



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

| | |
|-----------------|-------------------------------------|
| End point title | Change in percentage 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 occurrences (all) | 0 / 23 (0.00%) 0 | 4 / 22 (18.18%) 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 occurrences (all) | 2 / 23 (8.70%) 3 | 4 / 22 (18.18%) 10 | |
| Constipation subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 3 / 23 (13.04%) 3 | 1 / 22 (4.55%) 1 | |
| Cough Syncope subjects affected / exposed occurrences (all) | 1 / 23 (4.35%) 1 | 0 / 22 (0.00%) 0 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 2 / 22 (9.09%) 5 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| sore throat subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Psychiatric disorders Depression subjects affected / exposed occurrences (all) | 1 / 23 (4.35%) 1 | 0 / 22 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Muscle spasms subjects affected / exposed occurrences (all) | 0 / 23 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 1 / 23 (4.35%) 1 | 0 / 22 (0.00%) 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 | <p>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.</p> <p>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</p> <p>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</p> |
| 02 September 2014 | <p>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</p> <p>This amendment was to update documents in line with the Data Monitoring Committee recommendations.</p> <p>This amendment was given favourable REC opinion on: 26/08/2014 This was granted MHRA approval on: 02/09/2014</p> |
| 18 August 2016 | <p>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.</p> <p>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.</p> <p>This amendment was given favourable REC opinion on: 26/08/2014 This was granted MHRA approval on: 18/08/2016</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported