Clinical trial results:
A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of FG-3019 in Patients with Idiopathic Pulmonary Fibrosis

Summary

EudraCT number	2014-005658-20
Trial protocol	BG
Global end of trial date	16 November 2017

Results information

Result version number	v1
This version publication date	11 April 2020
First version publication date	11 April 2020

Trial information

Trial identification

Sponsor protocol code	FGCL-3019-067

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01890265
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	FibroGen, Inc.
Sponsor organisation address	409 Illinois Street, San Francisco, United States, CA 94158
Public contact	Clinical Trial Information Desk, FibroGen, Inc., 067study@fibrogen.com
Scientific contact	Clinical Trial Information Desk, FibroGen, Inc., 067study@fibrogen.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	16 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety, tolerability, and efficacy of pamrevlumab in subjects with idiopathic pulmonary fibrosis (IPF).

Protection of trial subjects:

This trial was designed and monitored in accordance with procedures that comply with the United States Food and Drug Administration regulations, the ethical principles of Good Clinical Practice as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 July 2013
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	Australia: 3
Country: Number of subjects enrolled	United States: 64
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	South Africa: 9
Country: Number of subjects enrolled	New Zealand: 10
Country: Number of subjects enrolled	India: 12
Country: Number of subjects enrolled	Bulgaria: 4
Worldwide total number of subjects	103
EEA total number of subjects	4

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)	29
From 65 to 84 years	74
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This Phase 2 study was conducted at 44 study centers in 7 countries from July 2013 to November 2017. Adult subjects with a history of IPF ≤5 years duration and a forced vital capacity (FVC) predicted value ≥55% at screening were randomized in the main study to receive pamrevlumab or placebo by intravenous (IV) infusion every 3 weeks (Q3W).

Pre-assignment

Screening details:

The main study consisted of a screening period of up to 6 weeks, a 48-week randomized treatment period and a follow-up period of 4 weeks. Subjects who completed the main study and met the eligibility criteria were offered participation in an extended open-label treatment period.

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, Carer, Assessor

Blinding implementation details:

Subjects, investigators and study staff were blinded to treatment assignments and did not have access to the randomization codes. The high-resolution computed tomography (HRCT) readers were blinded to treatment assignments.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pamrevlumab 30 mg/kg Q3W

Arm description:

Subjects were randomized to receive pamrevlumab 30 mg/kg by IV infusion Q3W.

Arm type	Experimental
Investigational medicinal product name	Pamrevlumab
Investigational medicinal product code	FG-3019
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received an IV infusion of pamrevlumab 30 mg/kg Q3W. Pamrevlumab is a fully human immunoglobulin G1 kappa monoclonal antibody and was administered in normal saline. The pamrevlumab solution formulation contained sodium chloride, L-histidine hydrochloride (HCl), L-histidine and polysorbate 20.

Arm title	Placebo Q3W

Arm description:

Subjects were randomized to receive placebo matching pamrevlumab by IV infusion Q3W.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received placebo matching pamrevlumab by IV infusion Q3W. Placebo was a sterile, aqueous solution for dilution into 0.9% serum chloride injection prior to IV infusion. The solution formulation contained sodium chloride, L-histidine HCl, L-histidine and polysorbate 20.

Number of subjects in period 1	Pamrevlumab 30 mg/kg Q3W	Placebo Q3W
Started	50	53
Completed	40	40
Not completed	10	13
Consent withdrawn by subject	-	2
Adverse event, non-fatal	2	1
Progressive disease	6	6
Other (Death)	2	3
Other (Unspecified reason)	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Pamrevlumab 30 mg/kg Q3W
Reporting group description:	
Subjects were randomized to receive pamrevlumab 30 mg/kg by IV infusion Q3W.	
Reporting group title	Placebo Q3W
Reporting group description:	
Subjects were randomized to receive placebo matching pamrevlumab by IV infusion Q3W.	

Reporting group values	Pamrevlumab 30 mg/kg Q3W	Placebo Q3W	Total
Number of subjects	50	53	103
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	68.3	68.4	
standard deviation	± 7.05	± 7.20	-
Gender categorical Units: Subjects			
Female	17	10	27
Male	33	43	76
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	1	1	2
Not Hispanic or Latino	49	52	101
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	5	3	8
Black or African American	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
White	41	44	85
Other	4	5	9

End points

End points reporting groups

Reporting group title	Pamrevlumab 30 mg/kg Q3W
Reporting group description:	
Subjects were randomized to receive pamrevlumab 30 mg/kg by IV infusion Q3W.	
Reporting group title	Placebo Q3W
Reporting group description:	
Subjects were randomized to receive placebo matching pamrevlumab by IV infusion Q3W.	

Primary: Change from Baseline to Week 48 in FVC (Percent of Predicted FVC Value [% predicted])

End point title	Change from Baseline to Week 48 in FVC (Percent of Predicted FVC Value [% predicted])
End point description:	
FVC in liters was measured during the spirometry assessments at screening and during the randomized treatment period at Day 1 and every 12 weeks. The FVC (% predicted) was calculated using an algorithm for the corresponding gender-race-age group (Hankinson et al, Am J Resp Crit Care Med. 1999; 159:179-87). The least squares (LS) mean change from baseline to Week 48 (end of the randomized treatment period) in FVC (% predicted) is presented for the intention-to-treat (ITT) population which included randomized subjects who met all protocol eligibility criteria. Baseline was defined as the mean of the last screening visit and the Day 1 visit values. Analysis of treatment difference in change from baseline to Week 48 used a random coefficient regression model which included treatment arm, visit, treatment by visit interaction, and baseline as fixed effects and linear slope as random effect, based on the missing at random assumption. Observed data from all visits were included in the model.	
End point type	Primary
End point timeframe:	
Baseline (screening and Day 1) up to Week 48 of randomized treatment period.	

End point values	Pamrevlumab 30 mg/kg Q3W	Placebo Q3W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: % predicted FVC				
least squares mean (confidence interval 95%)	-2.85 (-4.41 to -1.29)	-7.17 (-10.83 to -3.52)		

Statistical analyses

Statistical analysis title	Absolute treatment difference
Statistical analysis description:	
The absolute LS mean treatment difference (pamrevlumab - placebo) for change from baseline to Week 48 in FVC (% predicted) is presented.	
Comparison groups	Pamrevlumab 30 mg/kg Q3W v Placebo Q3W

Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0331 [1]
Method	Random coefficient regression
Parameter estimate	LS mean difference
Point estimate	4.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	8.3

Notes:

[1] - The analysis of the change from baseline to Week 48 in FVC (% predicted) was based on the random coefficient regression model based on observed cases.

Secondary: Mean Change from Baseline to Week 24 and Week 48 in the HRCT Quantitative Lung Fibrosis (QLF) Score

End point title	Mean Change from Baseline to Week 24 and Week 48 in the HRCT Quantitative Lung Fibrosis (QLF) Score

End point description:

The extent of pulmonary fibrosis was measured by HRCT scans of the chest at screening and at Weeks 24 and 48, to determine the HRCT QLF score. Each lung was divided into 5 lobes and a computer algorithm calculated the percent of fibrotic reticulation in each lung lobe. The fibrosis score of the whole lung was defined as the average of the 5 lung lobes. The mean changes from baseline to Week 24 and Week 48 in the HRCT QLF score are presented for subjects in the ITT population and who also had a baseline fibrosis evaluation. Baseline was defined as the screening evaluation. Missing data were imputed using the multiple imputation (MI) method to handle missing values.

End point type	Secondary

End point timeframe:

Baseline (screening), Week 24 and Week 48.

End point values	Pamrevlumab 30 mg/kg Q3W	Placebo Q3W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: Percent of fibrosis				
least squares mean (standard error)				
Week 24	0.9 (± 0.52)	2.6 (± 0.58)		
Week 48	2.8 (± 1.02)	5.9 (± 1.45)		

Statistical analyses

Statistical analysis title	Week 24: Absolute treatment difference

Statistical analysis description:

The absolute LS mean treatment difference (pamrevlumab - placebo) for change from baseline to Week 24 in QLF score is presented.

Comparison groups	Pamrevlumab 30 mg/kg Q3W v Placebo Q3W

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0236
Method	ANCOVA with MI
Parameter estimate	LS mean difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	-0.2

Statistical analysis title	Week 48: Absolute treatment difference

Statistical analysis description:

The absolute LS mean treatment difference (pamrevlumab - placebo) for change from baseline to Week 48 in QLF score is presented.

Comparison groups	Pamrevlumab 30 mg/kg Q3W v Placebo Q3W
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0729
Method	ANCOVA with MI
Parameter estimate	LS mean difference
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	0.3

Secondary: Percentage of Subjects with IPF Progression Events up to Week 48

End point title	Percentage of Subjects with IPF Progression Events up to Week 48

End point description:

IPF progression events included death from any cause or absolute decline in FVC (% predicted) value of ≥10%, confirmed by repeat spirometry. Classification of FVC (% predicted) declined ≥10% was based on observed and imputed data. Missing data in FVC (% predicted) were imputed using the predicted values from the random coefficient module with treatment, visit, visit-by-treatment interaction, and baseline FVC (% predicted) as fixed effects and linear slope as random effect. The percentage of subjects with progression events at Week 48 is presented for the ITT population.

End point type	Secondary

End point timeframe:

Baseline (screening and Day 1) up to Week 48.

End point values	Pamrevlumab 30 mg/kg Q3W	Placebo Q3W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: percentage of subjects				
number (not applicable)	10.0	31.4		

Statistical analyses

Statistical analysis title	Absolute treatment difference
Statistical analysis description:	
The absolute treatment difference (pamrevlumab - placebo) for percentage of subjects with IPF progression at Week 48 is presented.	
Comparison groups	Pamrevlumab 30 mg/kg Q3W v Placebo Q3W
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0133
Method	Regression, Logistic
Parameter estimate	Absolute difference
Point estimate	-21.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.6
upper limit	-6.2

Secondary: Mean Change from Baseline to Week 24 and Week 48 in the Health-Related Quality of Life (HRQoL) Saint George's Respiratory Questionnaire (SGRQ) Domain and Total Scores

End point title	Mean Change from Baseline to Week 24 and Week 48 in the Health-Related Quality of Life (HRQoL) Saint George's Respiratory Questionnaire (SGRQ) Domain and Total Scores
End point description:	
HRQoL was assessed by the SGRQ to measure health impairment, and includes 17 questions in 3 domains: Symptoms, Activity and Impacts. The domain and total scores range from 0 to 100, with 0 indicating the best and 100 indicating the worst possible health status. The LS mean changes from baseline to Week 24 and Week 48 for each domain score and for the total score are presented for subjects in the ITT population and who also had baseline and at least 1 follow-up value. Missing data at post-baseline visits were imputed as the predicted values from the random coefficient model which included treatment, visit, visit-by-treatment interaction and baseline SGRQ score as fixed effects and linear slope of visit as random effect.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1), Week 24 and Week 48.	

End point values	Pamrevlumab 30 mg/kg Q3W	Placebo Q3W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	46		
Units: Score				
least squares mean (standard error)				
Week 24 Symptoms Score	-0.66 (± 1.963)	-1.44 (± 1.984)		
Week 24 Activity Score	-0.41 (± 1.847)	0.63 (± 1.867)		
Week 24 Impacts Score	-1.08 (± 1.835)	-0.51 (± 1.855)		
Week 24 Total Score	-0.75 (± 1.544)	-0.61 (± 1.561)		
Week 48 Symptoms Score	-3.38 (± 2.345)	1.89 (± 2.370)		
Week 48 Activity Score	-4.42 (± 2.464)	1.72 (± 2.490)		
Week 48 Impacts Score	-1.76 (± 2.682)	3.03 (± 2.711)		
Week 48 Total Score	-2.83 (± 2.255)	2.54 (± 2.279)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean Change from Baseline to Week 48 in FVC

End point title	Mean Change from Baseline to Week 48 in FVC

End point description:

The LS mean change from baseline to Week 48 in the FVC was estimated using the random coefficient linear regression model which included treatment, visit, visit-by-treatment interaction, baseline FVC, age, sex and height as fixed effects and linear slope as random effect. Data is presented for the ITT population. Observed data from all visits were included in the model.

End point type	Other pre-specified

End point timeframe:

Baseline (Day 1) to Week 48.

End point values	Pamrevlumab 30 mg/kg Q3W	Placebo Q3W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: Liters				
least squares mean (standard error)	-0.129 (± 0.0271)	-0.308 (± 0.0743)		

Statistical analyses

Statistical analysis title	Absolute treatment difference

Statistical analysis description:

The absolute LS mean treatment difference (pamrevlumab - placebo) for change from baseline to Week 48 in FVC (liters) is presented.

Comparison groups	Pamrevlumab 30 mg/kg Q3W v Placebo Q3W
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0249 [2]
Method	Random coefficient regression
Parameter estimate	LS mean difference
Point estimate	0.178
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.023
upper limit	0.334

Notes:

[2] - The analysis of the change from baseline to Week 48 in FVC (liters) was based on the random coefficient regression model based on observed cases.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs are reported for the randomized treatment period, collected from Day 1 to the end of the follow-up period (approximately 13 months).

Adverse event reporting additional description:

The safety population included randomized subjects who received any amount of study treatment. TEAEs were defined as new or worsening AEs that occurred after the start of first infusion of the study treatment and within 28 days of last infusion, or before the first pamrevlumab infusion in the extended treatment period, whichever occurred first.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Pamrevlumab 30 mg/kg Q3W

Reporting group description:

Subjects were randomized to receive pamrevlumab 30 mg/kg by IV infusion Q3W.

Reporting group title	Placebo Q3W

Reporting group description:

Subjects were randomized to receive placebo matching pamrevlumab by IV infusion Q3W.

Serious adverse events	Pamrevlumab 30 mg/kg Q3W	Placebo Q3W	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 50 (24.00%)	8 / 53 (15.09%)	
number of deaths (all causes)	3	6	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of the tongue			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			

subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Peripheral artery aneurysm			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 50 (0.00%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Angina pectoris			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Idiopathic pulmonary fibrosis			
subjects affected / exposed	0 / 50 (0.00%)	4 / 53 (7.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Interstitial lung disease			
subjects affected / exposed	2 / 50 (4.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 50 (4.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 50 (2.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Acute respiratory failure			

subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Antisynthetase syndrome			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pamrevlumab 30 mg/kg Q3W	Placebo Q3W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 50 (84.00%)	41 / 53 (77.36%)	
Vascular disorders			
Flushing			
subjects affected / exposed	3 / 50 (6.00%)	4 / 53 (7.55%)	
occurrences (all)	15	21	
Hypertension			
subjects affected / exposed	3 / 50 (6.00%)	0 / 53 (0.00%)	
occurrences (all)	4	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 50 (20.00%)	4 / 53 (7.55%)	
occurrences (all)	21	4	
Oedema peripheral			
subjects affected / exposed	4 / 50 (8.00%)	2 / 53 (3.77%)	
occurrences (all)	5	2	
Chest pain			
subjects affected / exposed	4 / 50 (8.00%)	1 / 53 (1.89%)	
occurrences (all)	4	1	
Chest discomfort			
subjects affected / exposed	3 / 50 (6.00%)	1 / 53 (1.89%)	
occurrences (all)	3	1	
Pain			
subjects affected / exposed	4 / 50 (8.00%)	0 / 53 (0.00%)	
occurrences (all)	5	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 50 (28.00%)	23 / 53 (43.40%)	
occurrences (all)	22	25	
Dyspnoea			
subjects affected / exposed	13 / 50 (26.00%)	11 / 53 (20.75%)	
occurrences (all)	13	12	
Idiopathic pulmonary fibrosis			
subjects affected / exposed	10 / 50 (20.00%)	7 / 53 (13.21%)	
occurrences (all)	15	8	

Nasopharyngitis			
subjects affected / exposed	9 / 50 (18.00%)	5 / 53 (9.43%)	
occurrences (all)	12	7	
Upper-airway cough syndrome			
subjects affected / exposed	4 / 50 (8.00%)	2 / 53 (3.77%)	
occurrences (all)	6	2	
Throat irritation			
subjects affected / exposed	1 / 50 (2.00%)	4 / 53 (7.55%)	
occurrences (all)	1	4	
Pulmonary hypertension			
subjects affected / exposed	3 / 50 (6.00%)	1 / 53 (1.89%)	
occurrences (all)	3	1	
Sinus congestion			
subjects affected / exposed	3 / 50 (6.00%)	1 / 53 (1.89%)	
occurrences (all)	3	1	
Sleep apnoea syndrome			
subjects affected / exposed	3 / 50 (6.00%)	0 / 53 (0.00%)	
occurrences (all)	3	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 50 (6.00%)	5 / 53 (9.43%)	
occurrences (all)	4	5	
Insomnia			
subjects affected / exposed	4 / 50 (8.00%)	1 / 53 (1.89%)	
occurrences (all)	4	2	
Investigations			
Heart sounds abnormal			
subjects affected / exposed	3 / 50 (6.00%)	0 / 53 (0.00%)	
occurrences (all)	3	0	
Oxygen consumption increased			
subjects affected / exposed	0 / 50 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 50 (4.00%)	3 / 53 (5.66%)	
occurrences (all)	2	3	

Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	 0 / 50 (0.00%) 0	 3 / 53 (5.66%) 5	
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	 4 / 50 (8.00%) 14 4 / 50 (8.00%) 6	 6 / 53 (11.32%) 7 0 / 53 (0.00%) 0	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all)	 7 / 50 (14.00%) 17 8 / 50 (16.00%) 21 2 / 50 (4.00%) 2 4 / 50 (8.00%) 4	 7 / 53 (13.21%) 8 4 / 53 (7.55%) 4 4 / 53 (7.55%) 4 0 / 53 (0.00%) 0	
Renal and urinary disorders Nephrolithiasis subjects affected / exposed occurrences (all)	 0 / 50 (0.00%) 0	 3 / 53 (5.66%) 3	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Musculoskeletal pain	 5 / 50 (10.00%) 5 5 / 50 (10.00%) 6	 5 / 53 (9.43%) 5 2 / 53 (3.77%) 3	

subjects affected / exposed	3 / 50 (6.00%)	2 / 53 (3.77%)	
occurrences (all)	4	2	
Myalgia			
subjects affected / exposed	3 / 50 (6.00%)	1 / 53 (1.89%)	
occurrences (all)	3	1	
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	15 / 50 (30.00%)	10 / 53 (18.87%)	
occurrences (all)	19	11	
Sinusitis			
subjects affected / exposed	8 / 50 (16.00%)	8 / 53 (15.09%)	
occurrences (all)	9	9	
Urinary tract infection			
subjects affected / exposed	10 / 50 (20.00%)	4 / 53 (7.55%)	
occurrences (all)	13	5	
Bronchitis			
subjects affected / exposed	2 / 50 (4.00%)	6 / 53 (11.32%)	
occurrences (all)	3	7	
Viral infection			
subjects affected / exposed	0 / 50 (0.00%)	5 / 53 (9.43%)	
occurrences (all)	0	6	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 50 (6.00%)	2 / 53 (3.77%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 2014	- Increased target enrollment and stratified subjects by prior therapy (nintedanib and/or pirfenidone). - Amended procedures for replacing subjects to account for early dropouts. - Revised enrollment criteria for extended treatment period from <3% absolute decrease in FVC (%predicted) after 48 weeks to no decrease or an increase in FVC (% predicted) after 48 weeks. - Revised assessments so diffusing capacity of the lung for carbon monoxide was performed at screening only. - Removed evaluation of dyspnoea; evaluations for prothrombin time and partial prothromboplastin time and reduced frequency of laboratory tests. - Removed exclusion criteria for subjects with an international normalized ratio of >1.5. - Permitted enrollment of subjects with a cancer diagnosis >3 years prior to screening and of subjects with a history of in situ cancer. - Added an optional whole blood sample collection on Day 1 for DNA analysis.
09 March 2015	- Increased number of sites to 76 to maximize enrollment. - Clarified extended treatment period procedures. - Clairfication regarding prior therapy with pirfenidone and/or nintedanib, and for subjects who had previously received perfenidone and/or nintedanib and experienced a decrease of >10% in FVC (% predicted). - Clarified that subjects could not receive sildenafil for IPF but could for a different indication. - Expanded the rationale for the placebo arm. - Clarified mandatory discontinuation criteria, and specification of minimum washout period for prohibited drugs as 5 half-lives prior to Day 1 dosing. - Clarified study termination description that pamrevlumab would not be provided if the planned analysis showed it was not effective for IPF treatment. - Clarification that FVC criterion for disease progression should be on pre-bronchodilator values. - Clarification that SAEs related to disease progression, lung transplantation and worsening of baseline conditions requiring elective surgery were to be reported as SAEs. - Added HRCT to study procedure descriptions, and added statement that serial spirometry would be performed as part of pulmonary function tests.
28 May 2015	- Follow-up period extended from 7 weeks to 10 weeks. - Required use of double-barrier contraception methods during the study and for 3 months after the last dose of study drug for women of childbearing potential and male partners of women of childbearing potential.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported