# Clinical trial results:
# A 15-Week, Phase 2, Double-Blind, Randomized, Placebo-Controlled, Flexible Dose Study to Investigate the Efficacy, Safety and Tolerability of PF-06649751 in Subjects With Early Stage Parkinson's Disease

## Summary

| | |
|---|---|
| EudraCT number | 2016-001575-71 |
| Trial protocol | DE ES |
| Global end of trial date | 29 January 2018 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 02 January 2019 |
| First version publication date | 02 January 2019 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | B7601011 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02847650 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Pfizer, Inc. |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, NY 10017 |
| Public contact | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |

Notes:

**Paediatric regulatory details**

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

Notes:

**Results analysis stage**

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 29 July 2018 |

| | |
|---|---|
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 January 2018 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effect of PF-06649751 administered once daily on motor symptoms in subjects with early stage Parkinson's disease.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial subjects.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 17 October 2016 |
| 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 | United States: 33 |
| Country: Number of subjects enrolled | France: 1 |
| Country: Number of subjects enrolled | Germany: 22 |
| Country: Number of subjects enrolled | Israel: 1 |
| Worldwide total number of subjects | 57 |
| EEA total number of subjects | 23 |

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) | 28 |
| From 65 to 84 years | 29 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The study was conducted at 23 centers in the United States (US), Germany, France and Israel, from 17 October 2016 to 29 January 2018.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | PF-06649751 |

Arm description:

Eligible subjects were up-titrated in a double-blind fashion to an optimal dose level of PF-06649751 according to a flexible dose titration scheme (from 0.25 mg to 15 mg once daily [QD]). The 15-week treatment period included 9 weeks of dose optimization and 6 weeks of stable dosing. Blinded PF-06649751 was provided as tablets for oral administration in the outpatient setting (each morning, daily for the duration of the treatment period). Reaching of the maximum allowed dose level (15 mg) was not mandatory; subjects might achieve a satisfactory clinical response at a lower dose level. There was an additional follow-up period of 28 days following discontinuation of PF-06649751.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | PF-06649751 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects (and caregivers, as applicable) were instructed to take 3 tablets of the investigational product at approximately the same time each morning, swallow each tablet whole with water, and not to manipulate or chew the tablet prior to swallowing. All tablets were required to be taken within approximately 5 minutes. The tablets could be taken with or without food. The timing of the investigational product administration on each day of the double-blind treatment was documented by the subject via the subject dosing diary.

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Matching placebo tablet for QD dosing in the 15-week double-blind treatment period. There was an additional follow-up period of 28 days following discontinuation of placebo.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects (and caregivers, as applicable) were instructed to take 3 tablets of the investigational product at approximately the same time each morning, swallow each tablet whole with water, and not to manipulate or chew the tablet prior to swallowing. All tablets were required to be taken within approximately 5 minutes. The tablets could be taken with or without food. The timing of the

investigational product administration on each day of the double-blind treatment was documented by the subject via the subject dosing diary.

| **Number of subjects in period 1** | PF-06649751 | Placebo |
|---|---|---|
| Started | 29 | 28 |
| Completed | 25 | 22 |
| Not completed | 4 | 6 |
| Protocol deviation | - | 1 |
| Adverse event, non-fatal | 2 | 4 |
| Consent withdrawn by subject | 1 | 1 |
| Lost to follow-up | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | PF-06649751 |
| Reporting group description: | |
| Eligible subjects were up-titrated in a double-blind fashion to an optimal dose level of PF-06649751 according to a flexible dose titration scheme (from 0.25 mg to 15 mg once daily [QD]). The 15-week treatment period included 9 weeks of dose optimization and 6 weeks of stable dosing. Blinded PF-06649751 was provided as tablets for oral administration in the outpatient setting (each morning, daily for the duration of the treatment period). Reaching of the maximum allowed dose level (15 mg) was not mandatory; subjects might achieve a satisfactory clinical response at a lower dose level. There was an additional follow-up period of 28 days following discontinuation of PF-06649751. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Matching placebo tablet for QD dosing in the 15-week double-blind treatment period. There was an additional follow-up period of 28 days following discontinuation of placebo. | |

| Reporting group values | PF-06649751 | Placebo | Total |
|---|---|---|---|
| Number of subjects | 29 | 28 | 57 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 12 | 16 | 28 |
| From 65-84 years | 17 | 12 | 29 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 64.76 | 63.36 | |
| standard deviation | ± 8.34 | ± 9.16 | - |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 9 | 14 | 23 |
| Male | 20 | 14 | 34 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 1 | 3 | 4 |
| White | 28 | 25 | 53 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Hispanic or Latino | 2 | 1 | 3 |
| Not Hispanic or Latino | 27 | 27 | 54 |
| Unknown or Not Reported | 0 | 0 | 0 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | PF-06649751 |

Reporting group description:

Eligible subjects were up-titrated in a double-blind fashion to an optimal dose level of PF-06649751 according to a flexible dose titration scheme (from 0.25 mg to 15 mg once daily [QD]). The 15-week treatment period included 9 weeks of dose optimization and 6 weeks of stable dosing. Blinded PF-06649751 was provided as tablets for oral administration in the outpatient setting (each morning, daily for the duration of the treatment period). Reaching of the maximum allowed dose level (15 mg) was not mandatory; subjects might achieve a satisfactory clinical response at a lower dose level. There was an additional follow-up period of 28 days following discontinuation of PF-06649751.

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

Matching placebo tablet for QD dosing in the 15-week double-blind treatment period. There was an additional follow-up period of 28 days following discontinuation of placebo.

### Primary: Change From Baseline in the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III Total Score at Week 15

| | |
|---|---|
| End point title | Change From Baseline in the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III Total Score at Week 15 |

End point description:

MDS-UPDRS Part III was used to assess the motor signs of Parkinson's disease. It was comprised of 33 sub-scores based on 18 items, several with right, left or other body distribution scores. Each question was anchored with 5 responses that were linked to commonly accepted clinical terms: 0=normal, 1=slight, 2=mild, 3=moderate, and 4=severe. The MDS-UPDRS Part III total score range is 0-132. Higher score indicates more severe motor signs of Parkinson's disease. A negative change from baseline represents an improvement in motor function. Analysis population included all treated subjects (ie, who received at least 1 dose of study treatment [PF-06649751 or placebo]) who had a baseline and Week 15 MDS-UPDRS score Part III.

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

End point timeframe:

Baseline (Day -1/randomization), Week 15

| End point values | PF-06649751 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 25 | 22 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -9.0 (± 1.54) | -4.3 (± 1.65) | | |

### Statistical analyses

| Statistical analysis title | MDS-UPDRS Part III Total Score at Week 15 |
|---|---|
| Comparison groups | Placebo v PF-06649751 |
| Number of subjects included in analysis | 47 |
| Analysis specification | Pre-specified |

| | |
|---|---|
| Analysis type | other |
| P-value | = 0.0407 |
| Method | Mixed models analysis |
| Parameter estimate | Least Squares Mean Difference |
| Point estimate | -4.8 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -8.6 |
| upper limit | -1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.26 |

## Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

| | |
|---|---|
| End point title | Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) |

End point description:

An AE was any untoward medical occurrence in a subject who received study treatment without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; life-threatening (immediate risk of death); initial or prolonged inpatient hospitalization; persistent or significant disability/incapacity; congenital anomaly/birth defect. Treatment-emergent AEs were those with initial onset or increasing in severity after the first dose of study treatment. Analysis population included all treated subjects.

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

End point timeframe:

From first dose of study treatment up to 28 days after last dose (up to Day 133)

| **End point values** | PF-06649751 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 28 | | |
| Units: subjects | | | | |
| AEs\| | 25 | 18 | | |
| SAEs\| | 1 | 0 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality)

| | |
|---|---|
| End point title | Number of Subjects With Laboratory Test Abnormalities (Without Regard to Baseline Abnormality) |

End point description:

Following safety laboratory parameters were assessed against pre-defined abnormality criteria: hematology (hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, mean corpuscular

hemoglobin, mean corpuscular hemoglobin concentration, platelet count, white blood cell count, absolute total neutrophils, absolute eosinophils, absolute basophils, absolute monocytes, and absolute lymphocytes); chemistry (blood urea nitrogen/urea and creatinine, glucose , calcium, sodium, potassium, chloride, total bicarbonate, aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, uric acid, albumin, total protein); urinalysis (pH, qualitative glucose, qualitative protein, qualitative blood, ketones, nitrites, leukocyte esterase, urine bilirubin, urobilinogen, urine creatinine, microscopy, and specific gravity). Analysis population included all treated subjects with at least 1 observation of the given laboratory test.

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

End point timeframe:

Baseline (Day -1/randomization) up to Day 119 follow-up visit

| **End point values** | PF-06649751 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 28 | | |
| Units: subjects | 19 | 19 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Vital Signs Data Meeting Categorical Summarization and Orthostatic Hypotension Criteria

| End point title | Number of Subjects With Vital Signs Data Meeting Categorical Summarization and Orthostatic Hypotension Criteria |
|---|---|

End point description:

Vital signs categorical summarization criteria: 1) supine and standing systolic blood pressure (SBP) <90 millimeters of mercury (mmHg); 2) supine and standing diastolic blood pressure (DBP) <50 mmHg; 3) supine pulse rate <40 or >120 beats per minute (bpm); 4) standing pulse rate <40 or >140 bpm; 5) maximum change from baseline (increase or decrease) in supine and standing DBP greater than or equal to (>=) 20 mmHg; 6) maximum change from baseline (increase or decrease) in supine and standing SBP >=30 mmHg. Orthostatic hypotension criterion was defined as a decrease of >=20 mmHg for SBP or >=10 mmHg for DBP 2 minutes after standing from a supine position. Analysis population included all subjects who received at least 1 dose of study treatment (PF-06649751 or placebo).

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

End point timeframe:

Baseline (Day -1/randomization) up to Day 119 follow-up visit

| **End point values** | PF-06649751 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 28 | | |
| Units: subjects | | | | |
| Supine SBP <90 mmHg\| | 0 | 0 | | |
| Standing SBP <90 mmHg\| | 0 | 0 | | |
| Supine DBP <50 mmHg\| | 0 | 0 | | |
| Standing DBP <50 mmHg\| | 0 | 0 | | |
| Supine pulse rate <40 bpm\| | 0 | 0 | | |

| | | | | |
|---|---|---|---|---|
| Supine pulse rate >120 bpm\| | 0 | 0 | | |
| Standing pulse rate <40 bpm\| | 0 | 0 | | |
| Standing pulse rate >140 bpm\| | 0 | 0 | | |
| Maximum increase in standing DBP >=20 mmHg\| | 0 | 0 | | |
| Maximum increase in standing SBP >=30 mmHg\| | 0 | 0 | | |
| Maximum increase in supine DBP >=20 mmHg\| | 0 | 1 | | |
| Maximum increase in supine SBP >=30 mmHg\| | 0 | 3 | | |
| Maximum decrease in standing DBP >=20 mmHg\| | 8 | 2 | | |
| Maximum decrease in standing SBP >=30 mmHg\| | 4 | 1 | | |
| Maximum decrease in supine DBP >=20 mmHg\| | 9 | 1 | | |
| Maximum decrease in supine SBP >=30 mmHg\| | 5 | 0 | | |
| SBP postural difference(supine-standing) >=20mmHg\| | 1 | 2 | | |
| DBP postural difference(supine-standing) >=10mmHg\| | 3 | 1 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects Meeting the Categorical Summarization Criteria for Electrocardiogram (ECG) Parameters

| End point title | Number of Subjects Meeting the Categorical Summarization Criteria for Electrocardiogram (ECG) Parameters |
|---|---|

End point description:

ECG categorical summarization criteria: 1) QRS duration (time from ECG Q wave to the end of the S wave corresponding to ventricle depolarization): >=140 milliseconds (msec), >=50% increase from baseline; 2) PR interval (the interval between the start of the P wave and the start of the QRS complex, corresponding to the time between the onset of the atrial depolarization and onset of ventricular depolarization): >=300 msec, >=25% increase when baseline is >200 msec or >=50% increase when baseline is less than or equal to (<=) 200 msec; 3) QT interval (time from ECG Q wave to the end of the T wave corresponding to electrical systole): absolute value of >=500 msec; 4) QTcF interval (QT corrected for heart rate using Fridericia's formula): absolute value of 450 to <480 msec, 480 to <500 msec, >=500 msec; an increase from baseline of 30 to <60 msec or >=60 msec. Analysis population included all treated subjects. "n" represents the number of subjects evaluable for each specified category.

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

End point timeframe:

Baseline (Day -1/randomization) up to Day 119 follow-up visit

| End point values | PF-06649751 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 28 | | |
| Units: subjects | | | | |
| PR interval >=300 msec\|(n=28,28) | 0 | 0 | | |
| QRS duration >=140 msec\|(n=29,28) | 0 | 0 | | |
| QT interval >=500 msec\|(n=29,28) | 0 | 0 | | |
| QTcF interval >=450 to <480 msec\|(n=29,28) | 0 | 0 | | |
| QTcF interval >=480 to <500 msec\|(n=29,28) | 0 | 0 | | |
| QTcF interval >=500 msec\|(n=29,28) | 0 | 0 | | |
| Percent increase in PR interval >=25/50%\|(n=28,28) | 0 | 0 | | |
| Percent increase in QRS duration >=50%\|(n=29,28) | 0 | 0 | | |
| QTcF interval increase >=30 to <60 msec\|(n=29,28) | 1 | 2 | | |
| QTcF interval increase >=60 msec\|(n=29,28) | 0 | 0 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Worsening and New Onset Suicidality as Assessed by Columbia Suicide Severity Rating Scale (C-SSRS)

| End point title | Number of Subjects With Worsening and New Onset Suicidality as Assessed by Columbia Suicide Severity Rating Scale (C-SSRS) |
|---|---|

End point description:

The C-SSRS is an interview based rating scale to systematically assess suicidal ideation and suicidal behavior. C-SSRS responses were mapped to the Columbia Classification Algorithm of Suicide Assessment (C-CASA). Subjects with new onset suicidality were those without suicidal ideation and behavior at baseline and reported any suicidal behavior or ideation post-baseline as assessed by C-CASA code mapped from C-SSRS data. Subjects with worsening suicidality were those who moved to a lower numbered C-CASA category than was reported at baseline. Analysis population included all treated subjects.

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

End point timeframe:

Baseline (Day -1/randomization) up to Day 119 follow-up visit

| End point values | PF-06649751 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 28 | | |
| Units: subjects | | | | |
| Worsening suicidality\| | 0 | 0 | | |
| New onset suicidality\| | 1 | 0 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS) Total Score at Days 35, 63, and 105

| End point title | Change From Baseline in Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS) Total Score at Days 35, 63, and 105 |
|---|---|

End point description:

The QUIP-RS has 4 primary questions pertaining to commonly reported thoughts, urges/desires, and behaviors associated with impulsive-compulsive disorder , each applied to the 4 impulsive-compulsive disorders (compulsive gambling, buying, eating, and sexual behavior) and 3 related disorders (medication use, punding, and hobbyism). Each question is anchored with the following 5 responses: Never (0), Rarely (1), Sometimes (2), Often (3), and Very Often (4). The scoring range for each item (ie, disorder) is 0-16. The QUIP-RS total score range is 0-64. Higher score indicates a greater level of the impulsive compulsive disorder. Analysis population included all treated subjects. "n" represents the number of subjects evaluable for this endpoint at specified time points.

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

End point timeframe:

Baseline (Day -1 or randomization); Days 35, 63, 105

| **End point values** | PF-06649751 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 28 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change from baseline at Day 35\| (n=28,28) | 0.2 (± 5.23) | 1.9 (± 9.49) | | |
| Change from baseline at Day 63\| (n=27,24) | -1.1 (± 5.99) | 1.1 (± 9.02) | | |
| Change from baseline at Day 105\| (n=26,22) | -1.6 (± 4.54) | -0.2 (± 5.38) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Total Physician Withdrawal Checklist (PWC20) Score

| End point title | Total Physician Withdrawal Checklist (PWC20) Score |
|---|---|

End point description:

The PWC-20 is a 20-item reliable and sensitive instrument for the assessment of benzodiazepine-like discontinuation symptoms. The total PWC-20 score is the sum of 20 item scores and ranges between 0

and 60. The higher score indicates more frequent/severe symptoms. Analysis population included all treated subjects who had PWC-20 evaluation.

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

End point timeframe:

Day 119

| **End point values** | PF-06649751 | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 26 | | |
| Units: units on a scale | | | | |
| median (full range (min-max)) | 1.50 (0 to 12.00) | 1.00 (0 to 11.00) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of study treatment up to 28 days after last dose (up to Day 133)

Adverse event reporting additional description:

The same event may appear as both an AE and an SAE. However, what is presented are distinct events. An event may be categorized as serious in 1 subject and as non-serious in another subject, or 1 subject may have experienced both a serious and non-serious event during the study.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | PF-06649751 |

Reporting group description:

Eligible subjects were up-titrated in a double-blind fashion to an optimal dose level of PF-06649751 according to a flexible dose titration scheme (from 0.25 mg to 15 mg once daily [QD]). The 15-week treatment period included 9 weeks of dose optimization and 6 weeks of stable dosing. Blinded PF-06649751 was provided as tablets for oral administration in the outpatient setting (each morning, daily for the duration of the treatment period). Reaching of the maximum allowed dose level (15 mg) was not mandatory; subjects might achieve a satisfactory clinical response at a lower dose level. There was an additional follow-up period of 28 days following discontinuation of PF-06649751.

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

Matching placebo tablet for QD dosing in the 15-week double-blind treatment period. There was an additional follow-up period of 28 days following discontinuation of PF-06649751.

| **Serious adverse events** | PF-06649751 | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Psychiatric disorders | | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | PF-06649751 | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 22 / 29 (75.86%) | 12 / 28 (42.86%) | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 0 / 28 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 28 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 28 (3.57%) | |
| occurrences (all) | 2 | 1 | |
| Dysgeusia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 28 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Dystonia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 28 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 28 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Headache | | | |
| subjects affected / exposed | 7 / 29 (24.14%) | 2 / 28 (7.14%) | |
| occurrences (all) | 10 | 2 | |
| Somnolence | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 1 / 28 (3.57%) | |
| occurrences (all) | 4 | 1 | |
| Tremor | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 2 / 28 (7.14%) | |
| occurrences (all) | 5 | 5 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 28 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|---|---|
| Fatigue | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 3 / 28 (10.71%) | |
| occurrences (all) | 4 | 3 | |
| Psychiatric disorders | | | |
| Abnormal dreams | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 28 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Anxiety | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 28 (3.57%) | |
| occurrences (all) | 2 | 1 | |
| Insomnia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 28 (7.14%) | |
| occurrences (all) | 2 | 2 | |
| Depression | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 28 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Irritability | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 28 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Restlessness | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 28 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Gastrointestinal disorders | | | |
| Dry mouth | | | |
| subjects affected / exposed | 5 / 29 (17.24%) | 0 / 28 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 9 / 29 (31.03%) | 2 / 28 (7.14%) | |
| occurrences (all) | 15 | 2 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 3 / 28 (10.71%) | |
| occurrences (all) | 1 | 3 | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 28 (7.14%) | |
| occurrences (all) | 1 | 2 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|---|---|---|
| Arthralgia | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 0 / 28 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Back pain | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 1 / 28 (3.57%) | |
| occurrences (all) | 4 | 1 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 0 / 28 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 28 (3.57%) | |
| occurrences (all) | 2 | 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 0 / 28 (0.00%) | |
| occurrences (all) | 3 | 0 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 20 July 2016 | • Clarified that 104 healthy volunteer subjects have participated in the completed Phase 1 studies, with 88 having received PF-06649751.<br>• Updated Schedule of Activities.<br>• Included results of Study 8001294.<br>• Updated Exclusion Criteria.<br>• Clarified that the increase in dose level from Stage 1 to Stage 2 was a mandatory step at Visit 2 (from Day 8).<br>• Updated additional safety laboratory tests added at Screening and Visit 15 (and during the study if deemed necessary by the investigator) for monitoring of vascular inflammation.<br>• Added Prep B2 Banked Biospecimen sample collection at Visit 1 (Randomization) and Visit 15.<br>• Updated blood volume table.<br>• Included End of Trial template language.<br>• Updated Appendix 2.<br>• Minor administrative updates throughout.<br>• Updated references. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

This study was terminated early by the sponsor due to a companion study, B7601003 (a dose ranging, Phase 2b study in motor fluctuators) meeting futility criteria at Interim Analysis.

Notes: