



Clinical trial results: Improving Inhaler Treatment and Small Airways Assessment in Chronic Obstructive Pulmonary Disease

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2011-005544-10 |
| Trial protocol | GB |
| Global end of trial date | 27 November 2017 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 19 October 2019 |
| First version publication date | 19 October 2019 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | NIHRCDF |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01721291 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Imperial College London |
| Sponsor organisation address | South Kensington Campus, London, United Kingdom, SW7 2AZ |
| Public contact | Dr Omar Usmani, National Heart & Lung Institute, +44 20 7351 8051, o.usmani@imperial.ac.uk |
| Scientific contact | Dr Omar Usmani, National Heart & Lung Institute, +44 20 7351 8051, o.usmani@imperial.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 | 27 November 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 November 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 November 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

What is the lung deposition behaviour of inhaled bronchodilator (salbutamol) aerosols of different particle size within the airways of patients with chronic obstructive pulmonary disease (COPD)? How does this distribution compare to that observed in healthy subjects with no lung disease?

Protection of trial subjects:

no protection

Background therapy:

no background therapy

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 01 October 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 65 |
| Worldwide total number of subjects | 65 |
| EEA total number of subjects | 65 |

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) | 34 |
| From 65 to 84 years | 31 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were recruited at Royal Brompton Hospital, London between 01.10.2012 and 27.11.2017

Pre-assignment

Screening details:

A total numbers of 70 participants were screened for eligibility, of whom were 65 randomized, the remaining 5 participant were excluded due to not meeting inclusion criteria. The study had two term, first was the deposition study with healthy and COPD patients, second part was the lung physiology study with COPD and Asthmatic patients.

Period 1

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | COPD 1. |

Arm description:

COPD patients

| | |
|--|---------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Salbutamol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Visit1 - 1.5um particle 30ug slow, Visit2 - 1.5um particle 30ug fast, Visit3 - 3um particle 30ug slow, Visit4 - 3um particle 30ug fast, Visit5 - 6um particle 30ug slow, Visit6 - 6um particle 30ug fast, Visit7 - pMDI 200ug slow.

| | |
|------------------|---------|
| Arm title | Healthy |
|------------------|---------|

Arm description:

Healthy participant

| | |
|--|---------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Salbutamol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Visit1 - 1.5um particle 30ug slow, Visit2 - 1.5um particle 30ug fast, Visit3 - 3um particle 30ug slow, Visit4 - 3um particle 30ug fast, Visit5 - 6um particle 30ug slow, Visit6 - 6um particle 30ug fast, Visit7 - pMDI 200ug slow.

| | |
|------------------|---------|
| Arm title | COPD 2. |
|------------------|---------|

Arm description:

COPD patients

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|---------------------|
| Investigational medicinal product name | Salbutamol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Visit1 - 1.5um particle 15ug, Visit2 - 1.5um particle 30ug, Visit3 - 3um particle 15ug, Visit4 - 3um particle 30ug , Visit5 - 6um particle 15ug, Visit6 - 6um particle 30ug, Visit7 - pMDI 200ug.

| | |
|------------------|-----------|
| Arm title | Asthmatic |
|------------------|-----------|

Arm description:

Asthmatic

| | |
|--|---------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Salbutamol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Visit1 - 1.5um particle 15ug, Visit2 - 1.5um particle 30ug, Visit3 - 3um particle 15ug, Visit4 - 3um particle 30ug , Visit5 - 6um particle 15ug, Visit6 - 6um particle 30ug, Visit7 - pMDI 200ug.

| Number of subjects in period 1 | COPD 1. | Healthy | COPD 2. |
|---------------------------------------|---------|---------|---------|
| Started | 14 | 12 | 26 |
| Completed | 12 | 12 | 26 |
| Not completed | 2 | 0 | 0 |
| Consent withdrawn by subject | 1 | - | - |
| did not like the treatment | 1 | - | - |

| Number of subjects in period 1 | Asthmatic |
|---------------------------------------|-----------|
| Started | 13 |
| Completed | 12 |
| Not completed | 1 |
| Consent withdrawn by subject | 1 |
| did not like the treatment | - |

Baseline characteristics

Reporting groups

| | |
|------------------------------|-----------|
| Reporting group title | COPD 1. |
| Reporting group description: | |
| COPD patients | |
| Reporting group title | Healthy |
| Reporting group description: | |
| Healthy participant | |
| Reporting group title | COPD 2. |
| Reporting group description: | |
| COPD patients | |
| Reporting group title | Asthmatic |
| Reporting group description: | |
| Asthmatic | |

| Reporting group values | COPD 1. | Healthy | COPD 2. |
|--------------------------------|--------------|--------------|--------------|
| Number of subjects | 14 | 12 | 26 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 5 | 5 | 12 |
| From 65-84 years | 9 | 7 | 14 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 66.08 | 64.08 | 64.5 |
| full range (min-max) | 56 to 77 | 50 to 76 | 58 to 79 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 8 | 5 | 17 |
| Male | 6 | 7 | 9 |
| Force experation in 1s (FEV1) | | | |
| Units: litre(s) | | | |
| arithmetic mean | 1.63 | 2.55 | 1.46 |
| full range (min-max) | 0.97 to 2.24 | 1.55 to 3.76 | 0.71 to 2.13 |

| Reporting group values | Asthmatic | Total | |
|------------------------|-----------|-------|--|
| Number of subjects | 13 | 65 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 12 | 34 | |
| From 65-84 years | 1 | 31 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 40.4 | - | |
| full range (min-max) | 19 to 66 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 8 | 38 | |
| Male | 5 | 27 | |

| | | | |
|--------------------------------|-------------|---|--|
| Force experation in 1s (FEV1) | | | |
| Units: litre(s) | | | |
| arithmetic mean | 2.85 | | |
| full range (min-max) | 2.03 to 3.9 | - | |

End points

End points reporting groups

| | |
|--|---------------------|
| Reporting group title | COPD 1. |
| Reporting group description: COPD patients | |
| Reporting group title | Healthy |
| Reporting group description: Healthy participant | |
| Reporting group title | COPD 2. |
| Reporting group description: COPD patients | |
| Reporting group title | Asthmatic |
| Reporting group description: Asthmatic | |
| Subject analysis set title | Healthy_1.5 um slow |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Healthy participants with treatment of 1.5 um Salbutamol | |
| Subject analysis set title | Healthy_1.5 um fast |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Healthy participants with treatment of 1.5 um Salbutamol fast | |
| Subject analysis set title | COPD_1.5 um slow |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: COPD participants with treatment of 1.5 um Salbutamol | |
| Subject analysis set title | COPD_1.5 um fast |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: COPD participants with treatment of 1.5 um Salbutamol fast | |
| Subject analysis set title | Healthy_3 um slow |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Healthy participants with treatment of 3 um Salbutamol slow | |
| Subject analysis set title | Healthy_3 um fast |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Healthy participants with treatment of 3 um Salbutamol fast | |
| Subject analysis set title | COPD_3 um slow |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: COPD with treatment of 3 um Salbutamol slow | |
| Subject analysis set title | COPD_3 um fast |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: COPD participants with treatment of 3 um Salbutamol fast | |
| Subject analysis set title | Healthy_6 um slow |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Healthy participants with treatment of 6 µm Salbutamol slow

| | |
|----------------------------|--------------------|
| Subject analysis set title | COPD_6 µm fast |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Healthy participants with treatment of 6 µm Salbutamol fast

| | |
|----------------------------|--------------------|
| Subject analysis set title | COPD_6 µm slow |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

COPD participants with treatment of 6 µm Salbutamol slow

| | |
|----------------------------|--------------------|
| Subject analysis set title | Healthy_6 µm fast |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Healthy participants with treatment of 6 µm Salbutamol fast

| | |
|----------------------------|--------------------|
| Subject analysis set title | COPD_1.5µm, 15ug |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

COPD participants with treatment of 15 ug Salbutamol

| | |
|----------------------------|--------------------|
| Subject analysis set title | COPD_1.5µm, 30ug |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

COPD participants with treatment of 1.5µm, 30 ug Salbutamol

| | |
|----------------------------|--------------------|
| Subject analysis set title | COPD_3µm, 15 ug |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

COPD participants with treatment of 3µm, 15 ug Salbutamol

| | |
|----------------------------|--------------------|
| Subject analysis set title | COPD_3µm, 30 ug |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

COPD participants with treatment of 3µm, 30 ug Salbutamol

| | |
|----------------------------|--------------------|
| Subject analysis set title | COPD_6µm, 15 ug |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

COPD participants with treatment of 6µm, 15 ug Salbutamol

| | |
|----------------------------|--------------------|
| Subject analysis set title | COPD_6µm,30 ug |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

COPD participants with treatment of 6µm, 30 ug Salbutamol

| | |
|----------------------------|--------------------|
| Subject analysis set title | COPD_pMDI |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participant treatment with pMDI and Salbutamol

| | |
|----------------------------|------------------------|
| Subject analysis set title | Asthmatics_1.5µm, 15ug |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Asthmatics participants with treatment of 1.5µm, 15 ug Salbutamol

| | |
|----------------------------|------------------------|
| Subject analysis set title | Asthmatics_1.5µm, 30ug |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Asthmatics participants with treatment of 1.5µm, 30 ug Salbutamol

| | |
|----------------------------|----------------------|
| Subject analysis set title | Asthmatics_3µm, 15ug |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Asthmatics participants with treatment of 3um, 15 ug Salbutamol

| | |
|----------------------------|----------------------|
| Subject analysis set title | Asthmatics_3um, 30ug |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Asthmatics participants with treatment of 3um, 30 ug Salbutamol

| | |
|----------------------------|----------------------|
| Subject analysis set title | Asthmatics_6um, 15ug |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Asthmatics participants with treatment of 6um, 15 ug Salbutamol

| | |
|----------------------------|----------------------|
| Subject analysis set title | Asthmatics_6um, 30ug |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Asthmatics participants with treatment of 6um, 15 ug Salbutamol

| | |
|----------------------------|--------------------|
| Subject analysis set title | Asthmatics_pMDI |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Asthmatics participants with treatment of pMDI and Salbutamol

Primary: Penetration index

| | |
|-----------------|-------------------|
| End point title | Penetration index |
|-----------------|-------------------|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

5min

| End point values | Healthy_1.5 um slow | Healthy_1.5 um fast | COPD_1.5 um slow | COPD_1.5 um fast |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 12 | 12 |
| Units: ratio | | | | |
| arithmetic mean (standard deviation) | 0.8 (± 0.08) | 0.72 (± 0.12) | 0.69 (± 0.13) | 0.58 (± 0.14) |

| End point values | Healthy_3 um slow | Healthy_3 um fast | COPD_3 um slow | COPD_3 um fast |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 12 | 12 |
| Units: ratio | | | | |
| arithmetic mean (standard deviation) | 0.75 (± 0.11) | 0.63 (± 0.15) | 0.65 (± 0.18) | 0.48 (± 0.16) |

| End point values | Healthy_6 um slow | COPD_6 um fast | COPD_6 um slow | Healthy_6 um fast |
|------------------|-------------------|----------------|----------------|-------------------|
|------------------|-------------------|----------------|----------------|-------------------|

| | | | | |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 12 | 12 |
| Units: ratio | | | | |
| arithmetic mean (standard deviation) | 0.51 (\pm 0.1) | 0.46 (\pm 0.04) | 0.37 (\pm 0.12) | 0.32 (\pm 0.08) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Comparisons of Penetration Index for COPD |
| Comparison groups | COPD_1.5 um slow v COPD_1.5 um fast v COPD_3 um slow v COPD_3 um fast v COPD_6 um fast v COPD_6 um slow |
| Number of subjects included in analysis | 72 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Confidence interval | |
| level | 95 % |
| sides | 1-sided |
| lower limit | -0.0489 |
| upper limit | 0.2739 |
| Variability estimate | Standard deviation |

Primary: Multi-breath nitrogen washout (MBNW) indices of conducting airways (Scnd)

| | |
|-----------------|--|
| End point title | Multi-breath nitrogen washout (MBNW) indices of conducting airways (Scnd) ^[1] |
|-----------------|--|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

120min

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis has been performed on this endpoint.

| | | | | |
|--|----------------------|-----------------------|------------------------|------------------------|
| End point values | COPD_1.5 um slow | COPD_1.5 um fast | COPD_3 um slow | COPD_3 um fast |
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 12 | 12 |
| Units: litre(s) -1 | | | | |
| arithmetic mean (full range (min-max)) | 0.047 (0 to 0.089) | 0.04 (0.011 to 0.089) | 0.047 (0.022 to 0.069) | 0.044 (0.011 to 0.078) |

| | | | | |
|-------------------------|-----------|-----------|--|--|
| End point values | COPD_6 um | COPD_6 um | | |
|-------------------------|-----------|-----------|--|--|

| | fast | slow | | |
|--|------------------------|------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 12 | | |
| Units: litre(s) -1 | | | | |
| arithmetic mean (full range (min-max)) | 0.047 (0.011 to 0.089) | 0.045 (0.022 to 0.078) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Multi-breath nitrogen washout (MBNW) indices of acinar airways (Sacin)

| | |
|------------------------|--|
| End point title | Multi-breath nitrogen washout (MBNW) indices of acinar airways (Sacin) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 120min | |

| End point values | COPD_1.5 um slow | COPD_1.5 um fast | COPD_3 um slow | COPD_3 um fast |
|--|-----------------------|------------------------|------------------------|------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 12 | 12 |
| Units: litre(s) -1 | | | | |
| arithmetic mean (full range (min-max)) | 0.462 (0.229 to 1.27) | 0.508 (0.179 to 0.734) | 0.471 (0.158 to 1.534) | 0.437 (0.198 to 1.090) |

| End point values | COPD_6 um fast | COPD_6 um slow | Healthy_6 um fast | |
|--|------------------------|------------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 12 | 12 | 12 | |
| Units: litre(s) -1 | | | | |
| arithmetic mean (full range (min-max)) | 0.487 (0.163 to 1.365) | 0.426 (0.170 to 0.949) | 0 (0 to 0) | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Multi-breath nitrogen washout indices (Sacin) |
| Comparison groups | COPD_1.5 um slow v COPD_1.5 um fast v COPD_3 um slow v COPD_3 um fast v COPD_6 um fast v COPD_6 um slow v Healthy_6 um fast |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 84 |
| Analysis specification | Post-hoc |
| Analysis type | superiority ^[2] |
| P-value | < 0.05 ^[3] |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Confidence interval | |
| sides | 1-sided |
| Variability estimate | Standard deviation |

Notes:

[2] - 2-way ANOVA

[3] - No significance was found between any of the parameters

Adverse events

Adverse events information

Timeframe for reporting adverse events:

6 months

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|-----------|
| Dictionary name | SNOMED CT |
|-----------------|-----------|

| | |
|--------------------|----|
| Dictionary version | 10 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | COPD 1. |
|-----------------------|---------|

Reporting group description:

COPD patients

| | |
|-----------------------|---------|
| Reporting group title | Healthy |
|-----------------------|---------|

Reporting group description:

Healthy participant

| | |
|-----------------------|---------|
| Reporting group title | COPD 2. |
|-----------------------|---------|

Reporting group description:

COPD patients

| | |
|-----------------------|-----------|
| Reporting group title | Asthmatic |
|-----------------------|-----------|

Reporting group description:

Asthmatic

| Serious adverse events | COPD 1. | Healthy | COPD 2. |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 26 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | Asthmatic | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

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

| Non-serious adverse events | COPD 1. | Healthy | COPD 2. |
|---|-----------------|----------------|----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 12 (50.00%) | 0 / 12 (0.00%) | 2 / 26 (7.69%) |
| Surgical and medical procedures | | | |
| Hernia operation | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cataract operation | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cardiac disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 1 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Pulled muscle | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Chest infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sore throat | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |

| Non-serious adverse events | Asthmatic | | |
|---|----------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| Surgical and medical procedures | | | |
| Hernia operation | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cataract operation | | | |

| | | | |
|---|--|--|--|
| subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | | |
| Cardiac disorders Hypertension subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | | |
| Musculoskeletal and connective tissue disorders Pulled muscle subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | | |
| Infections and infestations Chest infection subjects affected / exposed occurrences (all) Sore throat subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|---|
| 29 May 2013 | AMENDMENTS made to Protocol (Flow chart), PIS and Consent form |
| 07 August 2015 | Amendments to GP letter, Protocol Flow chart) PIS and Consent form |
| 11 April 2016 | The request relates to an extension to the current ethics approval to be extended to 31st March 2017. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported