AG-013736 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 18 | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Complete response (CR) | 0 | | | |
| Partial response (PR) | 11.1 | | | |
| ORR (CR + PR) | 11.1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR) in metastatic Renal Cell Cancer (mRCC) patients treated with PF-04856884 in combination with AG-013736 vs. AG-013736 alone

| | |
|-----------------|--|
| End point title | Duration of Response (DR) in metastatic Renal Cell Cancer (mRCC) patients treated with PF-04856884 in combination with AG-013736 vs. AG-013736 alone |
|-----------------|--|

End point description:

DR is defined as the time from the first documentation of objective tumor response (CR or PR) that is subsequently confirmed to the first documentation of tumor progression or to death due to cancer. Duration of tumor response was to be calculated as (the end date for DR – first CR or PR that is subsequently confirmed +1).

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 3 years | |

| | | | | |
|-----------------------------|-------------------------|--|--|--|
| End point values | PF-04856884 + AG-013736 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[6] | | | |
| Units: weeks | | | | |

Notes:

[6] - This endpoint was not assessed due to the early termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax (Time when maximum serum PF-04856884 concentration was reached)

| | |
|-----------------|--|
| End point title | Tmax (Time when maximum serum PF-04856884 concentration was reached) |
|-----------------|--|

End point description:

Pharmacokinetic parameter, Tmax (Time when maximum serum PF-04856884 concentration was reached) was done using non-compartmental methods.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 1, 2, 4, 6, 8, 192, 360, 361, 362, 365, 367 hours post dose and end of treatment

| End point values | PF-04856884 + AG-013736 | | | |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 18 | | | |
| Units: hour | | | | |
| arithmetic mean (standard deviation) | | | | |
| CYCLE1/DAY1 | 2 (± 1.645) | | | |
| CYCLE1/DAY22 | 3 (± 2.1122) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax (observed peak serum PF-04856884 concentration)

| | |
|-----------------|--|
| End point title | Cmax (observed peak serum PF-04856884 concentration) |
|-----------------|--|

End point description:

Pharmacokinetic parameter Cmax (observed peak PF-04856884 serum concentration) was estimated using noncompartmental methods.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 1, 2, 4, 6, 8, 192, 360, 361, 362, 365, 367 hours post dose and end of treatment

| End point values | PF-04856884 + AG-013736 | | | |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 18 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| CYCLE1/DAY1 | 337100 (± 76245) | | | |
| CYCLE1/DAY22 | 531400 (± 154780) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cmin (trough PF-04856884 serum concentration)

| | |
|---|---|
| End point title | Cmin (trough PF-04856884 serum concentration) |
| End point description: Pharmacokinetic parameter Cmin (trough PF-04856884 serum concentration) was estimated using noncompartmental methods. | |
| End point type | Secondary |
| End point timeframe: Pre-dose, 1, 2, 4, 6, 8, 192, 360, 361, 362, 365, 367 hours post dose and end of treatment | |

| | | | | |
|--------------------------------------|-------------------------|--|--|--|
| End point values | PF-04856884 + AG-013736 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 18 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| CYCLE1/DAY1 | 932.7 (± 3499.1) | | | |
| CYCLE1/DAY22 | 168900 (± 84507) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Anti-drug antibodies (ADA) Samples Confirmed Positive

| | |
|--|---|
| End point title | Number of Anti-drug antibodies (ADA) Samples Confirmed Positive |
| End point description: Detection of neutralizing anti-PF-04856884 antibodies was based on the ability of anti-PF-04856884 neutralizing antibodies to bind to Tag-PF-04856884. | |
| End point type | Secondary |
| End point timeframe: 0 and 360 hours post dose and end of study | |

| | | | | |
|--------------------------------|-------------------------|--|--|--|
| End point values | PF-04856884 + AG-013736 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 18 | | | |
| Units: ADA samples | | | | |
| Number of ADA samples Analyzed | 91 | | | |
| Number of ADA Samples Confi | 8 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) in adult participants with previously treated metastatic Renal Cell Cancer (mRCC) as measured by an Independent Radiological Assessment

| | |
|---|---|
| End point title | Progression free survival (PFS) in adult participants with previously treated metastatic Renal Cell Cancer (mRCC) as measured by an Independent Radiological Assessment |
| End point description: | |
| PFS is defined as the time (in days) from date of randomization to first documentation of investigator assessed tumor progression or death, whichever comes first. PFS was to be calculated as (first event date – the date of randomization +1). | |
| End point type | Secondary |
| End point timeframe: | |
| 3 years | |

| | | | | |
|-----------------------------|-------------------------|--|--|--|
| End point values | PF-04856884 + AG-013736 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[7] | | | |
| Units: days | | | | |

Notes:

[7] - This endpoint of estimating median PFS was not assessed due to early termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) at 2 years

| | |
|--|----------------------------------|
| End point title | Overall Survival (OS) at 2 years |
| End point description: | |
| OS is defined as the time from the first dose date to date of death. For participants not expiring, their survival times will be censored at the last date they are known to be alive, or 2 year whichever is earlier. The 2-year OS rate will be estimated from a time-to event analysis of OS. | |
| End point type | Secondary |
| End point timeframe: | |
| 5 years | |

| | | | | |
|-----------------------------|----------------------------|--|--|--|
| End point values | PF-04856884 + AG-013736 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[8] | | | |
| Units: months | | | | |

Notes:

[8] - This endpoint was not assessed due to the early termination of the study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the day the first dose of the investigational product was administered up to 1 year.

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one participant and as nonserious in another participant, or one participant may have experienced both a serious and nonserious event during the study.

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 17 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | PF 04856884 + AG 013736 |
|-----------------------|-------------------------|

Reporting group description:

Participants in Part I received PF-04856884 15 mg/kg/week and AG-013736 5 mg twice a day. Following the decision of 06 November 2012 not to continue with Part II of the study, any participant remaining in Part I continued to receive PF-04856884 at a reduced dose of 10 mg/kg/week in combination with AG-013736 (5 mg twice a week) or AG-013736 alone (5 mg twice a week).

| Serious adverse events | PF 04856884 + AG 013736 | | |
|---|-------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 12 / 18 (66.67%) | | |
| number of deaths (all causes) | 2 | | |
| number of deaths resulting from adverse events | 1 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Meningioma | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Vascular disorders | | | |
| Embolicism | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|-----------------------------------|--|--|
| Hypotension subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 18 (5.56%) 0 / 1 0 / 0 | | |
| Cardiac disorders Pericardial effusion subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 18 (5.56%) 1 / 1 0 / 0 | | |
| Nervous system disorders Cerebrovascular accident subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 18 (11.11%) 2 / 2 0 / 0 | | |
| Convulsion subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 18 (5.56%) 0 / 1 0 / 0 | | |
| Migrane subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 18 (5.56%) 0 / 1 0 / 0 | | |
| General disorders and administration site conditions Chest discomfort subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 18 (5.56%) 1 / 1 0 / 0 | | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 18 (5.56%) 0 / 1 0 / 0 | | |
| Ascites | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Ileus | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---------------------------------------|--|--|
| Infections and infestations Lung infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 18 (5.56%) 0 / 1 0 / 0 | | |
| Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 18 (11.11%) 0 / 2 0 / 0 | | |
| Metabolism and nutrition disorders Hyponatraemia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 18 (5.56%) 0 / 1 0 / 0 | | |
| Hypovolaemia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 18 (5.56%) 1 / 1 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 1 %

| | | | |
|---|----------------------------|--|--|
| Non-serious adverse events | PF 04856884 + AG 013736 | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 18 / 18 (100.00%) | | |
| Vascular disorders | | | |
| Embolism | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Hot flush | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences (all) | 3 | | |
| Hypertension | | | |
| subjects affected / exposed | 9 / 18 (50.00%) | | |
| occurrences (all) | 19 | | |
| Hypotension | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 4 / 18 (22.22%) | | |
| occurrences (all) | 4 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 6 | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Chills | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Fatigue | | | |
| subjects affected / exposed | 11 / 18 (61.11%) | | |
| occurrences (all) | 22 | | |
| Inflammation | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Localised oedema | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 2 | | |
| Oedema | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 5 / 18 (27.78%) | | |
| occurrences (all) | 9 | | |
| Pain | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 4 | | |
| Pyrexia | | | |

| | | | |
|---|--|--|--|
| subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) Seasonal allergy subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 3 1 / 18 (5.56%) 1 | | |
| Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all) Scrotal oedema subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Dyspnoea exertional subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Haemoptysis subjects affected / exposed occurrences (all) Hypoxia | 7 / 18 (38.89%) 10 5 / 18 (27.78%) 5 6 / 18 (33.33%) 8 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 3 | | |
| Rhinalgia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Depression | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences (all) | 5 | | |
| Flat affect | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Insomnia | | | |
| subjects affected / exposed | 7 / 18 (38.89%) | | |
| occurrences (all) | 7 | | |
| Restlessness | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 2 | | |
| Sleep disorder | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Investigations | | | |
| Blood creatine increased | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences (all) | 3 | | |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Coagulation time prolonged | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Haptoglobin increased | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Neutrophil count abnormal | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Weight decreased | | | |
| subjects affected / exposed | 4 / 18 (22.22%) | | |
| occurrences (all) | 17 | | |
| White blood cell count abnormal | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Tooth fracture | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Sinus tachycardia | | | |

| | | | |
|----------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 2 | | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 18 (22.22%) | | |
| occurrences (all) | 4 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Headache | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences (all) | 5 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 2 | | |
| Lethargy | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 2 | | |
| Memory impairment | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Migraine | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 4 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 6 | | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|---|--|--|
| Syncope subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukocytosis subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) | 4 / 18 (22.22%) 7 2 / 18 (11.11%) 2 1 / 18 (5.56%) 1 | | |
| Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | | |
| Eye disorders Eye pain subjects affected / exposed occurrences (all) Vision blurred subjects affected / exposed occurrences (all) Vitreous floaters subjects affected / exposed occurrences (all) Visual impairment subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 2 3 / 18 (16.67%) 3 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 | | |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) Abdominal distension subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 | | |

| | | | |
|----------------------------------|------------------|--|--|
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 7 | | |
| Aphthous stomatitis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 7 | | |
| Constipation | | | |
| subjects affected / exposed | 8 / 18 (44.44%) | | |
| occurrences (all) | 11 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 10 / 18 (55.56%) | | |
| occurrences (all) | 22 | | |
| Dry mouth | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences (all) | 3 | | |
| Eructation | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Faecal incontinence | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Gastritis | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 2 | | |
| Glossodynia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Nausea | | | |
| subjects affected / exposed | 11 / 18 (61.11%) | | |
| occurrences (all) | 18 | | |

| | | | |
|--|--|--|--|
| <p>Oral pain</p> <p>subjects affected / exposed</p> <p>2 / 18 (11.11%)</p> <p>occurrences (all)</p> <p>2</p> <p>Stomatitis</p> <p>subjects affected / exposed</p> <p>2 / 18 (11.11%)</p> <p>occurrences (all)</p> <p>2</p> <p>Toothache</p> <p>subjects affected / exposed</p> <p>2 / 18 (11.11%)</p> <p>occurrences (all)</p> <p>2</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>10 / 18 (55.56%)</p> <p>occurrences (all)</p> <p>24</p> | | | |
| <p>Hepatobiliary disorders</p> <p>Cholecystitis</p> <p>subjects affected / exposed</p> <p>1 / 18 (5.56%)</p> <p>occurrences (all)</p> <p>1</p> <p>Hepatic cyst</p> <p>subjects affected / exposed</p> <p>1 / 18 (5.56%)</p> <p>occurrences (all)</p> <p>1</p> | | | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Erythema</p> <p>subjects affected / exposed</p> <p>1 / 18 (5.56%)</p> <p>occurrences (all)</p> <p>1</p> <p>Nail disorder</p> <p>subjects affected / exposed</p> <p>1 / 18 (5.56%)</p> <p>occurrences (all)</p> <p>1</p> <p>Night sweats</p> <p>subjects affected / exposed</p> <p>2 / 18 (11.11%)</p> <p>occurrences (all)</p> <p>2</p> <p>Onychalgia</p> <p>subjects affected / exposed</p> <p>1 / 18 (5.56%)</p> <p>occurrences (all)</p> <p>1</p> <p>Palmar-plantar erythrodysaesthesia syndrome</p> <p>subjects affected / exposed</p> <p>2 / 18 (11.11%)</p> <p>occurrences (all)</p> <p>2</p> <p>Pruritus</p> | | | |

| | | | |
|---|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Skin disorder</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Urticaria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 18 (5.56%)</p> <p>2</p> <p>1 / 18 (5.56%)</p> <p>1</p> <p>1 / 18 (5.56%)</p> <p>1</p> <p>1 / 18 (5.56%)</p> <p>2</p> | | |
| <p>Renal and urinary disorders</p> <p>Nocturia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Proteinuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Urinary retention</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 18 (5.56%)</p> <p>1</p> <p>3 / 18 (16.67%)</p> <p>4</p> <p>1 / 18 (5.56%)</p> <p>1</p> | | |
| <p>Endocrine disorders</p> <p>Hyperthyroidism</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypothyroidism</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 18 (11.11%)</p> <p>2</p> <p>2 / 18 (11.11%)</p> <p>2</p> | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Groin pain</p> | <p>3 / 18 (16.67%)</p> <p>3</p> <p>5 / 18 (27.78%)</p> <p>7</p> | | |

| | | | |
|--------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 7 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Myalgia | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Pain in jaw | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 2 | | |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Candida infection | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 2 | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |

| | | | |
|------------------------------------|------------------|--|--|
| Cystitis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Ear infection | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Otitis media | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 3 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences (all) | 3 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 12 / 18 (66.67%) | | |
| occurrences (all) | 26 | | |
| Dehydration | | | |
| subjects affected / exposed | 3 / 18 (16.67%) | | |
| occurrences (all) | 7 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 2 | | |
| Hypercholesterolaemia | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 18 (11.11%) | | |
| occurrences (all) | 3 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |
| Hypovolaemia | | | |
| subjects affected / exposed | 1 / 18 (5.56%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|---|--------------|
| 06 November 2012 | PF-04856884 in combination with AG-013736 during Part I of the study showed a higher than expected frequency of arterial thrombotic events or venous thrombotic events in the 18 patients with mRCC. These specific events included pulmonary embolism in 2 patients, cerebrovascular accident in 2 patients, gastrointestinal disorder (presumed bowel ischemia) in 1 patient, and chest discomfort in 1 patient. Based on these safety concerns, Pfizer decided not to open patient enrolment onto Part II of the study. On 06 November 2012, based upon the safety findings from Part I of this study (B1131004) and due to strategic considerations, Pfizer decided not to open patient enrolment onto Part II of the study and terminated the study. | - |

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Since this application does not allow the character strings in the data fields, some data which is actually reported as "not reported" in the Clinical Study Report as "NOT REPORTED" have been reported as 0 in this disclosure.

Notes: