EU Clinical Trials Register

Clinical trial results:

A Phase IIb, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Sildenafil Added to Pirfenidone in Subjects With Advanced Idiopathic Pulmonary Fibrosis and Risk of Group 3 Pulmonary Hypertension

Summary

EudraCT number	2015-005131-40
Trial protocol	ES NL BE DE GR HU CZ IT
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	03 September 2020
First version publication date	03 September 2020

Trial information

Trial identification

Sponsor protocol code	MA29957

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02951429
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	Medical Communications, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.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	Interim
Date of interim/final analysis	11 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 September 2019
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

This Phase IIb, randomized, placebo-controlled, multicenter, international study will evaluate the efficacy, safety, and tolerability of sildenafil or placebo added to pirfenidone (Esbriet) treatment in subjects with advanced IPF and intermediate or high probability of Group 3 pulmonary hypertension (PH) who are on a stable dose of pirfenidone with demonstrated tolerability. Subjects were randomized to receive 1 year of treatment with either oral sildenafil or matching placebo while continuing to take pirfenidone.

Protection of trial subjects:

This study was conducted in accordance with the protocol and with the following:

● Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

● Applicable ICH Good Clinical Practice (GCP) Guidelines

● Applicable laws and regulations

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	13 January 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	11 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 23
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Egypt: 15
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Greece: 18
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Israel: 21
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	South Africa: 7
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Turkey: 26

Worldwide total number of subjects	177
EEA total number of subjects	100

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)	49
From 65 to 84 years	128
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Written informed consent for participation in the study was obtained before performing any study-specific screening tests or evaluations.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pirfenidone+Sildenafil

Arm description:

Participants received pirfenidone along with sildenafil, orally, three times a day for 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Sildenafil
Investigational medicinal product code	
Other name	RO0280296
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sildenafil will be given as 20 mg, TID.

Investigational medicinal product name	Pirfenidone
Investigational medicinal product code	
Other name	Esbriet, RO0220912
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pirfenidone will be given in the range of 1602 to 2403 milligram per day (mg/day), as 3 divided doses.

Arm title	Pirfenidone+Placebo

Arm description:

Participants received pirfenidone along with placebo matched to sildenafil, orally, three times a day for 52 weeks.

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 matched with sildenafil.

Investigational medicinal product name	Pirfenidone
Investigational medicinal product code	
Other name	Esbriet, RO0220912

Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pirfenidone will be given in the range of 1602 to 2403 milligram per day (mg/day), as 3 divided doses.

Number of subjects in period 1	Pirfenidone+Sildenafil	Pirfenidone+Placebo
Started	88	89
Completed	16	6
Not completed	72	83
Adverse event, serious fatal	28	36
Consent withdrawn by subject	7	11
Adverse event, non-fatal	3	7
Progressive Disease	1	1
Unknown	1	3
Lung Transplantation	9	6
Lost to follow-up	-	1
Participant ongoing in the study	23	17
Lack of efficacy	-	1

Baseline characteristics

Reporting groups

Reporting group title	Pirfenidone+Sildenafil

Reporting group description:

Participants received pirfenidone along with sildenafil, orally, three times a day for 52 weeks.

Reporting group title	Pirfenidone+Placebo

Reporting group description:

Participants received pirfenidone along with placebo matched to sildenafil, orally, three times a day for 52 weeks.

Reporting group values	Pirfenidone+Sildenafil	Pirfenidone+Placebo	Total
Number of subjects	88	89	177
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)	27	22	49
From 65-84 years	61	67	128
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	68.2	68.9	
standard deviation	± 7.7	± 7.1	-
Sex: Female, Male			
Units: Participants			
Female	19	24	43
Male	69	65	134
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	0	1	1
White	85	88	173
More than one race	0	0	0
Unknown or Not Reported	1	0	1
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	2	3	5
Not Hispanic or Latino	78	79	157
Unknown or Not Reported	8	7	15

End points

End points reporting groups

Reporting group title	Pirfenidone+Sildenafil
Reporting group description:	
Participants received pirfenidone along with sildenafil, orally, three times a day for 52 weeks.	
Reporting group title	Pirfenidone+Placebo
Reporting group description:	
Participants received pirfenidone along with placebo matched to sildenafil, orally, three times a day for 52 weeks.	

Primary: Percentage of Subjects With Disease Progression, as Determined by Relevant Decline in 6 Minute Walk Distance (6MWD) of At Least (>=) 15 Percent (%) From Baseline, Respiratory-Related Non-Elective Hospitalization, or Death From Any Cause

End point title	Percentage of Subjects With Disease Progression, as Determined by Relevant Decline in 6 Minute Walk Distance (6MWD) of At Least (>=) 15 Percent (%) From Baseline, Respiratory-Related Non-Elective Hospitalization, or Death From Any Cause

End point description:

Disease Progression defined as relative decline in 6MWD from baseline (defined as >25% from baseline or 15–25% from baseline associated with worsening oxygen saturation, worsening Borg score, or increased oxygen
requirements), respiratory-related non-elective hospitalizations, or all-cause mortality.

Population: Subjects with data available at week 52.

End point type	Primary
End point timeframe:	
Baseline up to Week 52	

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	89		
Units: Percentage				
number (not applicable)	72.7	69.7		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Pirfenidone+Sildenafil v Pirfenidone+Placebo

Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6527
Method	Clopper-Pearson
Parameter estimate	Difference (95% CI)
Point estimate	3.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.3
upper limit	17.97

Secondary: Time to First Occurrence of Disease Progression

End point title	Time to First Occurrence of Disease Progression

End point description:

Disease Progression defined as relative decline in 6MWD from baseline (defined as >25% from baseline or 15–25% from baseline associated with worsening oxygen saturation, worsening Borg score, or increased oxygen requirements), respiratory-related non-elective hospitalizations, or all-cause mortality.

Population: Subjects with data available at week 52.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	89		
Units: Weeks				
median (confidence interval 95%)	26.00 (20.57 to 38.14)	25.43 (13.00 to 37.71)		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Pirfenidone+Sildenafil v Pirfenidone+Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7568
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.34

Secondary: Time to Multiple Occurrence Event

End point title	Time to Multiple Occurrence Event
End point description:	
Population: Subjects with data available at week 52.	
End point type	Secondary
End point timeframe:	
Baseline up to Week 52	

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	89		
Units: Weeks				
median (confidence interval 95%)	20.57 (13.14 to 26.43)	13.29 (12.71 to 23.29)		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Pirfenidone+Sildenafil v Pirfenidone+Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.376
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.15

Secondary: Percentage of Subjects With Decline From Baseline in 6MWD of >= 15%

End point title	Percentage of Subjects With Decline From Baseline in 6MWD of >= 15%

End point description:

Population: Subjects with data available at week 52 to calculate a change from baseline.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	89		
Units: Percentage				
number (not applicable)	53.4	50.6		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Pirfenidone+Sildenafil v Pirfenidone+Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7046
Method	Clopper-Pearson
Parameter estimate	Difference (95% CI)
Point estimate	2.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.13
upper limit	17.84

Secondary: Time to First Occurrence of Relevant ≥15% Decline from Baseline in 6MWD

End point title	Time to First Occurrence of Relevant ≥15% Decline from Baseline in 6MWD

End point description:

Population: Subjects with data available at week 52 to calculate a change from baseline.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	89		
Units: Weeks				
median (confidence interval 95%)	39.00 (27.86 to 52.14)	38.71 (25.14 to 52.57)		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Pirfenidone+Sildenafil v Pirfenidone+Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.755
Method	Clopper-Pearson
Parameter estimate	Difference (95% CI)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.41

Secondary: Time to Respiratory-Related Non-Elective Hospitalization

End point title	Time to Respiratory-Related Non-Elective Hospitalization
End point description:	
9999 = non-calculable Population: Subjects with data available at week 52 to calculate a change from baseline.	
End point type	Secondary
End point timeframe:	
Baseline up to Week 52	

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	89		
Units: Weeks				
median (confidence interval 95%)	54.29 (36.29 to 9999)	9999 (42.14 to 9999)		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Pirfenidone+Sildenafil v Pirfenidone+Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9174
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.61

Secondary: Time to All-Cause Non-Elective Hospitalization

End point title	Time to All-Cause Non-Elective Hospitalization

End point description:

9999 = non calculable. KM-curves ends at 52 weeks and the upper CI is higher than 52 weeks and thus based on the data cannot be presented.

Population: Subjects with data available at week 52.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	89		
Units: Weeks				
median (confidence interval 95%)	45.57 (28.00 to 9999)	49.86 (32.00 to 9999)		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Pirfenidone+Sildenafil v Pirfenidone+Placebo

Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7748
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.62

Secondary: Time to Death From Any Cause

End point title	Time to Death From Any Cause
End point description:	

9999 = non-calculable

Population: Subjects with data available at week 52.

End point type	Secondary
End point timeframe:	

Baseline up to Week 52

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	89		
Units: Weeks				
median (confidence interval 95%)	9999 (54.43 to 9999)	9999 (9999 to 9999)		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Pirfenidone+Sildenafil v Pirfenidone+Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4258
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.5

Secondary: Percentage of Participants With Lung Transplantation

End point title	Percentage of Participants With Lung Transplantation
End point description:	
Population: Subjects with data available at week 52.	
End point type	Secondary
End point timeframe:	
Baseline up to Week 52	

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	89		
Units: Percentage				
number (not applicable)	10.2	6.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Respiratory-Related Death

End point title	Time to Respiratory-Related Death
End point description:	
9999 = non-calculable	
Population: Subjects with data available at week 52.	
End point type	Secondary
End point timeframe:	
Baseline up to Week 52	

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	89		
Units: Weeks				
median (confidence interval 95%)	9999 (54.43 to 9999)	9999 (9999 to 9999)		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Pirfenidone+Sildenafil v Pirfenidone+Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3161
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	1.46

Secondary: Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Peak Tricuspid Regurgitation Velocity

End point title	Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Peak Tricuspid Regurgitation Velocity

End point description:

Population: Subjects with data available at week 52 to calculate a change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	29		
Units: m/s				
arithmetic mean (standard deviation)	-0.014 (± 0.6326)	0.103 (± 0.6699)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Pulmonary Artery Pressure (PAPs)

End point title	Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Pulmonary Artery Pressure (PAPs)
End point description:	
Population: Subjects with data available at week 52 to calculate a change from baseline.	
End point type	Secondary
End point timeframe:	
Baseline, Week 52	

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	30		
Units: mmHg				
arithmetic mean (standard deviation)	2.0 (± 15.65)	3.6 (± 22.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Tricuspid Annular Plane Systolic Excursion (TAPSE)

End point title	Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Tricuspid Annular Plane Systolic Excursion (TAPSE)
End point description:	
Population: Subjects with data available at week 52 to calculate a change from baseline.	
End point type	Secondary
End point timeframe:	
Baseline, Week 52	

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	27		
Units: cm				
arithmetic mean (standard deviation)	-0.204 (± 0.4170)	-0.146 (± 0.4453)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Right Ventricle Basal Diameter

End point title	Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Right Ventricle Basal Diameter
End point description:	
Population: Subjects with data available at week 52 to calculate a change from baseline.	
End point type	Secondary
End point timeframe:	
Baseline, Week 52	

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	24		
Units: cm				
arithmetic mean (standard deviation)	0.462 (± 1.2305)	0.095 (± 1.2875)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Inferior Vena Cava Diameter

End point title	Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Inferior Vena Cava Diameter
End point description:	
Population: Subjects with data available at week 52 to calculate a change from baseline.	
End point type	Secondary
End point timeframe:	
Baseline, Week 52	

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	22		
Units: cm				
arithmetic mean (standard deviation)	-0.05 (± 0.595)	-0.09 (± 0.540)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Left Ventricular Ejection Fraction (LVEF)

End point title	Change From Baseline to Week 52 in Transthoracic Echocardiography (ECHO) Parameter: Left Ventricular Ejection Fraction (LVEF)
End point description:	
Population: Subjects with data available at week 52 to calculate a change from baseline.	
End point type	Secondary
End point timeframe:	
Baseline, Week 52	

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	30		
Units: Percentage				
arithmetic mean (standard deviation)	1.22 (± 9.166)	-0.85 (± 5.767)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 52 in Carbon Monoxide Diffusing Capacity/ Pulmonary Diffusing Capacity (DLCO)

End point title	Change From Baseline to Week 52 in Carbon Monoxide Diffusing Capacity/ Pulmonary Diffusing Capacity (DLCO)
End point description:	
Population: Subjects with data available at week 52 to calculate a change from baseline.	
End point type	Secondary
End point timeframe:	
Baseline, Week 52	

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	29		
Units: Percentage predicted				
arithmetic mean (standard deviation)	-2.918 (± 6.2296)	-2.440 (± 8.2820)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 52 in Forced Vital Capacity (FVC)

End point title	Change From Baseline to Week 52 in Forced Vital Capacity (FVC)
End point description:	
Population: Subjects with data available at week 52 to calculate a change from baseline.	
End point type	Secondary
End point timeframe:	
Baseline, Week 52	

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	33		
Units: Percentage predicted				
arithmetic mean (standard deviation)	-2.761 (± 7.8044)	-1.161 (± 11.1158)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects by World Health Organization (WHO) Functional Class at Week 52

End point title	Percentage of Subjects by World Health Organization (WHO) Functional Class at Week 52
End point description:	
Population: Subjects with data available at week 52 to calculate a change from baseline.	
End point type	Secondary
End point timeframe:	
Week 52	

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	36		
Units: Percentage				
number (not applicable)				
Class II	19.3	13.5		
Class III	33.0	24.7		
Class IV	3.4	1.1		
Missing	0	1.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in N-terminal Pro-Brain Natriuretic Peptide (NT-proBNP) Level (pg/mL) at Week 52

End point title	Change from Baseline in N-terminal Pro-Brain Natriuretic Peptide (NT-proBNP) Level (pg/mL) at Week 52
End point description:	
Population: Subjects with data available at week 52 to calculate a change from baseline.	
End point type	Secondary
End point timeframe:	
Baseline, Week 52	

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	28		
Units: pg/mL)				
arithmetic mean (standard deviation)	110.1 (± 612.98)	605.9 (± 1273.19)		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Pirfenidone+Sildenafil v Pirfenidone+Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5646
Method	Linear Mixed Effects Model
Parameter estimate	Estimate
Point estimate	-206.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	-920.03
upper limit	506.85

Secondary: St. George's Respiratory Questionnaire (SGRQ) Changes from Baseline at Week 52

End point title	St. George's Respiratory Questionnaire (SGRQ) Changes from Baseline at Week 52

End point description:

Population: Subjects with data available at week 52 to calculate a change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	31		
Units: Points on scale				
arithmetic mean (standard deviation)				
Total score	6.149 (± 12.3407)	11.437 (± 12.5187)		
Symptoms component score	2.498 (± 19.6074)	8.261 (± 19.5558)		
Activities component score	3.997 (± 15.4341)	10.871 (± 14.5246)		
Impacts component score	8.417 (± 15.0040)	12.118 (± 15.3487)		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Pirfenidone+Sildenafil v Pirfenidone+Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5255
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-3.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.98
upper limit	2.36

Secondary: University of California, San Diego–Shortness of Breath Questionnaire (UCSD-SOBQ) Changes from Baseline at Week 52

End point title	University of California, San Diego–Shortness of Breath Questionnaire (UCSD-SOBQ) Changes from Baseline at Week 52

End point description:

Population: Subjects with data available at week 52 to calculate a change from baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	25		
Units: Points on scale				
arithmetic mean (standard deviation)	12.5 (± 20.93)	18.8 (± 19.68)		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Pirfenidone+Sildenafil v Pirfenidone+Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4263
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18
upper limit	6

Secondary: Change from Baseline in Distance Walked, 6MWT at Week 52

End point title	Change from Baseline in Distance Walked, 6MWT at Week 52
End point description:	
Population: Subjects with data available at week 52 to calculate a change from baseline.	
End point type	Secondary
End point timeframe:	
Baseline up to Week 52	

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	30		
Units: meters				
arithmetic mean (standard deviation)	-52.9 (± 121.07)	-40.8 (± 91.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Oxygen Requirements, 6MWT at Week 52

End point title	Change from Baseline in Oxygen Requirements, 6MWT at Week 52
End point description:	
Population: Subjects with data available at week 52 to calculate a change from baseline.	
End point type	Secondary
End point timeframe:	
Baseline up to Week 52	

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	30		
Units: Liters				
arithmetic mean (standard deviation)	0.6 (± 1.27)	0.6 (± 1.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in other 6MWT Parameters at Week 52

End point title	Change from Baseline in other 6MWT Parameters at Week 52

End point description:

Population: Subjects with data available at week 52 to calculate a change from baseline.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	30		
Units: Percentage				
arithmetic mean (standard deviation)				
SpO2 before the test (at rest)	-0.5 (± 4.63)	-0.8 (± 3.77)		
SpO2 lowest during the test	-3.4 (± 8.93)	0.3 (± 5.27)		
SpO2 after the test	0.5 (± 9.97)	-2.3 (± 6.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Adverse Events

End point title	Percentage of Subjects with Adverse Events

End point description:

Population: Subjects with data available at week 52. AEs that started or worsened on or after first intake of randomized treatment until last positive dose + 28 days.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	89		
Units: Percentage				
number (not applicable)	98.9	93.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Borg scale Result at the End of the Test at Week 52

End point title	Borg scale Result at the End of the Test at Week 52

End point description:

End point type	Secondary

End point timeframe:
Baseline up to Week 52

End point values	Pirfenidone+Sildenafil	Pirfenidone+Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	30		
Units: Points on Scale				
arithmetic mean (standard deviation)	0.9 (± 3.00)	0.7 (± 3.24)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to primary data cut-off (up to 2 years 7 months). The safety data includes DBP and SFU up to 11-Nov-2019.

Adverse event reporting additional description:

Total # of Deaths (all causes n= 64) represent deaths occurring during Double blind treatment period+4 week FU+additional safety follow up to the database snapshot of 11-Nov-2019.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Pirfenidone+Placebo

Reporting group description:

Participants received pirfenidone along with placebo matched to sildenafil, orally, three times a day for 52 weeks.

Reporting group title	Pirfenidone+Sildenafil

Reporting group description:

Participants received pirfenidone along with sildenafil, orally, three times a day for 52 weeks.

Serious adverse events	Pirfenidone+Placebo	Pirfenidone+Sildenafil	
Total subjects affected by serious adverse events			
subjects affected / exposed	55 / 89 (61.80%)	54 / 88 (61.36%)	
number of deaths (all causes)	36	28	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer metastatic			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Squamous cell carcinoma of lung				
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Vascular disorders				
Cryoglobulinaemia				
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Dry gangrene				
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Extremity necrosis				
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)		
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	0 / 89 (0.00%)	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Surgical and medical procedures				
Lung transplant				
subjects affected / exposed	1 / 89 (1.12%)	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
General disorders and administration site conditions				
Death				
subjects affected / exposed	1 / 89 (1.12%)	3 / 88 (3.41%)		
occurrences causally related to treatment / all	0 / 1	0 / 3		
deaths causally related to treatment / all	0 / 1	0 / 3		
Inflammation				

subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)		
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

Acute respiratory failure

subjects affected / exposed	1 / 89 (1.12%)	2 / 88 (2.27%)		
occurrences causally related to treatment / all	0 / 1	0 / 2		
deaths causally related to treatment / all	0 / 1	0 / 1		

Chronic respiratory failure

subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

Dyspnoea

subjects affected / exposed	5 / 89 (5.62%)	7 / 88 (7.95%)		
occurrences causally related to treatment / all	0 / 5	1 / 9		
deaths causally related to treatment / all	0 / 3	1 / 1		

Hypoxia

subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		

Idiopathic pulmonary fibrosis

subjects affected / exposed	21 / 89 (23.60%)	19 / 88 (21.59%)		
occurrences causally related to treatment / all	1 / 31	0 / 23		
deaths causally related to treatment / all	0 / 8	0 / 3		

Interstitial lung disease

subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Pneumonitis

subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Pneumothorax

subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Pulmonary embolism		
subjects affected / exposed	2 / 89 (2.25%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary fibrosis		
subjects affected / exposed	2 / 89 (2.25%)	4 / 88 (4.55%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 2
Pulmonary hypertension		
subjects affected / exposed	2 / 89 (2.25%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary oedema		
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory acidosis		
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Respiratory failure		
subjects affected / exposed	3 / 89 (3.37%)	5 / 88 (5.68%)
occurrences causally related to treatment / all	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 3
Injury, poisoning and procedural complications		
Postoperative respiratory failure		
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal compression fracture		

subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	4 / 89 (4.49%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 89 (0.00%)	2 / 88 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure chronic			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 89 (1.12%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			

subjects affected / exposed	2 / 89 (2.25%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0
Coronary artery disease		
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Right ventricular failure		
subjects affected / exposed	1 / 89 (1.12%)	3 / 88 (3.41%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1
Supraventricular tachycardia		
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Nervous system disorders		
Brain stem infarction		
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebral haemorrhage		
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Cerebral infarction		
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Dizziness		
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Seizure		

subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Eye disorders			
Blindness transient			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 89 (1.12%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Urinary bladder polyp			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 89 (1.12%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster disseminated			
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lower respiratory tract infection		
subjects affected / exposed	1 / 89 (1.12%)	4 / 88 (4.55%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1
Pneumonia		
subjects affected / exposed	4 / 89 (4.49%)	7 / 88 (7.95%)
occurrences causally related to treatment / all	0 / 4	0 / 9
deaths causally related to treatment / all	0 / 1	0 / 2
Pneumonia bacterial		
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Pneumonia haemophilus		
subjects affected / exposed	1 / 89 (1.12%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia viral		
subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Postoperative wound infection		
subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)
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	1 / 89 (1.12%)	2 / 88 (2.27%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory tract infection viral		

subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Sepsis

subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0

Septic shock

subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0

Upper respiratory tract infection

subjects affected / exposed	1 / 89 (1.12%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Metabolism and nutrition disorders
  Cachexia

subjects affected / exposed	1 / 89 (1.12%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Fluid overload

subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Hyponatraemia

subjects affected / exposed	0 / 89 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

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

Non-serious adverse events	Pirfenidone+Placebo	Pirfenidone+Sildenafil	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 89 (65.17%)	53 / 88 (60.23%)	
Investigations			
Weight decreased			
subjects affected / exposed	3 / 89 (3.37%)	5 / 88 (5.68%)	
occurrences (all)	3	5	
Vascular disorders			
Hypotension			
subjects affected / exposed	9 / 89 (10.11%)	6 / 88 (6.82%)	
occurrences (all)	10	7	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 89 (2.25%)	5 / 88 (5.68%)	
occurrences (all)	2	5	
Headache			
subjects affected / exposed	2 / 89 (2.25%)	6 / 88 (6.82%)	
occurrences (all)	3	7	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 89 (6.74%)	8 / 88 (9.09%)	
occurrences (all)	6	8	
Oedema peripheral			
subjects affected / exposed	5 / 89 (5.62%)	3 / 88 (3.41%)	
occurrences (all)	5	4	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 89 (2.25%)	11 / 88 (12.50%)	
occurrences (all)	2	15	
Vomiting			
subjects affected / exposed	3 / 89 (3.37%)	5 / 88 (5.68%)	
occurrences (all)	3	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 89 (10.11%)	7 / 88 (7.95%)	
occurrences (all)	9	9	
Dyspnoea			

subjects affected / exposed	17 / 89 (19.10%)	22 / 88 (25.00%)	
occurrences (all)	18	23	
Idiopathic pulmonary fibrosis			
subjects affected / exposed	7 / 89 (7.87%)	8 / 88 (9.09%)	
occurrences (all)	10	8	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	5 / 89 (5.62%)	3 / 88 (3.41%)	
occurrences (all)	6	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	9 / 89 (10.11%)	6 / 88 (6.82%)	
occurrences (all)	15	6	
Influenza			
subjects affected / exposed	5 / 89 (5.62%)	2 / 88 (2.27%)	
occurrences (all)	6	2	
Respiratory tract infection			
subjects affected / exposed	4 / 89 (4.49%)	9 / 88 (10.23%)	
occurrences (all)	6	11	
Upper respiratory tract infection			
subjects affected / exposed	2 / 89 (2.25%)	8 / 88 (9.09%)	
occurrences (all)	4	9	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 89 (10.11%)	6 / 88 (6.82%)	
occurrences (all)	9	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2017	Protocol MA29957 has been amended to reflect the feedback received after the start of the study from the Steering Committee, sites or ethic committees.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported