# Clinical trial results:
# A PHASE 2 MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY OF THE SAFETY AND EFFICACY OF PF-03049423 IN SUBJECTS WITH ISCHEMIC STROKE

## Summary

| | |
|---|---|
| EudraCT number | 2010-021414-32 |
| Trial protocol | HU DE BG CZ |
| Global end of trial date | 20 December 2013 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 09 February 2016 |
| First version publication date | 09 July 2015 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | A9541004 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01208233 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Pfizer Inc |
| Sponsor organisation address | 235 E 42nd Street, New York, NY, United States, 10017 |
| Public contact | Clinical Trials.gov Call Centre, Pfizer Inc, 1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Clinical Trials.gov Call Centre, Pfizer Inc, 1 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 | 27 August 2014 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 20 December 2013 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

Primary Objective for Part 1: Safety Dose-Ranging Study
To evaluate the safety and tolerability of PF-03049423 following multiple dose administration to subjects with ischemic stroke following 14 days of dosing.

Primary Objective for Part 2: Proof-of-Concept study
To assess the efficacy of PF-03049423, relative to placebo, using the modified Rankin Score (mRS) in subjects with ischemic stroke at Day 90.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 17 December 2010 |
| 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 | Bulgaria: 35 |
| Country: Number of subjects enrolled | Czech Republic: 1 |
| Country: Number of subjects enrolled | France: 4 |
| Country: Number of subjects enrolled | Germany: 29 |
| Country: Number of subjects enrolled | Hungary: 33 |
| Country: Number of subjects enrolled | Korea, Republic of: 41 |
| Country: Number of subjects enrolled | Canada: 1 |
| Country: Number of subjects enrolled | India: 6 |
| Country: Number of subjects enrolled | Taiwan: 7 |
| Country: Number of subjects enrolled | United States: 21 |
| Worldwide total number of subjects | 178 |
| EEA total number of subjects | 102 |

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) | 81 |
| From 65 to 84 years | 96 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 181 subjects were assigned to study treatment, 178 of which received study treatment.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Period (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** | Cohort 1: PF-03049423 1 mg |

Arm description:

Subjects received PF-03049423 1 mg once daily for 90 days.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | PF-03049423 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

PF-03049423 1 mg was administered by the appropriate study personnel at Days 1 to 3 and for each of the later assessment days (Days 7, 14, 30, 60 and 90) and for any other days that the subject remained as an in-patient. All other dosing was self- or caregiver-administered once the subject became out-patient.

| | |
|---|---|
| **Arm title** | Cohort 1: Placebo |

Arm description:

Subjects received placebo matched to PF-03049423 1 mg once daily for 90 days.

| | |
|---|---|
| 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:

Placebo 1 mg was administered by the appropriate study personnel at Days 1 to 3 and for each of the later assessment days (Days 7, 14, 30, 60 and 90) and for any other days that the subject remained as an in-patient. All other dosing was self- or caregiver-administered once the subject became out-patient.

| | |
|---|---|
| **Arm title** | Cohort 2: PF-03049423 3 mg |

Arm description:

Subjects received PF-03049423 3 mg once daily for 90 days.

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | PF-03049423 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

PF-03049423 3 mg was administered by the appropriate study personnel at Days 1 to 3 and for each of the later assessment days (Days 7, 14, 30, 60 and 90) and for any other days that the subject remained as an in-patient. All other dosing was self- or caregiver-administered once the subject became out-patient.

| **Arm title** | Cohort 2: Placebo |
|---|---|

Arm description:

Subjects received placebo matched to PF-03049423 3 mg once daily for 90 days.

| 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:

Placebo 3 mg was administered by the appropriate study personnel at Days 1 to 3 and for each of the later assessment days (Days 7, 14, 30, 60 and 90) and for any other days that the subject remained as an in-patient. All other dosing was self- or caregiver-administered once the subject became out-patient.

| **Arm title** | Cohort 3: PF-03049423 6 mg |
|---|---|

Arm description:

Subjects received PF-03049423 6 mg once daily for 90 days.

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | PF-03049423 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

PF-03049423 6 mg was administered by the appropriate study personnel at Days 1 to 3 and for each of the later assessment days (Days 7, 14, 30, 60 and 90) and for any other days that the subject remained as an in-patient. All other dosing was self- or caregiver-administered once the subject became out-patient.

| **Arm title** | Cohort 3: Placebo |
|---|---|

Arm description:

Subjects received placebo matched to PF-0304942 6 mg once daily for 90 days.

| 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:

Placebo 6 mg was administered by the appropriate study personnel at Days 1 to 3 and for each of the later assessment days (Days 7, 14, 30, 60 and 90) and for any other days that the subject remained as an in-patient. All other dosing was self- or caregiver-administered once the subject became out-patient.

| **Number of subjects in period 1** | Cohort 1: PF-03049423 1 mg | Cohort 1: Placebo | Cohort 2: PF-03049423 3 mg |
|---|---|---|---|
| Started | 11 | 9 | 11 |
| Completed | 6 | 6 | 7 |
| Not completed | 5 | 3 | 4 |
| Adverse event, serious fatal | - | - | - |
| Consent withdrawn by subject | 1 | - | - |
| Did not meet entrance criteria | 2 | 1 | 1 |
| Study terminated by Sponsor | - | - | - |
| Adverse event, non-fatal | - | 1 | 2 |
| Subject withdrawn due to Sponsor request | 1 | 1 | - |
| Medication error without adverse event | - | - | - |
| Took prohibited concomitant medication: digoxin | - | - | - |
| No longer willing to participate in the trial | - | - | 1 |
| Subject took Tamsulosin for urinary disorder | 1 | - | - |
| Protocol deviation | - | - | - |

| **Number of subjects in period 1** | Cohort 2: Placebo | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo |
|---|---|---|---|
| Started | 10 | 70 | 67 |
| Completed | 9 | 46 | 46 |
| Not completed | 1 | 24 | 21 |
| Adverse event, serious fatal | - | 3 | 5 |
| Consent withdrawn by subject | - | 1 | 2 |
| Did not meet entrance criteria | - | 1 | - |
| Study terminated by Sponsor | - | 10 | 7 |
| Adverse event, non-fatal | - | 3 | 5 |
| Subject withdrawn due to Sponsor request | - | - | - |
| Medication error without adverse event | - | - | 1 |
| Took prohibited concomitant medication: digoxin | - | - | 1 |
| No longer willing to participate in the trial | 1 | 3 | - |
| Subject took Tamsulosin for urinary disorder | - | - | - |
| Protocol deviation | - | 3 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Cohort 1: PF-03049423 1 mg |
| Reporting group description: Subjects received PF-03049423 1 mg once daily for 90 days. | |
| Reporting group title | Cohort 1: Placebo |
| Reporting group description: Subjects received placebo matched to PF-03049423 1 mg once daily for 90 days. | |
| Reporting group title | Cohort 2: PF-03049423 3 mg |
| Reporting group description: Subjects received PF-03049423 3 mg once daily for 90 days. | |
| Reporting group title | Cohort 2: Placebo |
| Reporting group description: Subjects received placebo matched to PF-03049423 3 mg once daily for 90 days. | |
| Reporting group title | Cohort 3: PF-03049423 6 mg |
| Reporting group description: Subjects received PF-03049423 6 mg once daily for 90 days. | |
| Reporting group title | Cohort 3: Placebo |
| Reporting group description: Subjects received placebo matched to PF-0304942 6 mg once daily for 90 days. | |

| Reporting group values | Cohort 1: PF-03049423 1 mg | Cohort 1: Placebo | Cohort 2: PF-03049423 3 mg |
|---|---|---|---|
| Number of subjects | 11 | 9 | 11 |
| 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) | 5 | 4 | 1 |
| From 65-84 years | 6 | 5 | 10 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 62.3 | 64.7 | 69.8 |
| standard deviation | ± 14.3 | ± 6 | ± 8.3 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 4 | 2 | 7 |
| Male | 7 | 7 | 4 |

| Reporting group values | Cohort 2: Placebo | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo |
|---|---|---|---|
| Number of subjects | 10 | 70 | 67 |

| 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) | 5 | 33 | 33 |
| From 65-84 years | 5 | 36 | 34 |
| 85 years and over | 0 | 1 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 65.8 | 64.2 | 65.6 |
| standard deviation | ± 13.4 | ± 13.1 | ± 11.3 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 3 | 28 | 26 |
| Male | 7 | 42 | 41 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 178 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 81 | | |
| From 65-84 years | 96 | | |
| 85 years and over | 1 | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 70 | | |
| Male | 108 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Cohort 1: PF-03049423 1 mg |
| Reporting group description: | |
| Subjects received PF-03049423 1 mg once daily for 90 days. | |
| Reporting group title | Cohort 1: Placebo |
| Reporting group description: | |
| Subjects received placebo matched to PF-03049423 1 mg once daily for 90 days. | |
| Reporting group title | Cohort 2: PF-03049423 3 mg |
| Reporting group description: | |
| Subjects received PF-03049423 3 mg once daily for 90 days. | |
| Reporting group title | Cohort 2: Placebo |
| Reporting group description: | |
| Subjects received placebo matched to PF-03049423 3 mg once daily for 90 days. | |
| Reporting group title | Cohort 3: PF-03049423 6 mg |
| Reporting group description: | |
| Subjects received PF-03049423 6 mg once daily for 90 days. | |
| Reporting group title | Cohort 3: Placebo |
| Reporting group description: | |
| Subjects received placebo matched to PF-0304942 6 mg once daily for 90 days. | |

### Primary: Number of subjects with any abnormal laboratory test results (Part 1* and 2)

| | |
|---|---|
| End point title | Number of subjects with any abnormal laboratory test results (Part 1* and 2)[1] |

End point description:

The total number of subjects with laboratory test abnormalities (without regard to baseline abnormality) was assessed. *This endpoint was a primary endpoint for Part 1 (timeframe Days 1 to 14), as data for this timeframe were not reported separately, Part 1 and 2 data were reported together.
The Full Analysis Set (FAS) consisted of all randomized subjects who took any study medication (active or placebo).

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

End point timeframe:

Day 1 (Baseline) up to Day 90

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: This is a safety endpoint and no statistical analysis was planned and performed for this endpoint.

| End point values | Cohort 1: PF-03049423 1 mg | Cohort 1: Placebo | Cohort 2: PF-03049423 3 mg | Cohort 2: Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11[2] | 9[3] | 10[4] | 10[5] |
| Units: subjects | 8 | 8 | 10 | 9 |

Notes:

[2] - Subjects analyzed indicated number of subjects evaluated.

[3] - Subjects analyzed indicated number of subjects evaluated.

[4] - Subjects analyzed indicated number of subjects evaluated.

[5] - Subjects analyzed indicated number of subjects evaluated.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 70[6] | 66[7] | | |
| Units: subjects | 64 | 56 | | |

Notes:

[6] - Subjects analyzed indicated number of subjects evaluated.

[7] - Subjects analyzed indicated number of subjects evaluated.

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of subjects with vital signs data met criteria of potential clinical concern (Part 1* and 2)

| End point title | Number of subjects with vital signs data met criteria of potential clinical concern (Part 1* and 2)[8] |
|---|---|

End point description:

Vital signs included blood pressure (BP; supine, sitting and standing) and pulse rate. Vital signs criteria of potential clinical concern were 1), BP: systolic BP (SBP) greater than or equal to (>=) 30 or 50 millimeters of mercury (mm Hg) change from grand baseline in same posture, systolic less than (<) 90 mm Hg; diastolic BP (DBP) >=20 mm Hg change from grand baseline in same posture, diastolic <50 mm Hg; 2), pulse rate (supine, sitting and standing): <40 or greater than (>) 120 beats per minute (bpm); Standing: <40 or >140 bpm. *This endpoint was a primary endpoint for Part 1 (timeframe Days 1 to 14), as data for this timeframe were not reported separately, Part 1 and 2 data were reported together.
The FAS consisted of all randomized subjects who took any study medication (active or placebo).
n=number of evaluable subjects.
99999=No subjects were evaluated.

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

End point timeframe:

Day 1 (Baseline) up to follow-up (28 days after Day 90)

Notes:

[8] - 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: This is a safety endpoint and no statistical analysis was planned and performed for this endpoint.

| **End point values** | Cohort 1: PF-03049423 1 mg | Cohort 1: Placebo | Cohort 2: PF-03049423 3 mg | Cohort 2: Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11[9] | 9[10] | 11[11] | 10[12] |
| Units: subjects | | | | |
| Supine SBP <90 mm Hg, n=11,9,11,10,70,67 | 0 | 1 | 1 | 0 |
| Sitting SBP <90 mm Hg, n=10,8,9,5,55,59 | 0 | 1 | 1 | 0 |
| Standing SBP <90 mm Hg, n=7,7,9,8,49,48 | 0 | 0 | 0 | 0 |
| Supine DBP <50 mm Hg, n=11,9,11,10,70,67 | 0 | 0 | 2 | 1 |
| Sitting DBP <50 mm Hg, n=10,8,9,5,55,59 | 0 | 0 | 0 | 0 |

| | | | | |
|---|---|---|---|---|
| Standing DBP <50 mm Hg, n=7,7,9,8,49,48 | 0 | 0 | 0 | 1 |
| Supine pulse rate <40 bpm, n=11,9,11,10,70,67 | 0 | 0 | 0 | 0 |
| Supine pulse rate >120 bpm, n=11,9,11,10,70,67 | 0 | 0 | 1 | 0 |
| Increase:supine SBP >=30 mm Hg, n=11,9,11,10,70,67 | 2 | 3 | 5 | 3 |
| Increase: sitting SBP >=30 mm Hg, n=9,6,9,4,48,44 | 0 | 2 | 2 | 0 |
| Increase: standing SBP >=30 mm Hg, n=2,3,3,6,19,22 | 0 | 0 | 0 | 2 |
| Increase:supine DBP >=20 mm Hg, n=11,9,11,10,70,67 | 4 | 2 | 5 | 2 |
| Increase: sitting DBP >=20 mm Hg, n=9,6,9,4,48,44 | 3 | 1 | 2 | 2 |
| Increase: standing DBP >=20 mm Hg, n=2,3,3,6,19,22 | 0 | 0 | 0 | 2 |
| Decrease:supine SBP >=30 mm Hg, n=11,9,11,10,70,67 | 7 | 6 | 5 | 4 |
| Decrease: sitting SBP >=30 mm Hg, n=9,6,9,4,48,44 | 3 | 4 | 6 | 2 |
| Decrease: standing SBP >=30 mm Hg, n=2,3,3,6,19,22 | 2 | 2 | 0 | 2 |
| Decrease:supine DBP >=20 mm Hg, n=11,9,11,10,70,67 | 8 | 6 | 6 | 3 |
| Decrease: sitting DBP >=20 mm Hg, n=9,6,9,4,48,44 | 1 | 4 | 5 | 1 |
| Decrease: standing DBP >=20 mm Hg, n=2,3,3,6,19,22 | 2 | 2 | 1 | 2 |
| Decrease:supine SBP >=50 mm Hg, n=11,9,11,10,70,67 | 2 | 0 | 1 | 2 |
| Decrease: sitting SBP >=50 mm Hg, n=9,6,9,4,48,44 | 2 | 1 | 3 | 0 |
| Decrease: standing SBP >=50 mm Hg, n=2,3,3,6,19,22 | 1 | 0 | 0 | 0 |
| Sitting pulse rate <40 bpm, n=1,0,2,0,3,2 | 0 | 99999 | 0 | 99999 |
| Standing pulse rate <40 bpm, n=0,0,0,2,1,0 | 99999 | 99999 | 99999 | 0 |
| Sitting pulse rate >120 bpm, n=1,0,2,0,3,2 | 0 | 99999 | 0 | 99999 |
| Standing pulse rate >140 bpm, n=0,0,0,2,1,0 | 99999 | 99999 | 99999 | 0 |

Notes:

[9] - All randomized and treated subjects in this group.

[10] - All randomized and treated subjects in this group.

[11] - All randomized and treated subjects in this group.

[12] - All randomized and treated subjects in this group.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 70[13] | 67[14] | | |
| Units: subjects | | | | |
| Supine SBP <90 mm Hg, n=11,9,11,10,70,67 | 3 | 0 | | |
| Sitting SBP <90 mm Hg, n=10,8,9,5,55,59 | 2 | 2 | | |

| | | | | |
|---|---|---|---|---|
| Standing SBP <90 mm Hg, n=7,7,9,8,49,48 | 1 | 1 | | |
| Supine DBP <50 mm Hg, n=11,9,11,10,70,67 | 6 | 4 | | |
| Sitting DBP <50 mm Hg, n=10,8,9,5,55,59 | 3 | 1 | | |
| Standing DBP <50 mm Hg, n=7,7,9,8,49,48 | 2 | 3 | | |
| Supine pulse rate <40 bpm, n=11,9,11,10,70,67 | 1 | 0 | | |
| Supine pulse rate >120 bpm, n=11,9,11,10,70,67 | 5 | 7 | | |
| Increase:supine SBP >=30 mm Hg, n=11,9,11,10,70,67 | 13 | 17 | | |
| Increase: sitting SBP >=30 mm Hg, n=9,6,9,4,48,44 | 10 | 9 | | |
| Increase: standing SBP >=30 mm Hg, n=2,3,3,6,19,22 | 2 | 1 | | |
| Increase:supine DBP >=20 mm Hg, n=11,9,11,10,70,67 | 16 | 22 | | |
| Increase: sitting DBP >=20 mm Hg, n=9,6,9,4,48,44 | 9 | 12 | | |
| Increase: standing DBP >=20 mm Hg, n=2,3,3,6,19,22 | 3 | 3 | | |
| Decrease:supine SBP >=30 mm Hg, n=11,9,11,10,70,67 | 37 | 37 | | |
| Decrease: sitting SBP >=30 mm Hg, n=9,6,9,4,48,44 | 26 | 18 | | |
| Decrease: standing SBP >=30 mm Hg, n=2,3,3,6,19,22 | 10 | 11 | | |
| Decrease:supine DBP >=20 mm Hg, n=11,9,11,10,70,67 | 32 | 26 | | |
| Decrease: sitting DBP >=20 mm Hg, n=9,6,9,4,48,44 | 23 | 14 | | |
| Decrease: standing DBP >=20 mm Hg, n=2,3,3,6,19,22 | 6 | 11 | | |
| Decrease:supine SBP >=50 mm Hg, n=11,9,11,10,70,67 | 10 | 9 | | |
| Decrease: sitting SBP >=50 mm Hg, n=9,6,9,4,48,44 | 7 | 6 | | |
| Decrease: standing SBP >=50 mm Hg, n=2,3,3,6,19,22 | 1 | 2 | | |
| Sitting pulse rate <40 bpm, n=1,0,2,0,3,2 | 0 | 0 | | |
| Standing pulse rate <40 bpm, n=0,0,0,2,1,0 | 0 | 99999 | | |
| Sitting pulse rate >120 bpm, n=1,0,2,0,3,2 | 0 | 0 | | |
| Standing pulse rate >140 bpm, n=0,0,0,2,1,0 | 0 | 99999 | | |

Notes:

[13] - All randomized and treated subjects in this group.

[14] - All randomized and treated subjects in this group.

### Statistical analyses

No statistical analyses for this end point

## Primary: Number of subjects with electrocardiograms (ECGs) data met criteria of potential clinical concern (Part 1* and 2)

| End point title | Number of subjects with electrocardiograms (ECGs) data met criteria of potential clinical concern (Part 1* and 2)[15] |
|---|---|

End point description:

ECG criteria of potential clinical concern were 1), PR interval: >=300 milliseconds (msec); >=25% increase when baseline >200 msec; or increase >=50% when baseline <=200 msec; 2), QRS interval: >=140 msec; >=50% increase from baseline; 3), QT interval: >=500 msec, QTc interval using Fridericia's formula (QTcF interval): absolute value >=450 - <480 msec, >=480-<500 msec, >=500 msec; absolute change 30 - <60 msec, >=60 msec. *This endpoint was a primary endpoint for Part 1 (timeframe Days 1 to 14), as data for this timeframe were not reported separately, Part 1 and 2 data were reported together.
The FAS consisted of all randomized subjects who took any study medication (active or placebo). n=number of evaluable subjects.

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

End point timeframe:

Day 1 (Baseline) to Day 90

Notes:

[15] - 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: This is a safety endpoint and no statistical analysis was planned and performed for this endpoint.

| **End point values** | Cohort 1: PF-03049423 1 mg | Cohort 1: Placebo | Cohort 2: PF-03049423 3 mg | Cohort 2: Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11[16] | 9[17] | 11[18] | 10[19] |
| Units: subjects | | | | |
| PR interval >=300 msec, n=11,9,11,10,70,67 | 0 | 0 | 0 | 0 |
| QRS interval >=140 msec, n=11,9,11,10,70,67 | 1 | 0 | 1 | 1 |
| QT interval >=500 msec, n=11,9,11,10,70,67 | 0 | 0 | 0 | 0 |
| QTcF interval 450-480 msec, n=11,9,11,10,70,67 | 2 | 3 | 4 | 2 |
| QTcF interval 480-500 msec, n=11,9,11,10,70,67 | 0 | 1 | 0 | 1 |
| QTcF interval >=500 msec, n=11,9,11,10,70,67 | 0 | 0 | 1 | 0 |
| PR interval increase >=25%/50%, n=10,7,9,9,52,47 | 0 | 0 | 1 | 0 |
| QRS interval increase >=50%, n=10,9,11,10,69,66 | 0 | 0 | 0 | 0 |
| QTcF increase 30-60 msec, n=10,9,11,10,69,66 | 2 | 3 | 4 | 2 |
| QTcF increase >=60 msec, n=10,9,11,10,69,66 | 0 | 0 | 0 | 1 |

Notes:

[16] - All randomized and treated subjects in this group.

[17] - All randomized and treated subjects in this group.

[18] - All randomized and treated subjects in this group.

[19] - All randomized and treated subjects in this group.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 70[20] | 67[21] | | |
| Units: subjects | | | | |

| | | | | |
|---|---|---|---|---|
| PR interval >=300 msec, n=11,9,11,10,70,67 | 0 | 0 | | |
| QRS interval >=140 msec, n=11,9,11,10,70,67 | 0 | 1 | | |
| QT interval >=500 msec, n=11,9,11,10,70,67 | 4 | 1 | | |
| QTcF interval 450-480 msec, n=11,9,11,10,70,67 | 14 | 14 | | |
| QTcF interval 480-500 msec, n=11,9,11,10,70,67 | 4 | 3 | | |
| QTcF interval >=500 msec, n=11,9,11,10,70,67 | 0 | 1 | | |
| PR interval increase >=25%/50%, n=10,7,9,9,52,47 | 1 | 0 | | |
| QRS interval increase >=50%, n=10,9,11,10,69,66 | 0 | 1 | | |
| QTcF increase 30-60 msec, n=10,9,11,10,69,66 | 19 | 11 | | |
| QTcF increase >=60 msec, n=10,9,11,10,69,66 | 3 | 5 | | |

Notes:

[20] - All randomized and treated subjects in this group.

[21] - All randomized and treated subjects in this group.

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of subjects with significant change in physical examination findings (Part 1* and 2)

| End point title | Number of subjects with significant change in physical examination findings (Part 1* and 2)[22] |
|---|---|

End point description:

The complete physical examination included examination of the skin, eyes, ears, throat, neck, cardiac, respiratory, gastrointestinal, and musculoskeletal systems. The limited physical examination included examination of the cardiac, respiratory, gastrointestinal, and musculoskeletal systems. *This endpoint was a primary endpoint for Part 1 (timeframe Days 1 to 14), as data for this timeframe were not reported separately, Part 1 and 2 data were reported together.
The FAS consisted of all randomized subjects who took any study medication (active or placebo).

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

End point timeframe:

Day 1 (Baseline) up to Day 90

Notes:

[22] - 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: This is a safety endpoint and no statistical analysis was planned and performed for this endpoint.

| **End point values** | Cohort 1: PF-03049423 1 mg | Cohort 1: Placebo | Cohort 2: PF-03049423 3 mg | Cohort 2: Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11[23] | 9[24] | 11[25] | 10[26] |
| Units: subjects | 1 | 1 | 0 | 0 |

Notes:

[23] - Subjects who had physical examinations done at both baseline and last visit in this group.

[24] - Subjects who had physical examinations done at both baseline and last visit in this group.

[25] - Subjects who had physical examinations done at both baseline and last visit in this group.

[26] - Subjects who had physical examinations done at both baseline and last visit in this group.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 70[27] | 66[28] | | |
| Units: subjects | 2 | 0 | | |

Notes:

[27] - Subjects who had physical examinations done at both baseline and last visit in this group.

[28] - Subjects who had physical examinations done at both baseline and last visit in this group.

### Statistical analyses

No statistical analyses for this end point

## Primary: Number of subjects with significant change in neurological examination findings (Part 1* and 2)

| End point title | Number of subjects with significant change in neurological examination findings (Part 1* and 2)[29] |
|---|---|

End point description:

The complete neurological examination included an assessment of the motor, sensory, cranial nerves, reflexes, mental status and associated motor functions. The limited neurological exam could examine the same categories of neurologic assessments as the full examination, but would differ by the depth in the examination. The examination was required to be done to the extent needed to assess the subject for any potential changes in neurological status, as determined by the Investigator, but had to always include an assessment of motor, vision and hearing. *This endpoint was a primary endpoint for Part 1 (timeframe Days 1 to 14), as data for this timeframe were not reported separately, Part 1 and 2 data were reported together.
The FAS consisted of all randomized subjects who took any study medication (active or placebo).

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

End point timeframe:

Day 1 (Baseline) up to Day 90

Notes:

[29] - 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: This is a safety endpoint and no statistical analysis was planned and performed for this endpoint.

| **End point values** | Cohort 1: PF-03049423 1 mg | Cohort 1: Placebo | Cohort 2: PF-03049423 3 mg | Cohort 2: Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11[30] | 9[31] | 11[32] | 10[33] |
| Units: subjects | 1 | 1 | 0 | 0 |

Notes:

[30] - Subjects who had neurological examinations done at both baseline and last visit in this group.

[31] - Subjects who had neurological examinations done at both baseline and last visit in this group.

[32] - Subjects who had neurological examinations done at both baseline and last visit in this group.

[33] - Subjects who had neurological examinations done at both baseline and last visit in this group.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 70[34] | 66[35] | | |

| | | | | |
|---|---|---|---|---|
| Units: subjects | 4 | 0 | | |

Notes:

[34] - Subjects who had neurological examinations done at both baseline and last visit in this group.

[35] - Subjects who had neurological examinations done at both baseline and last visit in this group.

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of subjects with suicidal behavior and/or ideation as assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) (Part 1* and 2)

| End point title | Number of subjects with suicidal behavior and/or ideation as assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) (Part 1* and 2)[36] |
|---|---|

End point description:

Data were mapped to Columbia-Classification Algorithm of Suicide Assessment (C-CASA) event codes. C-SSRS assessed if subject experienced: completed suicide (Code 1), suicide attempt (Code 2), preparatory acts toward imminent suicidal behavior (Code 3), suicidal ideation (Code 4), self-injurious behavior, no suicidal intent (Code 7). Number of subjects with "Yes" response was assessed. *This was a primary endpoint for Part 1 (timeframe Days 1 to 14), as data for it were not reported separately, Part 1 and 2 data were reported together.
The FAS consisted of all randomized subjects who took any study medication (active or placebo).
n=number of subjects who had C-SSRS assessed at that visit.
99999=No subjects had C-SSRS assessed.

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

End point timeframe:

Day 7 (Baseline) up to follow up (28 days after Day 90)

Notes:

[36] - 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: This is a safety endpoint and no statistical analysis was planned and performed for this endpoint.

| End point values | Cohort 1: PF-03049423 1 mg | Cohort 1: Placebo | Cohort 2: PF-03049423 3 mg | Cohort 2: Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11[37] | 9[38] | 11[39] | 10[40] |
| Units: subjects | | | | |
| Day 7, n=0, 0, 1, 1, 64, 57 | 99999 | 99999 | 0 | 0 |
| Day 14, n=0, 0, 1, 1, 59, 53 | 99999 | 99999 | 0 | 0 |
| Day 30, n=0, 0, 1, 1, 60, 47 | 99999 | 99999 | 0 | 0 |
| Day 60, n=0, 0, 1, 1, 55, 44 | 99999 | 99999 | 0 | 0 |
| Day 90, n=0, 0, 1, 1, 61, 53 | 99999 | 99999 | 0 | 0 |
| Follow-up, n=0, 0, 1, 1, 59, 51 | 99999 | 99999 | 0 | 0 |

Notes:

[37] - All randomized and treated subjects in this group.

[38] - All randomized and treated subjects in this group.

[39] - All randomized and treated subjects in this group.

[40] - All randomized and treated subjects in this group.

| End point values | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|

| Subject group type | Reporting group | Reporting group | | |
|---|---|---|---|---|
| Number of subjects analysed | 70[41] | 67[42] | | |
| Units: subjects | | | | |
| Day 7, n=0, 0, 1, 1, 64, 57 | 1 | 2 | | |
| Day 14, n=0, 0, 1, 1, 59, 53 | 1 | 0 | | |
| Day 30, n=0, 0, 1, 1, 60, 47 | 2 | 0 | | |
| Day 60, n=0, 0, 1, 1, 55, 44 | 2 | 0 | | |
| Day 90, n=0, 0, 1, 1, 61, 53 | 1 | 1 | | |
| Follow-up, n=0, 0, 1, 1, 59, 51 | 0 | 0 | | |

Notes:

[41] - All randomized and treated subjects in this group.

[42] - All randomized and treated subjects in this group.

### Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of subjects with modified Rankin Scale (mRS) less than or equal to (<=2) at Day 90 (Part 2)

| End point title | Percentage of subjects with modified Rankin Scale (mRS) less than or equal to (<=2) at Day 90 (Part 2)[43] |
|---|---|

End point description:

The mRS is a 6-point scale of functional recovery. The scale grades subjects as having no symptoms (0), minor symptoms (1), minor handicap (2), moderate handicap (3), moderately severe handicap (4), severe handicap (5), or death (6).
n=number of subjects included for comparison between active drug and placebo.
The Inferential-Full Analysis Set (I-FAS) consisted of subjects within the FAS who were randomized to PF-03049423 6 mg or placebo group that was in the same cohort as the 6 mg group.

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

End point timeframe:

Day 90

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a primary efficacy endpoint for Part 2 and statistical comparison was conducted in Cohort 3 subjects.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 68[44] | 65[45] | | |
| Units: subjects | | | | |
| Last Observation Carried Forward (LOCF), n=68, 65 | 29 | 30 | | |
| Observed Cases (OC), n=51, 52 | 24 | 26 | | |

Notes:

[44] - Subjects who were randomized and treated in PF-03049423 highest dose (6 mg) group.

[45] - Subjects who were randomized and treated in placebo (matched to PF-03049423 6 mg dose) group.

### Statistical analyses

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo (LOCF) |
|---|---|

Statistical analysis description:

LOCF was used to impute missing data.

| | |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4962 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.735 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.41 |
| upper limit | 1.31 |

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo (OC) |
|---|---|
| Statistical analysis description: | |
| The analysis was based on OC. | |
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[46] |
| P-value | = 0.2517 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.561 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.29 |
| upper limit | 1.07 |

Notes:

[46] - The analysis was based on OC.

## Secondary: Change from baseline in Box and Blocks (B&B) Test at Day 90 for paretic and non-paretic hands (Part 2)

| End point title | Change from baseline in Box and Blocks (B&B) Test at Day 90 for paretic and non-paretic hands (Part 2)[47] |
|---|---|

End point description:

The B&B test is a measure of manual dexterity. The B&B apparatus consists of a box divided into 2 sections and 1-inch hardwood blocks. The blocks began in the compartment of the test box to the dominant side of the subject. The subject was required to transfer the blocks one at a time to the other side of the box as quickly as possible in 1 minute using the non-paretic hand. The box was then turned so all the blocks were in the same side as the paretic hand. The subject was then required to do the test with his/her paretic hand. If more than 1 block was picked up at a time it was counted as 1 block. The subject's fingertips needed to cross the partition for the block to be counted. The performance measure for this task was number of blocks moved within 1 minute. I-FAS consisted of subjects within the FAS who were randomized to PF-03049423 6 mg or placebo group that was in the same cohort as the 6 mg group. n=number of subjects included for comparison between active drug and placebo.

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

End point timeframe:

Day 1 (Baseline), Day 90

Notes:

[47] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This is a secondary efficacy endpoint for Part 2 and statistical comparison was conducted in Cohort 3 subjects.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 68[48] | 65[49] | | |
| Units: blocks moved per minute | | | | |
| least squares mean (standard error) | | | | |
| Paretic Hand, n=21, 24 | 26.881 (± 3.8667) | 26.741 (± 3.5627) | | |
| Non-Paretic Hand, n=45, 41 | 17.797 (± 2.1676) | 18.313 (± 2.2407) | | |

Notes:

[48] - Subjects who were randomized and treated in PF-03049423 highest dose (6 mg) group.

[49] - Subjects who were randomized and treated in placebo (matched to PF-03049423 6 mg dose) group.

## Statistical analyses

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo - Paretic Hand |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9716 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.141 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -4.972 |
| upper limit | 5.254 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.942 |

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo - Non-Paretic Hand |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8501 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.516 |

| | |
|---|---|
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -4.026 |
| upper limit | 2.995 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.7201 |

## Secondary: Change from baseline in B&B Test at Day 90 for paretic to non-paretic hand ratio (Part 2)

| | |
|---|---|
| End point title | Change from baseline in B&B Test at Day 90 for paretic to non-paretic hand ratio (Part 2)[50] |

End point description:

he B&B test is a measure of manual dexterity. The B&B apparatus consists of a box divided into 2 sections and 1-inch hardwood blocks. The blocks began in the compartment of the test box to the dominant side of the subject. The subject was required to transfer the blocks one at a time to the other side of the box as quickly as possible in 1 minute using the non-paretic hand. The box was then turned so all the blocks were in the same side as the paretic hand. The subject was then required to do the test with his/her paretic hand. The subject was told that if more than 1 block was picked up at a time it was to only count as 1 block. The subject was also told that their fingertips needed to cross the partition for the block to be counted. The performance measure for this task was the number of blocks moved within 1 minute.
The I-FAS consisted of subjects within the FAS who were randomized to PF-03049423 6 mg or placebo group that was in the same cohort as the 6 mg group.

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

End point timeframe:

Day 1 (Baseline), Day 90

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a secondary efficacy endpoint for Part 2 and statistical comparison was conducted in Cohort 3 subjects.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21[51] | 24[52] | | |
| Units: percentage change | | | | |
| least squares mean (standard error) | 41.83 (± 7.781) | 31.041 (± 7.1284) | | |

Notes:

[51] - Subjects who were in PF-03049423 6 mg group and included in statistical comparison.

[52] - Subjects who were in placebo group (Cohort 3) and included in statistical comparison.

## Statistical analyses

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo |
|---|---|

Statistical analysis description:

This comparison is for paretic to non-paretic hand ratio.

| | |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1417 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 10.789 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 1.401 |
| upper limit | 20.177 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 7.2392 |

## Secondary: Change from baseline in Hand Grip Strength Test at Day 90 for paretic and non-paretic hands (Part 2)

| | |
|---|---|
| End point title | Change from baseline in Hand Grip Strength Test at Day 90 for paretic and non-paretic hands (Part 2)[53] |

End point description:

The Hand Grip Strength Test measures the maximum isometric strength of the hand and forearm muscles. The subject was required to squeeze the dynamometer with maximum isometric effort while sitting with shoulder adducted and neutrally roated, elbow flexed at 90 degrees and the forearm in neutral position and wrist between 0 to 30 degrees dorsiflexion and a 0 to 15 degrees ulnar deviation. The subject performed this task 3 times with each hand, starting with the non-paretic hand. The performance measure for this task was the average score measured in pounds of pressure exerted.
The I-FAS consisted of subjects within the FAS who were randomized to PF-03049423 6 mg or placebo group that was in the same cohort as the 6 mg group.
n=number of subjects included for comparison between active drug and placebo.

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

End point timeframe:

Day 1 (Baseline), Day 90

Notes:

[53] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a secondary efficacy endpoint for Part 2 and statistical comparison was conducted in Cohort 3 subjects.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 68[54] | 65[55] | | |
| Units: pounds | | | | |
| least squares mean (standard error) | | | | |
| Paretic Hand, n=26, 26 | 20.556 (± 4.1829) | 30.886 (± 3.9964) | | |
| Non-Paretic Hand, n=46, 41 | 12.546 (± 2.3612) | 12.312 (± 2.5029) | | |

Notes:

[54] - Subjects who were randomized and treated in PF-03049423 highest dose (6 mg) group.

[55] - Subjects who were randomized and treated in placebo (matched to PF-03049423 6 mg dose)

group.

**Statistical analyses**

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo - Paretic Hand |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0611 |
| Method | Mixed models analysis |
| Parameter estimate | Median difference (final values) |
| Point estimate | -10.33 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -17.351 |
| upper limit | -3.31 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.4241 |

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo - Non-Paretic Hand |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9433 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.235 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -4.011 |
| upper limit | 4.48 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.2899 |

**Secondary: Change from baseline in Hand Grip Strength Test at Day 90 for paretic to non-paretic hand ratio (Part 2)**

| End point title | Change from baseline in Hand Grip Strength Test at Day 90 for paretic to non-paretic hand ratio (Part 2)[56] |
|---|---|

End point description:

The Hand Grip Strength Test measures the maximum isometric strength of the hand and forearm muscles. The subject was required to squeeze the dynamometer with maximum isometric effort while sitting with shoulder adducted and neutrally roated, elbow flexed at 90 degrees and the forearm in neutral position and wrist between 0 to 30 degrees dorsiflexion and a 0 to 15 degrees ulnar deviation. The subject performed this task 3 times with each hand, starting with the non-paretic hand. The performance measure for this task was the average score measured in pounds of pressure exerted. The I-FAS consisted of subjects within the FAS who were randomized to PF-03049423 6 mg or placebo group that was in the same cohort as the 6 mg group.

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

End point timeframe:

Day 1 (Baseline), Day 90

Notes:

[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a secondary efficacy endpoint for Part 2 and statistical comparison was conducted in Cohort 3 subjects.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26[57] | 26[58] | | |
| Units: percentage change | | | | |
| least squares mean (standard error) | 23.949 (± 5.4499) | 36.761 (± 5.1182) | | |

Notes:

[57] - Subjects who were in PF-03049423 6 mg group and included in statistical comparison.

[58] - Subjects who were in placebo group (Cohort 3) and included in statistical comparison.

### Statistical analyses

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo |
|---|---|

Statistical analysis description:

This analysis was for paretic to non-paretic hand ratio.

| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
|---|---|
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0654 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -12.812 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -21.668 |
| upper limit | -3.957 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.8448 |

## Secondary: Number of subjects with mRS (0-1) at Day 90 (Part 2)

| End point title | Number of subjects with mRS (0-1) at Day 90 (Part 2)[59] |
|---|---|

End point description:

The mRS is a 6-point scale of functional recovery. The scale grades subjects as having no symptoms (0), minor symptoms (1), minor handicap (2), moderate handicap (3), moderately severe handicap (4), severe handicap (5), or death (6).
The I-FAS consisted of subjects within the FAS who were randomized to PF-03049423 6 mg or placebo group that was in the same cohort as the 6 mg group.

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

End point timeframe:

Day 90

Notes:

[59] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a secondary efficacy endpoint for Part 2 and statistical comparison was conducted in Cohort 3 subjects.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 68[60] | 65[61] | | |
| Units: subjects | 17 | 16 | | |

Notes:

[60] - Subjects who were randomized and treated in PF-03049423 highest dose (6 mg) group.

[61] - Subjects who were randomized and treated in placebo (matched to PF-03049423 6 mg dose) group.

### Statistical analyses

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.951 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.972 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 1.76 |

## Secondary: Number of subjects with National Institutes of Health Stroke Scale (NIHSS) (0-1) at Day 90 (Part 2)

| End point title | Number of subjects with National Institutes of Health Stroke Scale (NIHSS) (0-1) at Day 90 (Part 2)[62] |
|---|---|

End point description:

The NIHSS is a graded 11-item neurological examination rating speech and language, cognition, visual field deficits, motor and sensory impairments and ataxia used for the clinical assessment of acute stroke therapy. The maximum total score is 42 in a subject with a severe neurological deficit; the minimum score is 0 in a subject without gross neurological deficits.

The I-FAS consisted of subjects within the FAS who were randomized to PF-03049423 6 mg or placebo group that was in the same cohort as the 6 mg group.

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

End point timeframe:

Day 90

Notes:

[62] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a secondary efficacy endpoint for Part 2 and statistical comparison was conducted in Cohort 3 subjects.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 68[63] | 65[64] | | |
| Units: subjects | 17 | 17 | | |

Notes:

[63] - Subjects who were randomized and treated in PF-03049423 highest dose (6 mg) group.

[64] - Subjects who were randomized and treated in placebo (matched to PF-03049423 6 mg dose) group.

### Statistical analyses

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7234 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.854 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.48 |
| upper limit | 1.51 |

## Secondary: Change from baseline in NIHSS at Day 90 (Part 2)

| End point title | Change from baseline in NIHSS at Day 90 (Part 2)[65] |
|---|---|

End point description:

The NIHSS is a graded 11-item neurological examination rating speech and language, cognition, visual field deficits, motor and sensory impairments and ataxia used for the clinical assessment of acute stroke therapy. The maximum total score is 42 in a subject with a severe neurological deficit; the minimum score is 0 in a subject without gross neurological deficits.
The I-FAS consisted of subjects within the FAS who were randomized to PF-03049423 6 mg or placebo group that was in the same cohort as the 6 mg group.

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

End point timeframe:

Day 1 (Baseline), Day 90

Notes:

[65] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a secondary efficacy endpoint for Part 2 and statistical comparison was conducted in Cohort 3 subjects.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 49[66] | 47[67] | | |
| Units: unit on a scale | | | | |
| least squares mean (standard error) | -6.511 (± 0.5384) | -6.228 (± 0.5655) | | |

Notes:

[66] - Subjects who were in PF-03049423 6 mg group and included in statistical comparison.

[67] - Subjects who were in placebo group (Cohort 3) and included in statistical comparison.

### Statistical analyses

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 96 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6759 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.283 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -1.156 |
| upper limit | 0.589 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.6755 |

## Secondary: Number of subjects with Barthel Index (BI) >= 95 and BI =100 at Day 90 (Part 2)

| End point title | Number of subjects with Barthel Index (BI) >= 95 and BI =100 at Day 90 (Part 2)[68] |
|---|---|

End point description:

The BI is an index of independence to score the ability of a subject with a neuromuscular or musculoskeletal disorder to care for him or herself. The index rates a subject's ability on the following 10 activities: feeding, moving from wheelchair to bed, personal toilet, getting on and off toilet, bathing self, walking on level surface, ascending and descending stairs, dressing, controlling bowels and controlling bladder. The maximum total score is 100 in a subject without functional impairment; the minimum score is 0 in a subject with major functional impairment.
The I-FAS consisted of subjects within the FAS who were randomized to PF-03049423 6 mg or placebo group that was in the same cohort as the 6 mg group.

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

End point timeframe:

Day 90

Notes:

[68] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This is a secondary efficacy endpoint for Part 2 and statistical comparison was conducted in Cohort 3 subjects.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 68[69] | 65[70] | | |
| Units: subjects | | | | |
| BI >=95 | 32 | 26 | | |
| BI=100 | 29 | 23 | | |

Notes:

[69] - Subjects who were randomized and treated in PF-03049423 highest dose (6 mg) group.

[70] - Subjects who were randomized and treated in placebo (matched to PF-03049423 6 mg dose) group.

## Statistical analyses

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo (BI >=95) |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4213 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.433 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 2.54 |

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo (BI=100) |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.276 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.651 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 2.98 |

## Secondary: BI at Day 90 (Part 2)

| End point title | BI at Day 90 (Part 2)[71] |
|---|---|

End point description:

The BI is an index of independence to score the ability of a subject with a neuromuscular or musculoskeletal disorder to care for him or herself. The index rates a subject's ability on the following 10 activities: feeding, moving from wheelchair to bed, personal toilet, getting on and off toilet, bathing self, walking on level surface, ascending and descending stairs, dressing, controlling bowels and controlling bladder. The maximum total score is 100 in a subject without functional impairment; the minimum score is 0 in a subject with major functional impairment.
The I-FAS consisted of subjects within the FAS who were randomized to PF-03049423 6 mg or placebo group that was in the same cohort as the 6 mg group.

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

End point timeframe:

Day 90

Notes:

[71] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a secondary efficacy endpoint for Part 2 and statistical comparison was conducted in Cohort 3 subjects.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 49[72] | 47[73] | | |
| Units: unit on a scale | | | | |
| least squares mean (standard error) | 79.151 (± 3.6248) | 73.552 (± 3.8471) | | |

Notes:

[72] - Subjects who were in PF-03049423 6 mg group and included in statistical comparison.

[73] - Subjects who were in placebo group (Cohort 3) and included in statistical comparison.

## Statistical analyses

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 96 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2118 |
| Method | Mixed models analysis |
| Parameter estimate | Median difference (final values) |
| Point estimate | 5.599 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.15 |
| upper limit | 11.348 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.4547 |

## Secondary: Domains of Interest: change from baseline in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Coding Sub Test at Day 90 (Part 2)

| End point title | Domains of Interest: change from baseline in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Coding Sub Test at Day 90 (Part 2)[74] |
|---|---|

End point description:

The test uses a reference key, the subject had 90 seconds to pair specific numbers with given geometric figures. Responses could be written or oral. The performance measure for this task was the total number of correct responses.
The I-FAS consisted of subjects within the FAS who were randomized to PF-03049423 6 mg or placebo group that was in the same cohort as the 6 mg group.

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

End point timeframe:

Day 1 (Baseline), Day 90

Notes:

[74] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a secondary efficacy endpoint for Part 2 and statistical comparison was conducted in Cohort 3 subjects.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33[75] | 28[76] | | |
| Units: number of correct responses | | | | |
| least squares mean (standard error) | 13.748 (± 1.5321) | 12.686 (± 1.6282) | | |

Notes:

[75] - Subjects who were in PF-03049423 6 mg group and included in statistical comparison.

[76] - Subjects who were in placebo group (Cohort 3) and included in statistical comparison.

### Statistical analyses

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 61 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5541 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.062 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -1.252 |
| upper limit | 3.375 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.7844 |

## Secondary: Domains of Interest: change from baseline in RBANS Naming Sub Test at Day 90 (Part 2)

| End point title | Domains of Interest: change from baseline in RBANS Naming Sub Test at Day 90 (Part 2)[77] |
|---|---|

End point description:

This test requires the subject to name 10 objects drawn in ink. The tester asked the subject to identify the picture. The subject had 20 seconds to respond to each picture presented. The performance measure was the number of objects named correctly.
The I-FAS consisted of subjects within the FAS who were randomized to PF-03049423 6 mg or placebo group that was in the same cohort as the 6 mg group.

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

End point timeframe:

Day 1 (Baseline), Day 90

Notes:

[77] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a secondary efficacy endpoint for Part 2 and statistical comparison was conducted in Cohort 3 subjects.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 41[78] | 37[79] | | |
| Units: number of objects named correctly | | | | |
| least squares mean (standard error) | 0.989 (± 0.3676) | 1.324 (± 0.3666) | | |

Notes:

[78] - Subjects who were in PF-03049423 6 mg group and included in statistical comparison.

[79] - Subjects who were in placebo group (Cohort 3) and included in statistical comparison.

### Statistical analyses

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 78 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.426 |
| Method | Mixed models analysis |
| Parameter estimate | Median difference (final values) |
| Point estimate | -0.334 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.874 |
| upper limit | 0.205 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.4178 |

## Secondary: Domains of Interest: change from baseline in Line Cancellation Test [(L+R)/28 × 100%, (L/14) × 100%, (R/14) × 100%] at Day 90 (Part 2)

| End point title | Domains of Interest: change from baseline in Line Cancellation Test [(L+R)/28 × 100%, (L/14) × 100%, (R/14) × 100%] at Day 90 (Part 2)[80] |
|---|---|

End point description:

The subject was presented with a page that had lines placed across the page. The subject was required to cross out all the lines on the page using their non-paretic hand after the tester had demonstrated what was required by crossing out the center line. The performance measure for this task was the total number of omissions made expressed as a percentage of the total number of items in the test. The test contains 4 variables: (L+R)/28 × 100%, (L/14) × 100%, (R/14) × 100%, and (L-R)/(L+R), where L = number of lines crossed on the left side of the paper; R = number of lines crossed on the right side of the paper.
The I-FAS consisted of subjects within the FAS who were randomized to PF-03049423 6 mg or placebo group that was in the same cohort as the 6 mg group.
n=number of subjects included for comparison between active drug and placebo for this outcome measure.

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

End point timeframe:

Day 1 (Baseline), Day 90

Notes:

[80] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a secondary efficacy endpoint for Part 2 and statistical comparison was conducted in Cohort 3 subjects.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 68[81] | 65[82] | | |
| Units: change in percentage of lines crossed | | | | |
| least squares mean (standard error) | | | | |
| (L+R)/28 × 100%, n=39, 35 | 19.459 (± 4.4433) | 16.983 (± 4.4551) | | |
| (L/14) × 100%, n=39, 35 | 22.824 (± 5.6691) | 18.95 (± 5.6639) | | |
| (R/14) × 100%, n=39, 35 | 16.481 (± 4.3564) | 15.431 (± 4.3647) | | |

Notes:

[81] - Subjects who were randomized and treated in PF-03049423 highest dose (6 mg) group.

[82] - Subjects who were randomized and treated in placebo (matched to PF-03049423 6 mg dose) group.

### Statistical analyses

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo - (L+R)/28 × 100% |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.65 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.477 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -4.547 |
| upper limit | 9.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.4394 |

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo - (L/14) × 100% |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5671 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 3.874 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -4.834 |
| upper limit | 12.583 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.7431 |

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo - (R/14) × 100% |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 133 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.843 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.049 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -5.771 |
| upper limit | 7.87 |

| | |
|---|---|
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.2816 |

## Secondary: Domains of Interest: change from baseline in Recognition Memory Test at Day 90 (Part 2)

| | |
|---|---|
| End point title | Domains of Interest: change from baseline in Recognition Memory Test at Day 90 (Part 2)[83] |

End point description:

This test assesses the ability to recognize pictures of objects. The subject was presented a series of pictures, a subset of which were the objects presented in the RBANS Naming Sub Test. After each picture was presented, the subject indicated either manually (ie, affirmative head nod) or verbally whether the picture was seen previously. The subject was given 5 seconds per picture to respond. The performance measure for this task was the total number of pictures correctly identified.
The I-FAS consisted of subjects within the FAS who were randomized to PF-03049423 6 mg or placebo group that was in the same cohort as the 6 mg group.

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

End point timeframe:

Day 1 (Baseline), Day 90

Notes:

[83] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a secondary efficacy endpoint for Part 2 and statistical comparison was conducted in Cohort 3 subjects.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44[84] | 37[85] | | |
| Units: pictures correctly identified | | | | |
| least squares mean (standard error) | -1.135 (± 0.4743) | 0.144 (± 0.4797) | | |

Notes:

[84] - Subjects who were in PF-03049423 6 mg group and included in statistical comparison.

[85] - Subjects who were in placebo group (Cohort 3) and included in statistical comparison.

### Statistical analyses

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0128 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.279 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -1.929 |
| upper limit | -0.629 |

| | |
|---|---|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.5041 |

## Secondary: Gait Velocity Test at Day 90 (Part 2)

| | |
|---|---|
| End point title | Gait Velocity Test at Day 90 (Part 2)[86] |

End point description:

The 10-meter walk test requires a 20 meter straight path, with 5 meters for acceleration, 10 meters for steady state walking, and 5 meters for deceleration. Markers were placed at the 5 and 15 meter positions along the path. The subject began to walk "at a comfortable pace" at 1 end of the path, and continued walking until he/she reached the other end. The rater used a stopwatch to determine how much time it took for the subject to traverse the 10 meter center of the path, starting the stopwatch as soon as the subject's limb crossed the first marker and stopping the stopwatch as soon as the subject's limb crossed the second marker.
The I-FAS consisted of subjects within the FAS who were randomized to PF-03049423 6 mg or placebo group that was in the same cohort as the 6 mg group.

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

End point timeframe:

Day 90

Notes:

[86] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a secondary efficacy endpoint for Part 2 and statistical comparison was conducted in Cohort 3 subjects.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 41[87] | 36[88] | | |
| Units: meters/second (m/s) | | | | |
| least squares mean (standard error) | 1.064 (± 0.104) | 0.975 (± 0.1128) | | |

Notes:

[87] - Subjects who were in PF-03049423 6 mg group and included in statistical comparison.

[88] - Subjects who were in placebo group (Cohort 3) and included in statistical comparison.

### Statistical analyses

| **Statistical analysis title** | PF-03049423 6 mg versus Placebo |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4713 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.089 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.07 |
| upper limit | 0.248 |

| | |
|---|---|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.1226 |

## Secondary: Plasma concentrations of PF-03049423 (Part 1 and 2)

| | |
|---|---|
| End point title | Plasma concentrations of PF-03049423 (Part 1 and 2)[89] |

End point description:

Pharmacokinetic (PK) concentration population included all subjects who were treated with PF-03049423 who had at least 1 measurable concentration. n=subjects with concentration above lower limit of quantification at the corresponding sampling time.
99999=No sample was collected.
99990=1 subject had concentration above lower limit of quantification, standard deviation cannot be calculated.

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

End point timeframe:

Days 1, 2, 7, 14, 30, 60 and 90

Notes:

[89] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The plasma concentration of PF-03049423 can only be reported in those subjects who received active treamtment but not placebo.

| End point values | Cohort 1: PF-03049423 1 mg | Cohort 2: PF-03049423 3 mg | Cohort 3: PF-03049423 6 mg | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11[90] | 11[91] | 70[92] | |
| Units: nanogram/milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 (0 hour predose), n=0, 1, 3 | 99999 (± 99999) | 0.05245 (± 0.17397) | 1.42 (± 11.591) | |
| Day 1 (1 hour post dose), n=11, 10, 63 | 5.825 (± 4.3514) | 17.5 (± 12.814) | 46.76 (± 36.153) | |
| Day 1 (2 hours post dose), n=11, 11, 61 | 7.063 (± 3.2729) | 30.18 (± 11.313) | 58.19 (± 32.837) | |
| Day 1 (8 hours post dose), n=11, 11, 68 | 7.361 (± 2.4032) | 25.39 (± 8.6644) | 52.47 (± 23.25) | |
| Day 2 (0 hour, predose), n=11, 11, 67 | 4.521 (± 1.5265) | 18.05 (± 4.7834) | 32.07 (± 13.776) | |
| Day 7 (0 hour, post dose), n=9, 7, 64 | 8.601 (± 2.9609) | 27.79 (± 7.6945) | 53.08 (± 30.237) | |
| Day 7 (1 hour post dose), n=0, 1, 59 | 99999 (± 99999) | 51.8 (± 99990) | 115.9 (± 65.329) | |
| Day 7 (2 hours post dose), n=0, 1, 59 | 99999 (± 99999) | 58.1 (± 99990) | 126.3 (± 57.759) | |
| Day 7 (6 hours post dose), n=0, 1, 61 | 99999 (± 99999) | 51.1 (± 99990) | 103.8 (± 41.09) | |
| Day 14 (0 hour predose), n=10, 8, 59 | 7.805 (± 2.9278) | 31.13 (± 9.8243) | 53.1 (± 28.085) | |
| Day 14 (1 hour post dose), n=9, 7, 0 | 16.47 (± 7.1782) | 76.71 (± 32.657) | 99999 (± 99999) | |
| Day 14 (2 hours post dose), n=9, 6, 0 | 17.06 (± 7.3799) | 70.37 (± 14.795) | 99999 (± 99999) | |
| Day 14 (6 [cohort 3:4] hours post dose), n=9,7,31 | 17.57 (± 4.1614) | 58.36 (± 11.72) | 118.2 (± 41.967) | |
| Day 30 (0 hour predose), n=6, 6, 58 | 5.339 (± 3.5712) | 29.68 (± 11.015) | 50.77 (± 31.473) | |

| | | | | |
|---|---|---|---|---|
| Day 30 (4 hours post dose), n=2, 5, 25 | 11.55 (± 2.6234) | 57.08 (± 13.99) | 96.27 (± 49.929) | |
| Day 60 (0 hour predose), n=6, 6, 53 | 6.36 (± 3.1028) | 24.55 (± 5.8206) | 49.37 (± 33.747) | |
| Day 60 (4 hours post dose), n=2, 5, 27 | 13.25 (± 0.7778) | 47.86 (± 7.3296) | 112.1 (± 58.56) | |
| Day 90 (0 hour predose), n=5, 6, 45 | 5.252 (± 1.5161) | 29.18 (± 15.909) | 47.02 (± 24.065) | |
| Day 90 (4 hours post dose), n=2, 5, 20 | 12.8 (± 0) | 49.4 (± 13.962) | 82.69 (± 29.005) | |

Notes:

[90] - All randomized and treated subjects in this group.

[91] - All randomized and treated subjects in this group.

[92] - All randomized and treated subjects in this group.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Domains of Interest: change from baseline in Line Cancellation Test at Day 90 [(L-R)/(L+R)] (Part 2)

| End point title | Domains of Interest: change from baseline in Line Cancellation Test at Day 90 [(L-R)/(L+R)] (Part 2)[93] |
|---|---|

End point description:

The subject was presented with a page that had lines placed across the page. The subject was required to cross out all the lines on the page using their non-paretic hand after the tester had demonstrated what was required by crossing out the center line. The performance measure for this task was the total number of omissions made expressed as a percentage of the total number of items in the test. The test contains 4 variables: (L+R)/28 × 100%, (L/14) × 100%, (R/14) × 100%, and (L-R)/(L+R), where L = number of lines crossed on the left side of the paper; R = number of lines crossed on the right side of the paper.
The I-FAS consisted of subjects within the FAS who were randomized to PF-03049423 6 mg or placebo group that was in the same cohort as the 6 mg group.

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

End point timeframe:

Day 1 (Baseline), Day 90

Notes:

[93] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a secondary efficacy endpoint for Part 2 and statistical comparison was conducted in Cohort 3 subjects.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39[94] | 34[95] | | |
| Units: change in ratio | | | | |
| least squares mean (standard error) | | | | |
| (L-R)/(L+R) | 0.083 (± 0.062) | -0.023 (± 0.0625) | | |

Notes:

[94] - Subjects who were in PF-03049423 6 mg group and included in statistical comparison.

[95] - Subjects who were in placebo group (Cohort 3) and included in statistical comparison.

### Statistical analyses

| Statistical analysis title | PF-03049423 6 mg versus Placebo |
|---|---|
| Comparison groups | Cohort 3: PF-03049423 6 mg v Cohort 3: Placebo |
| Number of subjects included in analysis | 73 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1512 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.106 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.011 |
| upper limit | 0.201 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0733 |

## Other pre-specified: All-cause mortality (Part 2)

| End point title | All-cause mortality (Part 2) |
|---|---|

End point description:

Deaths regardless causality were reported.
The FAS consisted of all randomized subjects who took any study medication (active or placebo).

| End point type | Other pre-specified |
|---|---|

End point timeframe:

The time began from the subject provided informed consent through 28 calendar days post last administration of investigational product.

| End point values | Cohort 1: PF-03049423 1 mg | Cohort 1: Placebo | Cohort 2: PF-03049423 3 mg | Cohort 2: Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11[96] | 9[97] | 11[98] | 10[99] |
| Units: subjects | 0 | 0 | 0 | 0 |

Notes:

[96] - All randomized and treated subjects in this group.

[97] - All randomized and treated subjects in this group.

[98] - All randomized and treated subjects in this group.

[99] - All randomized and treated subjects in this group.

| End point values | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 70[100] | 67[101] | | |
| Units: subjects | 6 | 7 | | |

Notes:

[100] - All randomized and treated subjects in this group.

[101] - All randomized and treated subjects in this group.

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Mortality directly related to stroke (Part 2)

| End point title | Mortality directly related to stroke (Part 2) |
|---|---|

End point description:

Deaths caused by stroke were reported.
The FAS consisted of all randomized subjects who took any study medication (active or placebo).

| End point type | Other pre-specified |
|---|---|

End point timeframe:

The time began from the subject provided informed consent through 28 calendar days post last administration of investigational product.

| End point values | Cohort 1: PF-03049423 1 mg | Cohort 1: Placebo | Cohort 2: PF-03049423 3 mg | Cohort 2: Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11[102] | 9[103] | 11[104] | 10[105] |
| Units: subjects | 0 | 0 | 0 | 0 |

Notes:

[102] - All randomized and treated subjects in this group.

[103] - All randomized and treated subjects in this group.

[104] - All randomized and treated subjects in this group.

[105] - All randomized and treated subjects in this group.

| End point values | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 70[106] | 67[107] | | |
| Units: subjects | 3 | 0 | | |

Notes:

[106] - All randomized and treated subjects in this group.

[107] - All randomized and treated subjects in this group.

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Treatment-emergent adverse events (AEs) resulting in discontinuation of study drug (Part 2)

| End point title | Treatment-emergent adverse events (AEs) resulting in discontinuation of study drug (Part 2) |
|---|---|

End point description:

An AE was defined as any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. Treatment-emergent were events between first dose of study drug and up to 28 days after last dose that were absent before treatment or that worsened relative to pre-treatment state.
The FAS consisted of all randomized subjects who took any study medication (active or placebo).

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Day 1 (Baseline) up to follow-up (28 days after Day 90)

| **End point values** | Cohort 1: PF-03049423 1 mg | Cohort 1: Placebo | Cohort 2: PF-03049423 3 mg | Cohort 2: Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11[108] | 9[109] | 11[110] | 10[111] |
| Units: subjects | 0 | 1 | 2 | 0 |

Notes:

[108] - All randomized and treated subjects in this group.

[109] - All randomized and treated subjects in this group.

[110] - All randomized and treated subjects in this group.

[111] - All randomized and treated subjects in this group.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 70[112] | 67[113] | | |
| Units: subjects | 3 | 5 | | |

Notes:

[112] - All randomized and treated subjects in this group.

[113] - All randomized and treated subjects in this group.

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Number of subjects with neuro-worsening (Part 2)

| End point title | Number of subjects with neuro-worsening (Part 2) |
|---|---|

End point description:

NIHSS change of 4 points or greater.
The FAS consisted of all randomized subjects who took any study medication (active or placebo).
99999=No data were reported separately for this outcome measure, which was instead included in routine clinical review of NIHSS data.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Day 1 (Baseline) up to Day 90

| End point values | Cohort 1: PF-03049423 1 mg | Cohort 1: Placebo | Cohort 2: PF-03049423 3 mg | Cohort 2: Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11[114] | 9[115] | 11[116] | 10[117] |
| Units: subjects | 99999 | 99999 | 99999 | 99999 |

Notes:

[114] - All randomized and treated subjects in this group.

[115] - All randomized and treated subjects in this group.

[116] - All randomized and treated subjects in this group.

[117] - All randomized and treated subjects in this group.

| End point values | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 70[118] | 67[119] | | |
| Units: subjects | 99999 | 99999 | | |

Notes:

[118] - All randomized and treated subjects in this group.

[119] - All randomized and treated subjects in this group.

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Number of subjects with SBP <100 mm Hg or SBP decline >=30 mm Hg from immediate pre-dose measurement, with or without neuro-worsening (defined as an NIHSS increase of 4 points or greater) within 2 hours post-dose (Part 2)

| End point title | Number of subjects with SBP <100 mm Hg or SBP decline >=30 mm Hg from immediate pre-dose measurement, with or without neuro-worsening (defined as an NIHSS increase of 4 points or greater) within 2 hours post-dose (Part 2) |
|---|---|

End point description:

The FAS consisted of all randomized subjects who took any study medication (active or placebo). 99999=No data were reported separately for this outcome measure, which was instead included in routine clinical review of BP data.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Day 1 (Baseline) up to Day 14

| End point values | Cohort 1: PF-03049423 1 mg | Cohort 1: Placebo | Cohort 2: PF-03049423 3 mg | Cohort 2: Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11[120] | 9[121] | 11[122] | 10[123] |
| Units: subjects | 99999 | 99999 | 99999 | 99999 |

Notes:

[120] - All randomized and treated subjects in this group.

[121] - All randomized and treated subjects in this group.

[122] - All randomized and treated subjects in this group.

[123] - All randomized and treated subjects in this group.

| **End point values** | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 70[124] | 67[125] | | |
| Units: subjects | 99999 | 99999 | | |

Notes:

[124] - All randomized and treated subjects in this group.

[125] - All randomized and treated subjects in this group.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the time the subject had taken at least 1 dose of study treatment through last subject visit. For SAEs, the time began from the subject provided informed consent through 28 calendar days post last administration of investigational product.

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 subject and as nonserious in another subject, or one subject may have experienced both a serious and nonserious event during the study.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 16.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Cohort 1: PF-03049423 1 mg |

Reporting group description:

Subjects received PF-03049423 1 mg once daily for 90 days.

| | |
|---|---|
| Reporting group title | Cohort 1: Placebo |

Reporting group description:

Subjects received placebo matched to PF-03049423 1 mg once daily for 90 days.

| | |
|---|---|
| Reporting group title | Cohort 2: PF-03049423 3 mg |

Reporting group description:

Subjects received PF-03049423 3 mg once daily for 90 days.

| | |
|---|---|
| Reporting group title | Cohort 2: Placebo |

Reporting group description:

Subjects received placebo matched to PF-03049423 3 mg once daily for 90 days.

| | |
|---|---|
| Reporting group title | Cohort 3: PF-03049423 6 mg |

Reporting group description:

Subjects received PF-03049423 6 mg once daily for 90 days.

| | |
|---|---|
| Reporting group title | Cohort 3: Placebo |

Reporting group description:

Subjects received placebo matched to PF-0304942 6 mg once daily for 90 days.

| Serious adverse events | Cohort 1: PF-03049423 1 mg | Cohort 1: Placebo | Cohort 2: PF-03049423 3 mg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 9 (11.11%) | 3 / 11 (27.27%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Metastases to bone | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Condition aggravated | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asphyxia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Disorientation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Electrocardiogram ST-T change | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic cerebral infarction | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematochezia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus paralytic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Urosepsis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Cohort 2: Placebo | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 15 / 70 (21.43%) | 18 / 67 (26.87%) |
| number of deaths (all causes) | 0 | 6 | 7 |
| number of deaths resulting from adverse events | 0 | 1 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Metastases to bone | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Condition aggravated | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asphyxia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

| | | | |
|---|---|---|---|
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 2 / 67 (2.99%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 70 (4.29%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Psychiatric disorders | | | |
| Disorientation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Electrocardiogram ST-T change | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Cardiac disorders** | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 2 / 67 (2.99%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Myocardial infarction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Nervous system disorders | | | |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 2 / 67 (2.99%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic cerebral infarction | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Blood and lymphatic system disorders** | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Gastrointestinal disorders** | | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus paralytic | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Hepatobiliary disorders** | | | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 2 / 67 (2.99%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Cohort 1: PF-03049423 1 mg | Cohort 1: Placebo | Cohort 2: PF-03049423 3 mg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 10 / 11 (90.91%) | 7 / 9 (77.78%) | 7 / 11 (63.64%) |
| Vascular disorders | | | |

| | | | |
|---|---|---|---|
| Aortic aneurysm | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Haematoma | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 4 / 9 (44.44%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 9 (11.11%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Face oedema | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Feeling cold | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 2 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 0 | 2 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 1 | 0 | 3 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Bronchiectasis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cough | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Pulmonary congestion | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 9 (22.22%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Sleep disorder | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase abnormal | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Aspartate aminotransferase abnormal | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood bilirubin abnormal | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood potassium decreased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Red blood cells urine positive | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 1 | 1 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| White blood cells urine positive | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Excoriation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Fall | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 0 | 3 |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Laceration | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 0 | 2 |
| Limb injury | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lip injury | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Congenital, familial and genetic disorders | | | |
| Atrial septal defect | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 9 (22.22%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Supraventricular extrasystoles | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Dementia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 9 (11.11%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 3 | 1 |
| Haemorrhagic transformation stroke | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 9 (11.11%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Headache | | | |
| subjects affected / exposed | 4 / 11 (36.36%) | 3 / 9 (33.33%) | 1 / 11 (9.09%) |
| occurrences (all) | 4 | 6 | 1 |
| Somnolence | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 0 | 2 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Neutrophilia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| Eye disorders | | | |

| | | | |
|---|---|---|---|
| Conjunctival hyperaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorder | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 9 (11.11%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 1 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 9 (22.22%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 3 | 2 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 0 | 4 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis contact | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Dermatitis diaper | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Erythema | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal and urinary disorders | | | |
| Albuminuria | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dysuria | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Haematuria | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal cyst | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urethral haemorrhage | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Back pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 1 | 0 | 4 |
| Gouty arthritis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 9 (11.11%) | 2 / 11 (18.18%) |
| occurrences (all) | 1 | 1 | 2 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 1 | 1 |
| Infections and infestations | | | |
| Genitourinary tract infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 9 (11.11%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fluid imbalance | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypokalaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 1 | 1 |

| **Non-serious adverse events** | Cohort 2: Placebo | Cohort 3: PF-03049423 6 mg | Cohort 3: Placebo |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 10 (90.00%) | 50 / 70 (71.43%) | 47 / 67 (70.15%) |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 1 / 67 (1.49%) |
| occurrences (all) | 0 | 1 | 1 |
| Haematoma | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 3 / 70 (4.29%) | 2 / 67 (2.99%) |
| occurrences (all) | 1 | 3 | 2 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 4 / 70 (5.71%) | 7 / 67 (10.45%) |
| occurrences (all) | 3 | 8 | 12 |
| General disorders and administration site conditions | | | |
| Face oedema | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Feeling cold | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 70 (4.29%) | 3 / 67 (4.48%) |
| occurrences (all) | 0 | 4 | 3 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 7 / 70 (10.00%) | 6 / 67 (8.96%) |
| occurrences (all) | 0 | 9 | 6 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Atelectasis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 70 (2.86%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Bronchiectasis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cough | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 4 / 70 (5.71%) | 2 / 67 (2.99%) |
| occurrences (all) | 0 | 4 | 2 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 3 / 67 (4.48%) |
| occurrences (all) | 0 | 1 | 3 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Pulmonary congestion | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Psychiatric disorders | | | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 5 / 70 (7.14%) | 3 / 67 (4.48%) |
| occurrences (all) | 0 | 5 | 3 |
| Depression | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 4 / 70 (5.71%) | 4 / 67 (5.97%) |
| occurrences (all) | 0 | 4 | 4 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 7 / 70 (10.00%) | 2 / 67 (2.99%) |
| occurrences (all) | 0 | 8 | 2 |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 4 / 70 (5.71%) | 1 / 67 (1.49%) |
| occurrences (all) | 0 | 5 | 1 |
| Investigations | | | |

| | | | |
|---|---|---|---|
| Alanine aminotransferase abnormal | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 3 / 67 (4.48%) |
| occurrences (all) | 0 | 1 | 3 |
| Aspartate aminotransferase abnormal | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 4 / 67 (5.97%) |
| occurrences (all) | 0 | 0 | 4 |
| Blood bilirubin abnormal | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood potassium decreased | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences (all) | 1 | 0 | 1 |
| Blood pressure increased | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 70 (1.43%) | 2 / 67 (2.99%) |
| occurrences (all) | 1 | 1 | 4 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Red blood cells urine positive | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| White blood cells urine positive | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|---|---|---|
| Contusion | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 70 (1.43%) | 1 / 67 (1.49%) |
| occurrences (all) | 1 | 1 | 1 |
| Excoriation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 70 (4.29%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 70 (2.86%) | 4 / 67 (5.97%) |
| occurrences (all) | 0 | 2 | 4 |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Laceration | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Limb injury | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lip injury | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Congenital, familial and genetic disorders | | | |
| Atrial septal defect | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 2 / 67 (2.99%) |
| occurrences (all) | 0 | 1 | 2 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 70 (2.86%) | 1 / 67 (1.49%) |
| occurrences (all) | 0 | 2 | 1 |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 70 (2.86%) | 1 / 67 (1.49%) |
| occurrences (all) | 0 | 2 | 1 |
| Coronary artery occlusion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Supraventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Dementia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 3 / 67 (4.48%) |
| occurrences (all) | 0 | 0 | 3 |
| Haemorrhagic transformation stroke | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences (all) | 0 | 0 | 1 |
| Headache | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 5 / 70 (7.14%) | 7 / 67 (10.45%) |
| occurrences (all) | 0 | 5 | 7 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 70 (2.86%) | 2 / 67 (2.99%) |
| occurrences (all) | 0 | 3 | 2 |
| Syncope | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 4 / 70 (5.71%) | 3 / 67 (4.48%) |
| occurrences (all) | 2 | 4 | 3 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neutrophilia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombocytopenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 70 (2.86%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Eye disorders | | | |
| Conjunctival hyperaemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Eye disorder | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 1 / 67 (1.49%) |
| occurrences (all) | 0 | 0 | 1 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 2 / 70 (2.86%) | 1 / 67 (1.49%) |
| occurrences (all) | 1 | 4 | 1 |
| Constipation | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 8 / 70 (11.43%) | 14 / 67 (20.90%) |
| occurrences (all) | 1 | 10 | 16 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 9 / 70 (12.86%) | 10 / 67 (14.93%) |
| occurrences (all) | 1 | 10 | 11 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 70 (1.43%) | 3 / 67 (4.48%) |
| occurrences (all) | 1 | 1 | 3 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 70 (2.86%) | 4 / 67 (5.97%) |
| occurrences (all) | 0 | 2 | 4 |
| Vomiting | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 4 / 67 (5.97%) |
| occurrences (all) | 0 | 1 | 7 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis contact | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dermatitis diaper | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Erythema | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 5 / 70 (7.14%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal and urinary disorders | | | |
| Albuminuria | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysuria | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 5 / 70 (7.14%) | 4 / 67 (5.97%) |
| occurrences (all) | 0 | 5 | 4 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 7 / 70 (10.00%) | 2 / 67 (2.99%) |
| occurrences (all) | 0 | 9 | 2 |
| Renal cyst | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 70 (1.43%) | 2 / 67 (2.99%) |
| occurrences (all) | 1 | 1 | 2 |
| Urethral haemorrhage | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urinary retention | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 70 (4.29%) | 1 / 67 (1.49%) |
| occurrences (all) | 0 | 3 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 3 / 70 (4.29%) | 3 / 67 (4.48%) |
| occurrences (all) | 2 | 4 | 4 |
| Back pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 1 / 67 (1.49%) |
| occurrences (all) | 0 | 1 | 2 |
| Gouty arthritis | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 70 (4.29%) | 1 / 67 (1.49%) |
| occurrences (all) | 0 | 5 | 1 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 9 / 70 (12.86%) | 4 / 67 (5.97%) |
| occurrences (all) | 0 | 13 | 4 |
| Infections and infestations | | | |
| Genitourinary tract infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 70 (1.43%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 3 / 70 (4.29%) | 2 / 67 (2.99%) |
| occurrences (all) | 0 | 3 | 2 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 8 / 70 (11.43%) | 8 / 67 (11.94%) |
| occurrences (all) | 1 | 8 | 10 |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|---|---|---|
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 0 / 67 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fluid imbalance | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 70 (0.00%) | 2 / 67 (2.99%) |
| occurrences (all) | 0 | 0 | 2 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 7 / 70 (10.00%) | 3 / 67 (4.48%) |
| occurrences (all) | 4 | 11 | 3 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 28 July 2010 | Addition of a safety Follow-Up visit 14 days after Day 90. |
| 12 November 2010 | To integrate recording of the time of last meal on PK days to follow an Food and Drug Administration (FDA) recommendation and to add measurement of direct and indirect bilirubin to comply with the corporate recommendations as to detect potential Hy's law cases. |
| 01 August 2011 | To reduce the number of procedures: particularly blood pressure measurements to eliminate the visits from Day 8 to Day 13.<br>This change – supported by extrapolation of available data – was subject to review of Cohort 1 patients data and approval by the Data and Safety Monitoring Board (DSMB).<br>Allowed patients with total paresis of the upper extremity to enter the study.<br>Clarified the eligibility criteria on the type of stroke.<br>Updated the suicidality assessments: addition of the Columbia Suicide Severity Rating Scale (C-SSRS).<br>Removed "Criteria for ECG Parameters and Vital Signs of Potential Clinical Concern for Pediatric Subjects". |
| 26 March 2012 | Addition of digoxin and digitoxin to prohibited concomitant medications list.<br>Study Procedures: Clarification of drug dispensing at day 7 and day 14.<br>The caregiver could not give drug if the subject had an nasogastric tube and further clarification regarding the use of an nasogastric tube.<br>FOR FRANCE ONLY according to local clinical guidelines approved November 2011:<br>1. Removed option for manual BP measurements,<br>2. Removed option for BP assessments in standing position,<br>3. Increased frequency of BP assessments in Part 2 of the study,<br>4. Required use of an electronic blood pressure measuring device. |
| 24 August 2012 | Change to inclusion criteria to allow computed tomography (CT) or magnetic resonance imaging (MRI) scan at screening and Day 90 for all subjects (ie, CT was not just for subjects contraindicated for MRI).<br>Change to inclusion criteria to advise that an additional 6 hours (ie, up to a total of 78 hours) could be allowable from stroke onset to initial dose of study drug in exceptional circumstances, such as an unexpected delay in receiving the data to allow randomisation, after consultation with the sponsor.<br>Change to inclusion criteria to expectation that subjects had to remain as in patients for the first 3 days. Subjects could remain as in-patients for the first seven days of dosing if that complies with regional standard of care.<br>Change to the inclusion criterion regarding ECG measurements. If a subject was ineligible on ECG and if it considered likely that there was a temporary perturbation of the subject's cardiac function related to the stroke, at the discretion of the investigator this ECG analysis could be repeated on one occasion within the 72 hour screening window. If the subject met the ECG eligibility criteria at the second timepoint, this would take precedence over the first analysis.<br>Change to inclusion criteria to note that participation in non-interventional studies (eg, solely involving blood draws for genetic analysis) could be allowable after consultation with the sponsor.<br>Update to the wording on definition of women of child bearing potential to bring into line with revised Pfizer policy.<br>Added wording to advise that the study is now in Part 2 at a 6 mg dose, and to update some procedures to bring them in line with the amended selection criteria. |

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.

The study was terminated prematurely due to demonstrated futility at interim analysis. The final results are consistent with interim results.

Notes: