

**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			
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			
Units: years			
arithmetic mean	62.3	64.7	69.8
standard deviation	± 14.3	± 6	± 8.3
Gender categorical			
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 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 Units: years			
arithmetic mean	65.8	64.2	65.6
standard deviation	± 13.4	± 13.1	± 11.3
Gender categorical Units: Subjects			
Female	3	28	26
Male	7	42	41

Reporting group values	Total		
Number of subjects	178		
Age categorical 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 Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical 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:	

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 (\geq) 30 or 50 millimeters of mercury (mm Hg) change from grand baseline in same posture, systolic less than ($<$) 90 mm Hg; diastolic BP (DBP) \geq 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:	

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); $\geq 25\%$ increase when baseline > 200 msec; or increase $\geq 50\%$ when baseline ≤ 200 msec; 2), QRS interval: ≥ 140 msec; $\geq 50\%$ 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 $\geq 25\%/50\%$, n=10,7,9,9,52,47	0	0	1	0
QRS interval increase $\geq 50\%$, 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 \geq 300 msec, n=11,9,11,10,70,67	0	0		
QRS interval \geq 140 msec, n=11,9,11,10,70,67	0	1		
QT interval \geq 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 \geq 500 msec, n=11,9,11,10,70,67	0	1		
PR interval increase \geq 25%/50%, n=10,7,9,9,52,47	1	0		
QRS interval increase \geq 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 \geq 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:

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. 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 rotated, 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 (\pm 5.4499)	36.761 (\pm 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:	
<p>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).</p> <p>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.</p>	
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 (\pm 0.5384)	-6.228 (\pm 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) \geq 95 and BI =100 at Day 90 (Part 2)

End point title	Number of subjects with Barthel Index (BI) \geq 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 (\pm 3.6248)	73.552 (\pm 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 (\pm 1.5321)	12.686 (\pm 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 (\pm 0.3676)	1.324 (\pm 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 treatment 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: $(L+R)/28 \times 100\%$, $(L/14) \times 100\%$, $(R/14) \times 100\%$, 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 occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 11 (0.00%) 0
Deep vein thrombosis subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 11 (9.09%) 1
Haematoma subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 11 (9.09%) 1
Hypertension subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	4 / 9 (44.44%) 5	0 / 11 (0.00%) 0
Hypotension subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0
General disorders and administration site conditions			
Face oedema subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 11 (9.09%) 1
Feeling cold subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 11 (9.09%) 2
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	2 / 11 (18.18%) 2
Pyrexia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 9 (0.00%) 0	2 / 11 (18.18%) 3
Respiratory, thoracic and mediastinal disorders			
Atelectasis subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 11 (9.09%) 1
Bronchiectasis subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0
Cough			

subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 11 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 9 (0.00%) 0	0 / 11 (0.00%) 0
Pleural effusion subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 11 (9.09%) 1
Pulmonary congestion subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 11 (0.00%) 0
Pulmonary embolism subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 11 (0.00%) 0
Psychiatric disorders			
Depressed mood subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0
Depression subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 11 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 9 (22.22%) 2	0 / 11 (0.00%) 0
Sleep disorder subjects affected / exposed occurrences (all)	3 / 11 (27.27%) 5	0 / 9 (0.00%) 0	0 / 11 (0.00%) 0
Investigations			
Alanine aminotransferase abnormal subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 11 (9.09%) 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 occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	2 / 11 (18.18%) 3
Joint dislocation subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 9 (0.00%) 0	0 / 11 (0.00%) 0
Laceration subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	2 / 11 (18.18%) 2
Limb injury subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 9 (0.00%) 0	0 / 11 (0.00%) 0
Lip injury subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 11 (9.09%) 1
Radius fracture subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 11 (9.09%) 1
Congenital, familial and genetic disorders Atrial septal defect subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 9 (22.22%) 2	0 / 11 (0.00%) 0
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 11 (9.09%) 1
Bradycardia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0
Coronary artery occlusion subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0
Supraventricular extrasystoles subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 9 (0.00%) 0	0 / 11 (0.00%) 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 occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 11 (0.00%) 0
Eye disorder subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 11 (0.00%) 0
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2	0 / 9 (0.00%) 0	0 / 11 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 9 (11.11%) 1	1 / 11 (9.09%) 1
Diarrhoea subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 11 (0.00%) 0
Dyspepsia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0
Gastritis subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 11 (9.09%) 1
Nausea subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	2 / 9 (22.22%) 3	1 / 11 (9.09%) 2
Vomiting subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	2 / 11 (18.18%) 4
Skin and subcutaneous tissue disorders			
Dermatitis contact subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2	0 / 9 (0.00%) 0	0 / 11 (0.00%) 0
Dermatitis diaper			

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

subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 9 (0.00%) 0	2 / 11 (18.18%) 4
Gouty arthritis subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	0 / 11 (0.00%) 0
Muscular weakness subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 9 (11.11%) 4	0 / 11 (0.00%) 0
Musculoskeletal pain subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 9 (11.11%) 1	2 / 11 (18.18%) 2
Pain in extremity subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 9 (11.11%) 1	1 / 11 (9.09%) 1
Infections and infestations			
Genitourinary tract infection subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 11 (9.09%) 1
Herpes zoster subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 9 (0.00%) 0	1 / 11 (9.09%) 1
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 9 (11.11%) 1	0 / 11 (0.00%) 0
Fluid imbalance subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 9 (0.00%) 0	1 / 11 (9.09%) 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 occurrences (all)	0 / 10 (0.00%) 0	0 / 70 (0.00%) 0	0 / 67 (0.00%) 0
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 70 (1.43%) 1	3 / 67 (4.48%) 3
Aspartate aminotransferase abnormal subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 70 (0.00%) 0	0 / 67 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 70 (0.00%) 0	4 / 67 (5.97%) 4
Blood bilirubin abnormal subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 70 (0.00%) 0	0 / 67 (0.00%) 0
Blood potassium decreased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 70 (0.00%) 0	1 / 67 (1.49%) 1
Blood pressure increased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 70 (1.43%) 1	2 / 67 (2.99%) 4
Hepatic enzyme increased subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	0 / 70 (0.00%) 0	0 / 67 (0.00%) 0
Red blood cells urine positive subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 70 (0.00%) 0	0 / 67 (0.00%) 0
Transaminases increased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 70 (0.00%) 0	0 / 67 (0.00%) 0
White blood cells urine positive subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 70 (0.00%) 0	0 / 67 (0.00%) 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 occurrences (all)	0 / 10 (0.00%) 0	1 / 70 (1.43%) 1	0 / 67 (0.00%) 0
Supraventricular extrasystoles subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 70 (1.43%) 1	0 / 67 (0.00%) 0
Nervous system disorders			
Dementia			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 70 (0.00%) 0	0 / 67 (0.00%) 0
Dizziness			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 70 (0.00%) 0	3 / 67 (4.48%) 3
Haemorrhagic transformation stroke			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 70 (0.00%) 0	1 / 67 (1.49%) 1
Headache			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	5 / 70 (7.14%) 5	7 / 67 (10.45%) 7
Somnolence			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 70 (2.86%) 3	2 / 67 (2.99%) 2
Syncope			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 70 (1.43%) 1	0 / 67 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	4 / 70 (5.71%) 4	3 / 67 (4.48%) 3
Leukocytosis			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 70 (0.00%) 0	0 / 67 (0.00%) 0
Neutrophilia			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 70 (0.00%) 0	0 / 67 (0.00%) 0
Thrombocytopenia			

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

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

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	3 / 70 (4.29%) 3	1 / 67 (1.49%) 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 occurrences (all)	0 / 10 (0.00%) 0	0 / 70 (0.00%) 0	0 / 67 (0.00%) 0
Fluid imbalance subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 70 (0.00%) 0	2 / 67 (2.99%) 2
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 4	7 / 70 (10.00%) 11	3 / 67 (4.48%) 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. 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). Allowed patients with total paresis of the upper extremity to enter the study. Clarified the eligibility criteria on the type of stroke. Updated the suicidality assessments: addition of the Columbia Suicide Severity Rating Scale (C-SSRS). 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. Study Procedures: Clarification of drug dispensing at day 7 and day 14. The caregiver could not give drug if the subject had an nasogastric tube and further clarification regarding the use of an nasogastric tube. FOR FRANCE ONLY according to local clinical guidelines approved November 2011: 1. Removed option for manual BP measurements, 2. Removed option for BP assessments in standing position, 3. Increased frequency of BP assessments in Part 2 of the study, 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). 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. 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. 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. 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. Update to the wording on definition of women of child bearing potential to bring into line with revised Pfizer policy. 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: