Clinical trial results:
A randomised placebo-controlled pilot trial of omeprazole in idiopathic pulmonary fibrosis (IPF)

Summary

EudraCT number	2013-003301-26
Trial protocol	GB
Global end of trial date	27 September 2016

Results information

Result version number	v1 (current)
This version publication date	05 January 2019
First version publication date	05 January 2019

Trial information

Trial identification

Sponsor protocol code	IAFIPF001

Additional study identifiers

ISRCTN number	ISRCTN07139948
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC reference: 13/YH/0284

Notes:

Sponsors

Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Joint Research Office, Level 1 Regent Point, Regent Farm Road, Gosforth, Newcastle upon Tyne, United Kingdom, NE3 3HD
Public contact	Professor John Simpson, Newcastle University, 0191 2087770, j.simpson@newcastle.ac.uk
Scientific contact	Professor John Simpson, Newcastle University, 0191 2087770, j.simpson@newcastle.ac.uk

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	01 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 September 2016
Global end of trial reached?	Yes
Global end of trial date	27 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal question is whether omeprazole reduces cough (quantified objectively) in patients with IPF, when compared with placebo.

Protection of trial subjects:

Omeprazole is a substituted benzimidazole, and belongs to the "proton pump inhibitor" (PPI) class of drugs. Omeprazole specifically inhibits the hydrogen-potassium-ATPase (H/K-ATPase) enzyme at the apical surface of gastric parietal cells. H/K-ATPase is responsible for delivering hydrogen ions to the lumen of the stomach, thus acidifying the contents. Omeprazole's dose-dependent and specific inhibition of the enzyme therefore neutralizes gastric acid contents. Omeprazole inhibits basal and induced gastric acid release.

Omeprazole has been used clinically for many years. It is licensed for use in gastro-oesophageal reflux, erosive oesophagitis, duodenal ulcer, gastric ulcer, eradication of Helicobacter pylori (in combination with antibiotics), and Zollinger-Ellison syndrome. It is also used for the prevention of gastric adverse events associated with use of non-steroidal anti-inflammatory drugs.

Patients will be advised by their doctor to report any unusual symptoms or reactions. Patients will be provided with a contact number on which they may contact a member of the study team to obtain advice and express any concerns, throughout the duration of the study. This information will be included in the patient information leaflet.

Background therapy:

Potential participants in the trial were asked to consent to a trial off PPI, if there was no return of symptoms, they were consented onto the full trial. If there was any return of symptoms and the trial off PPI was not tolerated, the patient went back onto their normal standard care.

Evidence for comparator:

N/A

Actual start date of recruitment	01 March 2014
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	United Kingdom: 45
Worldwide total number of subjects	45
EEA total number of subjects	45

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)	5
From 65 to 84 years	38
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Participants were identified by qualified research staff from current lists of potential patients attending local clinics, or identified and referred for participant in the trial from Participant Identification Centres (PICs) by their treating clinicians.

Pre-assignment

Screening details:

If the potential participant was currently taking antacids, prokinetics or raft alginates at the time of screening, they were eligible if they have been off these treatments for a period of two weeks. Participants consented to a trial off these treatments. If there was no return of symptoms, they could go onto the trial.

Pre-assignment period milestones

Number of subjects started	54[1]
Number of subjects completed	45

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Return of Symptoms: 9

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: If patients taking omeprazole (or a related stomach treatment) wished to take part, patient consented to a trial period off treatment for 2 weeks. If symptoms returned during that 2- week period the patient went back on treatment and did not take part in the study. If patients managed well without the treatment for 2 weeks, they were asked to sign a second consent form before starting the trial.

Period 1

Period 1 title	Visit 1
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Participants were randomised at period 3.

Arms

Arm title	Assessment

Arm description:

Assessment and medical tests

Arm type	pre-randomisation

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Assessment
Started	45
Completed	45

Period 2	
Period 2 title	Visit 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Blinding implementation details: Randomisation took place at period 3.	

Arms

Arm title	Assessment
Arm description: Assessment and medical tests	
Arm type	pre-randomisation
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Assessment
Started	45
Completed	45

Period 3	
Period 3 title	Visit 3
Is this the baseline period?	Yes[2]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor
Blinding implementation details: Randomisation was conducted by the Newcastle Clinical Trials Unit (NCTU) secure password-protected web based system. Patients were randomised on a 1:1 ratio to either Omeprazole 20mg twice daily or Placebo twice daily. No unblinding was required during the study.	

Arms

Are arms mutually exclusive?	Yes

Arm title	Omeprazole
Arm description:	
Omeprazole	
Arm type	Experimental
Investigational medicinal product name	Omeprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
20 mg twice daily	

Arm title	Placebo
Arm description:	
Placebo	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
One capsule, twice daily	

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: During period 1 and period 2 participants underwent tests and assessment, they were not randomised until period 3.

Number of subjects in period 3	Omeprazole	Placebo
Started	23	22
Completed	23	22

Period 4

Period 4 title	up to 90 days on Trial IMP
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomisation was conducted by the Newcastle Clinical Trials Unit (NCTU) secure password-protected web based system. Patients were randomised on a 1:1 ratio to either Omeprazole 20mg twice daily or Placebo twice daily. No unblinding was required during the study.

Arms

Are arms mutually exclusive?	Yes

Arm title	Omeprazole
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Omeprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 20 mg twice daily	
Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: One capsule, twice daily	

Number of subjects in period 4	Omeprazole	Placebo
Started	23	22
Completed	20	20
Not completed	3	2
Adverse event, serious fatal	1	-
Physician decision	2	1
Participant withdrew due to non serious AE	-	1

Period 5

Period 5 title	Visit 4
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomisation was conducted by the Newcastle Clinical Trials Unit (NCTU) secure password-protected web based system. Patients were randomised on a 1:1 ratio to either Omeprazole 20mg twice daily or Placebo twice daily. No unblinding was required during the study.

Arms

Are arms mutually exclusive?	Yes

Arm title	Omeprazole
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Omeprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 20 mg twice daily	
Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: One capsule, twice daily	

Number of subjects in period 5	Omeprazole	Placebo
Started	20	20
Completed	20	20

Period 6

Period 6 title	Visit 5
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor
Blinding implementation details: Randomisation was conducted by the Newcastle Clinical Trials Unit (NCTU) secure password-protected web based system. Patients were randomised on a 1:1 ratio to either Omeprazole 20mg twice daily or Placebo twice daily. No unblinding was required during the study.	

Arms

Are arms mutually exclusive?	Yes

Arm title	Omeprazole
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Omeprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 20 mg twice daily	
Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: One capsule, twice daily	

Number of subjects in period 6	Omeprazole	Placebo
Started	20	20
Completed	20	20

Period 7

Period 7 title	Visit 6
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor
Blinding implementation details: Randomisation was conducted by the Newcastle Clinical Trials Unit (NCTU) secure password-protected web based system. Patients were randomised on a 1:1 ratio to either Omeprazole 20mg twice daily or Placebo twice daily. No unblinding was required during the study.	

Arms

Are arms mutually exclusive?	Yes

Arm title	Omeprazole
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Omeprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 20 mg twice daily	
Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: One capsule, twice daily	

Number of subjects in period 7	Omeprazole	Placebo
Started	20	20
Completed	20	20

Baseline characteristics

Reporting groups	
Reporting group title	Omeprazole
Reporting group description: Omeprazole	
Reporting group title	Placebo
Reporting group description: Placebo	

Reporting group values	Omeprazole	Placebo	Total
Number of subjects	23	22	45
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)	2	3	5
From 65-84 years	20	18	38
85 years and over	1	1	2
Age continuous Units: years			
arithmetic mean	71.3	71	
standard deviation	± 6.7	± 7.3	-
Gender categorical Units: Subjects			
Female	4	6	10
Male	19	16	35
Ethnicity Units: Subjects			
Caucasian	23	22	45
Smoking History Units: Subjects			
Never Smoked	5	5	10
Ex-Smoker	18	16	34
Current Smoker	0	1	1
Kco Units: Subjects			
Done	23	21	44
Not done	0	1	1
Tlco Units: Subjects			
Done	23	21	44
Not done	0	1	1

6 minute walk test Units: Subjects			
Done	23	21	44
Not done	0	1	1
Number of Pack Years Units: Pack Years			
median	13	15	
full range (min-max)	0 to 74	2 to 60	-
Number of co-morbidities Units: Number			
arithmetic mean	3.6	3.2	
standard deviation	± 1.6	± 1.5	-
BMI Units: kg/m2			
arithmetic mean	28.9	29.6	
standard deviation	± 3.8	± 6	-
Blood Pressure diastolic Units: mmHg			
arithmetic mean	71	72.7	
standard deviation	± 13.4	± 9.3	-
Blood pressure systolic Units: mmHg			
arithmetic mean	120.5	126.2	
standard deviation	± 14.7	± 14.1	-
Heart Rate Units: beats per minute			
arithmetic mean	71.4	80.9	
standard deviation	± 13.4	± 12.7	-
Respiratory rate Units: per minute			
arithmetic mean	21.5	22.4	
standard deviation	± 3.5	± 3.8	-
FEV1 Units: Litres			
arithmetic mean	2.06	2.01	
standard deviation	± 0.51	± 0.6	-
FEV1 (% Predicted) Units: Percentage			
arithmetic mean	76.91	78.45	
standard deviation	± 15.42	± 18.44	-
FVC Units: Litres			
arithmetic mean	2.53	2.54	
standard deviation	± 0.68	± 0.76	-
FVC (% Predicted) Units: Percentage			
arithmetic mean	73.13	77.95	
standard deviation	± 17.12	± 17.62	-
FEV1/FVC Units: Percentage			
arithmetic mean	82	80	
standard deviation	± 5	± 13	-

Kco			
Units: mmol/min/Kpa/litre			
arithmetic mean	1.13	1.08	
standard deviation	± 0.28	± 0.26	-
Kco (% predicted)			
Units: percentage			
arithmetic mean	87.3	83	
standard deviation	± 20.94	± 22.04	-
Tlco			
Units: mmol/minute/Kpa			
arithmetic mean	4.11	3.86	
standard deviation	± 1.57	± 1.35	-
Tlco (% Predicted			
Units: Percentage			
arithmetic mean	49.52	48.43	
standard deviation	± 15.73	± 15.97	-
6 minute walk test			
Units: Metres			
median	416.5	372.5	
full range (min-max)	150 to 550	50 to 525	-
DeMeester Reflux Associated Symptom Questionnaire			
Units: Score			
arithmetic mean	0.87	1.45	
standard deviation	± 0.81	± 1.37	-
Gastrointestinal Quality of Life Index			
Units: Score			
arithmetic mean	106.3	104.77	
standard deviation	± 17.9	± 17.79	-
Leicester Cough Questionnaire			
Units: Score			
arithmetic mean	15.06	15.38	
standard deviation	± 3.23	± 3.2	-
Leicester Cough Questionnaire - Physical			
Units: Score			
arithmetic mean	5.04	5.23	
standard deviation	± 1.04	± 0.99	-
Leicester Cough Questionnaire - Psychological			
Units: score			
arithmetic mean	4.9	4.96	
standard deviation	± 1.33	± 1.25	-
Leicester Cough Questionnaire - Social			
Units: Score			
arithmetic mean	5.12	5.19	
standard deviation	± 1.06	± 1.29	-
Reflux Symptom Index Questionnaire			
Units: Score			
arithmetic mean	14.3	17.14	
standard deviation	± 9.55	± 9.02	-
Cough frequency			
Units: Coughs/Hour			

median	9.63	8.85	
inter-quartile range (Q1-Q3)	4.12 to 18.29	6.76 to 12.79	-
Daytime cough frequency Units: Coughs/hour			
median	13.38	11.59	
inter-quartile range (Q1-Q3)	6.05 to 24.26	8.51 to 17.41	-
Nightime cough frequency Units: Coughs/hour			
median	2.14	2.6	
inter-quartile range (Q1-Q3)	0.52 to 6.89	0.8 to 9.02	-
Concomitant Medications Units: Number			
arithmetic mean	7.1	7.4	
standard deviation	± 3.7	± 2.8	-

End points

End points reporting groups

Reporting group title	Assessment
Reporting group description: Assessment and medical tests	
Reporting group title	Assessment
Reporting group description: Assessment and medical tests	
Reporting group title	Omeprazole
Reporting group description: Omeprazole	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Omeprazole
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Omeprazole
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Omeprazole
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Omeprazole
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Change in 24 Cough Frequency

End point title	Change in 24 Cough Frequency
End point description:	

End point type	Primary
End point timeframe: Cough monitors returned at study visit 2 and study visit 5	

End point values	Omeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: coughs/hour				
median (full range (min-max))	-1 (-19 to 4.4)	0.8 (-27.25 to 38.58)		

Statistical analyses

Statistical analysis title	Change in cough frequency
Comparison groups	Omeprazole v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Omeprazole:Placebo (final values)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.09

Secondary: Change in DeMeester Reflux Associated Symptom Questionnaire score

End point title	Change in DeMeester Reflux Associated Symptom Questionnaire score

End point description:

End point type	Secondary

End point timeframe:

Questionnaires completed at Visit 1 and Visit 4

End point values	Omeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Score				
median (full range (min-max))	0 (-2 to 3)	0 (-2 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Gastrointestinal quality of life index score

End point title	Change in Gastrointestinal quality of life index score

End point description:

End point type	Secondary

End point timeframe:

Questionnaires completed at visit 1 and visit 4

End point values	Omeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Score				
median (full range (min-max))	4.5 (-33 to 25)	-0.5 (-32 to 22)		

Statistical analyses

Statistical analysis title	Change in GIQIL score
Comparison groups	Omeprazole v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[1]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	11.49

Notes:

[1] - Descriptive

Secondary: Change in Leicester Cough Questionnaire Score

End point title	Change in Leicester Cough Questionnaire Score

End point description:

End point type	Secondary

End point timeframe:

Questionnaires completed at visit 1 and visit 4

End point values	Omeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Score				
median (full range (min-max))	-0.29 (-5.61 to 5.34)	-0.9 (-7.27 to 9.32)		

Statistical analyses

Statistical analysis title	Change in LCQ score
Comparison groups	Omeprazole v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.19
upper limit	1.98

Notes:

[2] - Descriptive

Secondary: Change in Reflux Symptom Index Score

End point title	Change in Reflux Symptom Index Score

End point description:

End point type	Secondary

End point timeframe:

Questionnaires completed at visit 1 and visit 4

End point values	Omeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Score				
median (full range (min-max))	0 (-11 to 21)	1 (-25 to 14)		

Statistical analyses

Statistical analysis title	Change in RSI score
Comparison groups	Omeprazole v Placebo

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[3]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.77
upper limit	6.11

Notes:
[3] - Descriptive

Secondary: Change in Six Minute Walk Test distance

End point title	Change in Six Minute Walk Test distance

End point description:

End point type	Secondary

End point timeframe:
6MWT completed at visit 1 and visit 4

End point values	Omeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: Metres				
median (full range (min-max))	-10 (-225 to 62.6)	0 (-73.1 to 102)		

Statistical analyses

Statistical analysis title	Change in 6MWT distance
Comparison groups	Omeprazole v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other[4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-30.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-68.86
upper limit	8.13

Notes:
[4] - Descriptive

Secondary: Change in percentage predicted FVC

End point title	Change in percentage predicted FVC

End point description:

End point type	Secondary

End point timeframe:
Lung function tests performed at visit 1 and visit 4

End point values	Omeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: % Predicted				
median (full range (min-max))	-2 (-27 to 5)	0.5 (-4 to 14)		

Statistical analyses

Statistical analysis title	Change in % Predicted FVC
Comparison groups	Omeprazole v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[5]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.39
upper limit	-0.8

Notes:
[5] - Descriptive

Secondary: Change in precentage predicted TLCO

End point title	Change in precentage predicted TLCO

End point description:

End point type	Secondary

End point timeframe:
Lung function tests performed at visit 1 and visit 4

End point values	Omeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: % Predicted				
median (full range (min-max))	-2 (-14 to 17)	-5.5 (-12 to 16)		

Statistical analyses

Statistical analysis title	Change in % predicted TLCO
Comparison groups	Omeprazole v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[6]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.06
upper limit	7.98

Notes:

[6] - Descriptive

Secondary: Change in percentage predicted FEV1

End point title	Change in percentage predicted FEV1

End point description:

End point type	Secondary

End point timeframe:

Lung function tests performed at visit 1 and visit 4

End point values	Omeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: % Predicted				
median (full range (min-max))	-1 (-19 to 7)	2 (-3 to 63)		

Statistical analyses

Statistical analysis title	Change in % predicted FEV1
Comparison groups	Omeprazole v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[7]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.59
upper limit	-0.2

Notes:

[7] - Descriptive

Secondary: Change in percentage predicted KCO

End point title	Change in percentage predicted KCO

End point description:

End point type	Secondary

End point timeframe:

Lung function tests performed at visit 1 and visit 4

End point values	Omeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: % Predicted				
median (full range (min-max))	4 (-22 to 42)	-8.5 (-17 to 24)		

Statistical analyses

Statistical analysis title	Change in % predicted KCO
Comparison groups	Omeprazole v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[8]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	9.26

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	17.58

Notes:

[8] - Descriptive

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the baseline visit, through to visit 6.

Assessment type	Systematic

Dictionary used

Dictionary name	As reported
Dictionary version	1.0

Reporting groups

Reporting group title	Omeprazole
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Omeprazole	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 23 (17.39%)	4 / 22 (18.18%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung Neoplasm malignant	Additional description: New diagnosis – lung cancer.		
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Ischemia	Additional description: Hospital Admission – Right Ischaemic Leg		
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 23 (4.35%)	2 / 22 (9.09%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary fibrosis			

subjects affected / exposed	1 / 23 (4.35%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Cellulitis	Additional description: Hospital Admission cellulitis with possible chest infection		
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 23 (4.35%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis	Additional description: Hospital admission with Sepsis, likely related to skin		
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (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: 0 %

Non-serious adverse events	Omeprazole	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 23 (52.17%)	13 / 22 (59.09%)	
Injury, poisoning and procedural complications			
Back Injury			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	3	0	
Headache			

subjects affected / exposed	0 / 23 (0.00%)	4 / 22 (18.18%)	
occurrences (all)	0	5	
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	0 / 23 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Local swelling			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Oedema			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 23 (8.70%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
Acid reflux			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	4	
Diarrhoea			
subjects affected / exposed	1 / 23 (4.35%)	2 / 22 (9.09%)	
occurrences (all)	1	5	
Dyspepsia			
subjects affected / exposed	1 / 23 (4.35%)	3 / 22 (13.64%)	
occurrences (all)	1	9	
Gastric ulcer			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Salivary gland calculus			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Vomiting			

subjects affected / exposed	2 / 23 (8.70%)	4 / 22 (18.18%)	
occurrences (all)	3	10	
Constipation			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 23 (13.04%)	1 / 22 (4.55%)	
occurrences (all)	3	1	
Cough Syncope			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	0 / 23 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	5	
Oropharyngeal pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
sore throat			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			

Influenza			
subjects affected / exposed	1 / 23 (4.35%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Lower respiratory tract infection			
subjects affected / exposed	5 / 23 (21.74%)	2 / 22 (9.09%)	
occurrences (all)	5	2	
Urinary tract infection			
subjects affected / exposed	2 / 23 (8.70%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 23 (4.35%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 January 2014	Substantial Amendment 3 (Substantial Amendments 1 and 2 were submitted prior to MHRA and REC approval for the trial). The following documents were updated: Protocol updated to v3.0 20/11/2013 Study documents updated: GP/Information sheets v1.1 20/11/2013, Informed Consent Form v1.1, 20/11/2013, Patient Diary Card v1.0 06/12/2013, Patient Information Sheet v1.1 20/11/2013, Participant Consent Form: Discontinuation of medication v1.1 20/11/2013. This amendment was to clarify certain sections in the protocol in greater detail, such as: patient recruitment, statistical analysis, pharmacovigilance, reporting of adverse events during the study period. This amendment was given favourable REC opinion on: 10/01/2014 This was granted MHRA approval on: 15/01/2014 This amendment was to clarify certain sections in the protocol in greater detail, such as: patient recruitment, statistical analysis, pharmacovigilance, reporting of adverse events during the study period. This was submitted to REC on: 16/12/2013 and granted approval on: 10/01/2014 This was submitted to the MHRA on: 16/12/2013 and granted approval on: 15/01/2014
02 September 2014	Substantial Amendment 4 The following documents were updated: Participant consent form 2.0 03/07/2014, Participant consent form: discontinuation of medication v2.0 03/07/2014, Participant Information Sheet v2.0 03/07/2014. Production specification 2013-5 Revision B This amendment was to update documents in line with the Data Monitoring Committee recommendations. This amendment was given favourable REC opinion on: 26/08/2014 This was granted MHRA approval on: 02/09/2014
18 August 2016	Substantial Amendment 5 The following documents were updated: Participant consent form v3.1 05/08/2016, Participant consent form v3.1 05/08/2016, Participant Information Sheet v3.1 07/03/2016. SmPC v07 15/12/2015. This amendment was to update the Reference Safety Information for the trial, update the study end date and update documents in line with staff changes on the Trial. The details regarding the randomisation system and study unblinding information were updated as part of this amendment. A number of minor clerical errors were corrected and the Sponsor contact name in IRAS has been changed in line with staff changes. Sections 7.3, 3.5 and 5.3 of the protocol were updated to give greater clarity and new information. The PIS was updated in line with withdrawal information and Nintedanib was added as active trial of treatment in exclusion criteria. This amendment was given favourable REC opinion on: 26/08/2014 This was granted MHRA approval on: 18/08/2016

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported