Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled 2-Way Crossover Study to Evaluate the Efficacy, Safety and Tolerability of PF-03715455 Administered Twice Daily by Inhalation for 4 Weeks in Subjects with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)

Summary

EudraCT number	2014-002340-40
Trial protocol	GB
Global end of trial date	01 May 2015

Results information

Result version number	v1 (current)
This version publication date	23 April 2016
First version publication date	23 April 2016

Trial information

Trial identification

Sponsor protocol code	A9111004

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, 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	28 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 May 2015
Global end of trial reached?	Yes
Global end of trial date	01 May 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective was to determine the effect, at Week 4, of orally inhlaed PF-03715455 680 mcg twice daily on trough forced expiratory volume in 1 second (FEV1) in subjects with moderate to severe chronic obstructive pulmonary disease (COPD) on a stable regimen of short or long acting bronchodilators.

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	14 January 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 13
Worldwide total number of subjects	13
EEA total number of subjects	13

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)	7
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomly assigned in a 1:1 ratio to receive either PF-03715455 680 mcg twice daily for 4 weeks or matching placebo in Period 1. Participants who were randomized to PF-03715455 during Period 1 then received placebo for 4 weeks during Period 2 after a 28 to 49-day washout period, and vice versa.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	PF-03715455 680 mcg Twice Daily

Arm description:

PF-03715455 680 mcg dry powder capsule was administered by oral inhalation twice daily via a Miat mondose inhaler device for 4 weeks in each treatment period. Dosing in each treatment period was separated by a washout period of 28 to 49 days.

Arm type	Experimental
Investigational medicinal product name	PF-03715455
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

inhaled orally twice daily

Arm title	Placebo

Arm description:

Matching placebo was administered by oral inhalation twice daily via a Miat mondose inhaler device for 4 weeks in each treatment period. Dosing in each treatment period was separated by a washout period of 28 to 49 days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

inhaled orally twice daily

Number of subjects in period 1	PF-03715455 680 mcg Twice Daily	Placebo
Started	8	7
Completed	1	1
Not completed	7	6
Adverse event, non-fatal	-	1
Study terminated by sponsor	7	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	13	13	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	7	7	
From 65-84 years	6	6	
85 years and over	0	0	
Age Continuous | Units: years			
arithmetic mean	62		
standard deviation	± 6.5	-	
Gender, Male/Female Units: participants			
Female	8	8	
Male	5	5	

End points

End points reporting groups

Reporting group title	PF-03715455 680 mcg Twice Daily

Reporting group description:

PF-03715455 680 mcg dry powder capsule was administered by oral inhalation twice daily via a Miat mondose inhaler device for 4 weeks in each treatment period. Dosing in each treatment period was separated by a washout period of 28 to 49 days.

Reporting group title	Placebo

Reporting group description:

Matching placebo was administered by oral inhalation twice daily via a Miat mondose inhaler device for 4 weeks in each treatment period. Dosing in each treatment period was separated by a washout period of 28 to 49 days.

Primary: Change From Baseline in Trough Forced Expiratory Volume in 1 Second (FEV1) at Week 4

End point title	Change From Baseline in Trough Forced Expiratory Volume in 1 Second (FEV1) at Week 4[1]

End point description:

FEV1 is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration. Trough FEV1 was obtained from spirometry, performed before study treatment administration.

End point type	Primary

End point timeframe:

Baseline (Day 1), Day 29 (Week 4)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses were not planned and were not performed due to the limited number of subjects.

End point values	PF-03715455 680 mcg Twice Daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: liters				
arithmetic mean (standard deviation)				
Baseline (n=8,7)	1.368 (± 0.3534)	1.456 (± 0.5209)		
Change at Week 4 (n=6,6)	-0.047 (± 0.0983)	0.08 (± 0.231)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Sputum Cell Counts

End point title	Change From Baseline in Sputum Cell Counts

End point description:

End point type	Secondary

End point timeframe:

Baseline, Day 7 (Week 1), Day 21 (Week 3), Day 29 (Week 4)

End point values	PF-03715455 680 mcg Twice Daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: cells				

Notes:

[2] - As the study was prematurely terminated, efficacy analyses were not performed.

[3] - As the study was prematurely terminated, efficacy analyses were not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Trough FEV1 and Forced Vital Capacity (FVC) at Weeks 1, 3, and 4

End point title	Change From Baseline in Trough FEV1 and Forced Vital Capacity (FVC) at Weeks 1, 3, and 4

End point description:

FEV1 is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration. FVC is the volume of air which can be forcibly exhaled from the lungs after taking the deepest breath possible.

End point type	Secondary

End point timeframe:

Baseline, Day 7 (Week 1), Day 21 (Week 3), Day 29 (Week 4)

End point values	PF-03715455 680 mcg Twice Daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: liters				
arithmetic mean (standard deviation)				
FEV1: Change at Week 1 (n=8,7)	-0.065 (± 0.1231)	-0.001 (± 0.2559)		
FEV1: Change at Week 3 (n=8,7)	-0.039 (± 0.2194)	-0.026 (± 0.1033)		
FVC: Baseline (n=8,7)	2.535 (± 0.8639)	3.263 (± 1.2571)		
FVC: Change at Week 1 (n=8,7)	-0.019 (± 0.1336)	0.09 (± 0.163)		
FVC: Change at Week 3 (n=8,7)	0.049 (± 0.21)	-0.079 (± 0.1893)		

FVC: Change at Week 4 (n=6,6)	0.091 (± 0.1661)	0.233 (± 0.3014)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentrations (Cmax) of PF-03715455

End point title	Maximum Observed Plasma Concentrations (Cmax) of PF-03715455

End point description:

End point type	Secondary

End point timeframe:

Day 7 (Week 1), Day 21 (Week 3), Day 29 (Week 4)

End point values	PF-03715455 680 mcg Twice Daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				

Notes:

[4] - As the study was prematurely terminated, PK analysis was not conducted.

[5] - As the study was prematurely terminated, PK analysis was not conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Plasma Concentration (Ctrough) of PF-03715455

End point title	Trough Plasma Concentration (Ctrough) of PF-03715455

End point description:

Ctrough is the concentration prior to study drug administration.

End point type	Secondary

End point timeframe:

Day 7 (Week 1), Day 21 (Week 3), Day 29 (Week 4)

End point values	PF-03715455 680 mcg Twice Daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				

Notes:

[6] - As the study was prematurely terminated, PK analysis was not conducted.

[7] - As the study was prematurely terminated, PK analysis was not conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Trough FEV1 and Forced Vital Capacity (FVC) Over 4 Weeks

End point title	Change From Baseline in Trough FEV1 and Forced Vital Capacity (FVC) Over 4 Weeks

End point description:

FEV1 is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration. FVC is the volume of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. Change over 4 weeks is presented.

End point type	Secondary

End point timeframe:

Baseline, Week 1 to Week 4

End point values	PF-03715455 680 mcg Twice Daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: liters				
arithmetic mean (standard deviation)				
FEV1: Change Over 4 Weeks (n=6,6)	-0.047 (± 0.0983)	0.08 (± 0.231)		
FVC: Change Over 4 Weeks (n=6,6)	0.091 (± 0.1661)	0.233 (± 0.3014)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

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

End point description:

An AE was any untoward medical occurrence in a participant who received study drug. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial

or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between first dose of study drug and up to Day 49 that were absent before treatment or that worsened relative to pre-treatment state. AEs included both SAEs and non-SAEs.

End point type	Other pre-specified

End point timeframe:

Baseline up to Day 29 (Week 4)

End point values	PF-03715455 680 mcg Twice Daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: participants				
AEs	3	4		
SAEs	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants with Clinically Significant Treatment Emergent Electrocardiogram (ECG) Findings

End point title	Number of Participants with Clinically Significant Treatment Emergent Electrocardiogram (ECG) Findings

End point description:

Clinically significant ECG findings include: PR interval >=300 milliseconds (msec) or >=25% increase when baseline is >200 msec and >=50% increase when baseline is less than or equal to 200 msec; QRS interval >=200 msec or >=25/50% increase from baseline; QT interval >=500 msec; corrected QT interval using Fridericia's formula (QTcF) >=450 msec or >=30 msec increase.

End point type	Other pre-specified

End point timeframe:

Baseline up to Day 29 (Week 4)

End point values	PF-03715455 680 mcg Twice Daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: participants				
PR Interval >=300 msec	0	0		
QRS Complex >=200 msec	0	0		
QT Interval >=500 msec	0	0		
QTcF Interval 450-<480 msec	0	0		
QTcF Interval 480-<500 msec	0	0		
QTcF Interval >=500 msec	0	0		

PR Interval >=25/50% Increase From Baseline	0	0		
QRS Complex >=25/50% Increase From Baseline	0	0		
QTcF Interval 30-<60 msec Increase From Baseline	0	0		
QTcF Interval >=60 msec Increase From Baseline	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Systolic and Diastolic Blood Pressure

End point title	Change From Baseline in Systolic and Diastolic Blood Pressure

End point description:

Systolic blood pressure (SBP) and diastolic pressure (DBP) were evaluated in the supine position.

End point type	Other pre-specified

End point timeframe:

Baseline, Day 7 (Week 1), Day 21 (Week 3), Day 29 (Week 4), Day 49 (follow-up)

End point values	PF-03715455 680 mcg Twice Daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
SBP: Baseline (n=8,7)	130 (± 19.16)	122.7 (± 13.92)		
SBP: Change at Week 1 (n=7,6)	-7.4 (± 13.24)	1.3 (± 3.01)		
SBP: Change at Week 3 (n=5,5)	-3.4 (± 12.03)	-0.6 (± 9.02)		
SBP: Change at Week 4 (n=8,7)	-2 (± 15.34)	8.1 (± 7.06)		
SBP: Change at Follow-Up (n=7,6)	1.4 (± 13.49)	4.7 (± 11.24)		
DBP: Baseline (n=8,7)	69.9 (± 9.72)	65.1 (± 9.01)		
DBP: Change at Week 1 (n=7,6)	0.6 (± 6.95)	8.7 (± 8.69)		
DBP: Change at Week 3 (n=5,5)	2.4 (± 7.09)	4.4 (± 5.13)		
DBP: Change at Week 4 (n=8,7)	2.1 (± 3.91)	2.4 (± 8.46)		
DBP: Change at Follow-Up (n=7,6)	5.4 (± 6.63)	2.8 (± 5.04)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Pulse Rate

End point title	Change From Baseline in Pulse Rate

End point description:	
Pulse rate was evaluated in the supine position.	
End point type	Other pre-specified
End point timeframe:	
Baseline, Day 7 (Week 1), Day 21 (Week 3), Day 29 (Week 4), Day 49 (follow-up)	

End point values	PF-03715455 680 mcg Twice Daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: beats per minute (bpm)				
arithmetic mean (standard deviation)				
Baseline (n=8,7)	66.5 (± 11.82)	64.3 (± 9.71)		
Change at Week 1 (n=7,6)	3.6 (± 7.41)	3.5 (± 3.56)		
Change at Week 3 (n=5,5)	-1.6 (± 3.36)	0 (± 3.16)		
Change at Week 4 (n=8,7)	1.3 (± 2.93)	1.3 (± 6.24)		
Change at Follow-Up (n=7,6)	2 (± 4.76)	1 (± 3.35)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants With Laboratory Abnormalities Meeting the Criteria for Potential Clinical Concern

End point title	Number of Participants With Laboratory Abnormalities Meeting the Criteria for Potential Clinical Concern
End point description:	
The following laboratory parameters were analyzed: hematology (hemoglobin, hematocrit, red blood cell [RBC] count, RBC morphology, platelet count, white blood cell [WBC] count, total neutrophils, eosinophils, monocytes, basophils, lymphocytes); blood chemistry (blood urea nitrogen [BUN], creatinine, glucose, calcium, sodium, potassium, chloride, total bicarbonate, aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, direct and indirect bilirubin, gamma-glutamyl transpeptidase [GGT], alkaline phosphatase, uric acid, albumin, total protein, high sensitivity C-reactive protein [CRP]); urinalysis (specific gravity, pH, glucose, protein, blood, ketones, nitrites, leukocyte esterase, microscopy [only if urine dipstick was positive for blood or protein]).	
End point type	Other pre-specified
End point timeframe:	
Baseline up to Week 4	

End point values	PF-03715455 680 mcg Twice Daily	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: participants	6	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to follow-up period (Day 49)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Matching placebo was administered by oral inhalation twice daily via a Miat mondose inhaler device for 4 weeks in each treatment period. Dosing in each treatment period was separated by a washout period of 28 to 49 days.	
Reporting group title	PF-03715455 680 mcg Twice Daily
Reporting group description:	
PF-03715455 680 mcg dry powder capsule was administered by oral inhalation twice daily via a Miat mondose inhaler device for 4 weeks in each treatment period. Dosing in each treatment period was separated by a washout period of 28 to 49 days.	

Serious adverse events	Placebo	PF-03715455 680 mcg Twice Daily	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	PF-03715455 680 mcg Twice Daily	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 7 (57.14%)	3 / 8 (37.50%)	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	1 / 7 (14.29%)	1 / 8 (12.50%)	
occurrences (all)	1	1	

Vascular disorders Haematoma subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	
Gastrointestinal disorders Dyspepsia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	
Reproductive system and breast disorders Vulvovaginal pruritus subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	
Musculoskeletal and connective tissue disorders Haemarthrosis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0 2 / 7 (28.57%) 2	1 / 8 (12.50%) 1 0 / 8 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

As this study was prematurely terminated by the sponsor, no formal safety or efficacy conclusions can be drawn due to insufficient participant numbers. In addition, PK analysis was not conducted.

Notes: