



Clinical trial results:

Proof of concept study to evaluate single and chronic dosing effects of ultra-long acting bronchodilator therapy on mannitol challenge in asthmatic patients taking inhaled corticosteroids

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-001953-28 |
| Trial protocol | GB |
| Global end of trial date | 15 July 2016 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 29 July 2017 |
| First version publication date | 29 July 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 2012RC15 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02039011 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University of Dundee - NHS Tayside |
| Sponsor organisation address | Residency Block, Level 3, Ninewells Hospital, George Pirie Way, Dundee, United Kingdom, DD1 9SY |
| Public contact | Professor Brian Lipworth, Scottish Centre for Respiratory Research, 44 01382 383188, b.j.lipworth@dundee.ac.uk |
| Scientific contact | Professor Brian Lipworth, Scottish Centre for Respiratory Research, 44 01382 383188, b.j.lipworth@dundee.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 | 15 July 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 July 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 July 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare first and last dose protection against mannitol challenge for indacaterol alone versus indacaterol plus tiotropium given once daily as add-on therapy to pre-existing inhaled corticosteroids.

Protection of trial subjects:

The study was approved the Tayside committee for medical ethics (reference: 13/ES/0072) and full informed consent was obtained from all patients. Participants were only selected if they fulfilled the pre-determined inclusion criteria. Medical histories were obtained and physical examinations conducted prior to randomisation into the study, and a medically qualified person confirmed that it was safe for participants to receive the study drug. A screening blood sample was taken at screening with tests appropriate to the risk of the study. An emergency card was issued to each subject, detailing the study, the Chief Investigator, the drug under investigation and emergency contact numbers. An emergency mobile was kept 24 hours a day by the study doctor, and participants were advised to phone if they felt that their asthma was worsening during the step-down/run-in period. Only subjects deemed clinically stable were recruited into the study. They received a written PIS detailing the trial requirements and the extent of their participation before attending for a screening visit. They had the PIS for at least 24 hours and were encouraged to discuss the study and their potential involvement with both study staff and others, such as family and friends. If participant becomes clinically unstable as assessed by the study physician then they will revert to their usual asthma medication and be withdrawn from the study. A pre-Sponsorship study risk assessment was carried out by the TASC Research Governance Manager prior to Sponsorship approval being granted.

Background therapy:

After initial screening, any LABA therapy was first withdrawn for 2 weeks followed by halving the ICS dose, to a minimum of 400µg/day (as beclometasone equivalent dose). If patients were on secondary controllers such as leukotriene receptor antagonists, these were also stopped. Participants then entered a 2 week run in on this dose of ICS, which was then continued throughout the study.

Evidence for comparator:

Tiotropium (TIO) is a long acting muscarinic antagonists (LAMA), which is functionally selective for the post junctional M3 muscarinic receptor, found on airway smooth muscle. TIO reduces asthma exacerbations by 21% in patients when used as add on therapy in patients receiving inhaled corticosteroids and long-acting beta-agonists (ICS/LABA). TIO exhibits only modest improvements in FEV1, which amounts to approximately 100ml at trough, which is less than the minimally important difference of 230ml. It is therefore hard to explain the protective effect on exacerbations on solely the basis of this small improvement in airway calibre alone.

No studies have looked at effects of TIO on AHR assessed by bronchial challenge using non cholinergic agents. One study showed that as expected TIO produced prolonged functional antagonism of M3 mediated smooth muscle constriction induced by the cholinergic agonist methacholine. As TIO is only currently indicated as add-on therapy to ICS/LABA, the objective of this study was to evaluate the impact of adding TIO to ICS/LABA on AHR, in patients with persistent asthma and whether TIO might also prevent against LABA induced subsensitivity. We chose an indirect bronchial challenge, namely mannitol, as this is thought to more closely reflect physiological stimuli and acts by release of pro-inflammatory mediators. Moreover mannitol challenge has been shown to be related to an inflammatory phenotype in asthma.

| | |
|---|---------------|
| Actual start date of recruitment | 24 March 2014 |
| 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: 39 |
| Worldwide total number of subjects | 39 |
| EEA total number of subjects | 39 |

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 | 5 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from March 2014 to May 2016. Of the 39 patients screened, 18 were randomised, and 14 completed per protocol.

Pre-assignment

Screening details:

Males & females, non-smokers, >18 years, persistent asthma on ICS or ICS/LABA, FEV1 >50% predicted, mannitol responsive, no chest infections or oral steroids in the last 3 months. After screening, LABAs were stopped for 2 weeks, then ICS dose halved to a minimum of 400µg/day BDP, which continued throughout study. Secondary controllers were stopped.

Pre-assignment period milestones

| | |
|--|---------------------|
| Number of subjects started | 39 |
| Intermediate milestone: Number of subjects | Screening Visit: 39 |
| Number of subjects completed | 18 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|--------------------------------------|
| Reason: Number of subjects | Did not meet inclusion criteria: 17 |
| Reason: Number of subjects | Inability to comply with protocol: 4 |

Period 1

| | |
|------------------------------|---------------------------------------|
| Period 1 title | Randomised Treatment (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | No |
| Arm title | INDACATEROL |

Arm description:

Patients received 4 weeks of indacaterol (Onbrez Breezhaler) alone at a dose of 150µg OD as add-on to pre-existing ICS.

There was a 2 week washout in between treatments while continuing to take the same dose of ICS.

Including screening, there were 7 visits in total. Visits were performed, in the mornings, at baseline after run-in and washout, and at 24 hours (i.e. trough) after the first and last doses of each randomised treatment period. Patients were allowed short acting beta-2 agonists (SABAs) as a reliever during the study, but were asked to abstain from SABA use at least 6 hours before each visit. The visits were conducted in the mornings (8am-10am).

Cross-over design – Participants received both IMPs (participated in both arms) during the course of the study

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Indacaterol |
| Investigational medicinal product code | |
| Other name | Onbrez Breezhaler |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Inhalation use |

Dosage and administration details:

Indacaterol (Onbrez Breezhaler) 150µg OD was taken for 4 weeks.

| | |
|------------------|--------------------------|
| Arm title | TIOTROPIUM + INDACATEROL |
|------------------|--------------------------|

Arm description:

Patients received 4 weeks of indacaterol (Onbrez Breezhaler) at a dose of 150µg OD, combined with tiotropium (Spiriva Handihaler) 18µg OD as add-on to pre-existing ICS.

There was a 2 week washout in between treatments while continuing to take the same dose of ICS.

Including screening, there were 7 visits in total. Visits were performed, in the mornings, at baseline after run-in and washout, and at 24 hours (i.e. trough) after the first and last doses of each randomised treatment period. Patients were allowed short acting beta-2 agonists (SABAs) as a reliever during the study, but were asked to abstain from SABA use at least 6 hours before each visit. The visits were conducted in the mornings (8am-10am).

Cross-over design – Participants received both IMPs (participated in both arms) during the course of the study

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tiotropium |
| Investigational medicinal product code | |
| Other name | Spiriva Handihaler |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Inhalation use |

Dosage and administration details:

Tiotropium (Spiriva Handihaler) 18µg OD was taken for 4 weeks.

| | |
|--|-------------------|
| Investigational medicinal product name | Indacaterol |
| Investigational medicinal product code | |
| Other name | Onbrez Breezhaler |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Inhalation use |

Dosage and administration details:

Indacaterol (Onbrez Breezhaler) 150µg OD was taken for 4 weeks.

| Number of subjects in period 1 | INDACATEROL | TIOTROPIUM + INDACATEROL |
|---------------------------------------|-------------|--------------------------|
| Started | 18 | 17 |
| Completed | 15 | 17 |
| Not completed | 3 | 0 |
| Adverse event, non-fatal | 2 | - |
| Protocol deviation | 1 | - |

Baseline characteristics

Reporting groups^[1]

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Randomised Treatment (overall period) |
|-----------------------|---------------------------------------|

Reporting group description:

Inclusion Criteria: Non-smoking male or female patients, aged at least 18 years, with persistent asthma already receiving ICS or ICS/LABA. Minimum FEV1 of > 50% predicted, and mannitol responsive (i.e., provocative dose required to reduce FEV1 by 15% (PD15) <635 mg.

Exclusion Criteria: History of respiratory tract infection or oral corticosteroid use in the last three months prior to screening.

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: The worldwide number enrolled is the number of subjects screened into the study (39).

The number of subjects in the baseline period is the number who were then randomised into the study (18).

Of these 18 subjects, 14 completed both arms of the cross-over trial and were able to be analysed.

| Reporting group values | Randomised Treatment (overall period) | Total | |
|--|---------------------------------------|-------|--|
| Number of subjects | 18 | 18 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 17 | 17 | |
| From 65-84 years | 1 | 1 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 48 | | |
| standard deviation | ± 15 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 12 | 12 | |
| Male | 6 | 6 | |

Subject analysis sets

| | |
|----------------------------|--------------------|
| Subject analysis set title | Completed Subjects |
|----------------------------|--------------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Inclusion Criteria: Non-smoking male or female patients, aged at least 18 years, with persistent asthma already receiving ICS or ICS/LABA. Minimum FEV1 of > 50% predicted, and mannitol responsive (i.e., provocative dose required to reduce FEV1 by 15% (PD15) <635 mg.

Exclusion Criteria: History of respiratory tract infection or oral corticosteroid use in the last three months prior to screening.

| Reporting group values | Completed Subjects | | |
|---|--------------------|--|--|
| Number of subjects | 14 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 13 | | |
| From 65-84 years | 1 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 46 | | |
| standard deviation | ± 15 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 9 | | |
| Male | 5 | | |

End points

End points reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | INDACATEROL |
|-----------------------|-------------|

Reporting group description:

Patients received 4 weeks of indacaterol (Onbrez Breezhaler) alone at a dose of 150µg OD as add-on to pre-existing ICS.

There was a 2 week washout in between treatments while continuing to take the same dose of ICS.

Including screening, there were 7 visits in total. Visits were performed, in the mornings, at baseline after run-in and washout, and at 24 hours (i.e. trough) after the first and last doses of each randomised treatment period. Patients were allowed short acting beta-2 agonists (SABAs) as a reliever during the study, but were asked to abstain from SABA use at least 6 hours before each visit. The visits were conducted in the mornings (8am-10am).

Cross-over design – Participants received both IMPs (participated in both arms) during the course of the study

| | |
|-----------------------|--------------------------|
| Reporting group title | TIOTROPIUM + INDACATEROL |
|-----------------------|--------------------------|

Reporting group description:

Patients received 4 weeks of indacaterol (Onbrez Breezhaler) at a dose of 150µg OD, combined with tiotropium (Spiriva Handihaler) 18µg OD as add-on to pre-existing ICS.

There was a 2 week washout in between treatments while continuing to take the same dose of ICS.

Including screening, there were 7 visits in total. Visits were performed, in the mornings, at baseline after run-in and washout, and at 24 hours (i.e. trough) after the first and last doses of each randomised treatment period. Patients were allowed short acting beta-2 agonists (SABAs) as a reliever during the study, but were asked to abstain from SABA use at least 6 hours before each visit. The visits were conducted in the mornings (8am-10am).

Cross-over design – Participants received both IMPs (participated in both arms) during the course of the study

| | |
|----------------------------|--------------------|
| Subject analysis set title | Completed Subjects |
|----------------------------|--------------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Inclusion Criteria: Non-smoking male or female patients, aged at least 18 years, with persistent asthma already receiving ICS or ICS/LABA. Minimum FEV1 of > 50% predicted, and mannitol responsive (i.e., provocative dose required to reduce FEV1 by 15% (PD15) <635 mg.

Exclusion Criteria: History of respiratory tract infection or oral corticosteroid use in the last three months prior to screening.

Primary: Mannitol PD15 (mg)

| | |
|-----------------|--------------------|
| End point title | Mannitol PD15 (mg) |
|-----------------|--------------------|

End point description:

single dose vs chronic dosing

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

End point timeframe:

1 day to 28 days

| End point values | INDACATEROL | TIOTROPIUM + INDACATEROL | | |
|---|------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 14 | | |
| Units: mg | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| baseline | 390 (291 to 521) | 390 (291 to 521) | | |
| single | 537 (438 to 619) | 487 (329 to 624) | | |
| chronic | 455 (342 to 606) | 388 (255 to 593) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | per protocol |
| Statistical analysis description: | |
| The study was powered at 80% to detect a minimal important difference of one doubling dose in mannitol PD 15 (the primary outcome), as change from baseline, comparing indacaterol alone with indacaterol plus tiotropium, after single and chronic dosing, and a within-subject SD of 1.3 doubling dose, requiring a sample size of 14 using a crossover design, with alpha error of 0.05 (2 tailed). All data were first examined for normality and distribution. Repeated measures analysis of variance (ANO | |
| Comparison groups | INDACATEROL v TIOTROPIUM + INDACATEROL |
| Number of subjects included in analysis | 28 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | ANOVA |

Secondary: FEV1 (L)

| | |
|---|-----------|
| End point title | FEV1 (L) |
| End point description: | |
| single (1 day) vs chronic (28 day) dosing | |
| End point type | Secondary |
| End point timeframe: | |
| 1 day - 28 days | |

| End point values | INDACATEROL | TIOTROPIUM + INDACATEROL | | |
|---|---------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 14 | | |
| Units: litre(s) | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| baseline | 2.56 (2.18 to 2.95) | 2.56 (2.18 to 2.95) | | |

| | | | | |
|---------|---------------------|---------------------|--|--|
| single | 2.69 (2.28 to 3.1) | 2.78 (2.38 to 3.19) | | |
| chronic | 2.64 (2.26 to 3.02) | 2.71 (2.33 to 3.09) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: FEV1 Predicted (%)

End point title FEV1 Predicted (%)

End point description:

single (1 day) vs chronic (28 day) dosing

End point type Secondary

End point timeframe:

1 day - 28 days

| End point values | INDACATEROL | TIOTROPIUM + INDACATEROL | | |
|---|-----------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 14 | | |
| Units: percent | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| baseline | 87 (78 to 97) | 87 (78 to 97) | | |
| single | 91 (82 to 100) | 95 (85 to 105) | | |
| chronic | 90 (81 to 100) | 93 (83 to 102) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: FEF25-75 (L)

End point title FEF25-75 (L)

End point description:

single (1 day) vs chronic (28 day) dosing

End point type Secondary

End point timeframe:

1 day - 28 days

| End point values | INDACATEROL | TIOTROPIUM + INDACATEROL | | |
|---|---------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 14 | | |
| Units: litre(s) | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| baseline | 1.79 (1.22 to 2.36) | 1.79 (1.22 to 2.36) | | |
| single | 2.02 (1.93 to 2.65) | 2.22 (1.49 to 2.95) | | |
| chronic | 1.91 (1.25 to 2.57) | 1.94 (1.38 to 2.49) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: R5 (kPA/l.s)

| | |
|--|--------------|
| End point title | R5 (kPA/l.s) |
| End point description: | |
| Single (1 day) vs chronic (28 days) dosing | |
| End point type | Secondary |
| End point timeframe: | |
| 1 day - 28 days | |

| End point values | INDACATEROL | TIOTROPIUM + INDACATEROL | | |
|---|---------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 14 | | |
| Units: kPA/l.s | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| baseline | 0.54 (0.44 to 0.64) | 0.54 (0.44 to 0.64) | | |
| single | 0.45 (0.37 to 0.52) | 0.39 (0.34 to 0.43) | | |
| chronic | 0.44 (0.37 to 0.5) | 0.45 (0.39 to 0.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: R5-R20 (kPA/l.s)

| | |
|-----------------|------------------|
| End point title | R5-R20 (kPA/l.s) |
|-----------------|------------------|

End point description:

Single (1 day) vs chronic (28 days) dosing

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

1 - 28 days

| End point values | INDACATEROL | TIOTROPIUM + INDACATEROL | | |
|--|------------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 14 | | |
| Units: kPa/l.s | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| baseline | 0.14 (0.07 to 0.22) | 0.14 (0.07 to 0.22) | | |
| single | 0.07 (0.03 to 0.11) | 0.05 (0.03 to 0.07) | | |
| chronic | 0.07 (0.04 to 0.1) | 0.08 (0.04 to 0.11) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: AX (kPa/l)

| | |
|-----------------|------------|
| End point title | AX (kPa/l) |
|-----------------|------------|

End point description:

Single (1 day) vs chronic (28 days) dosing

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

1- 28 days

| End point values | INDACATEROL | TIOTROPIUM + INDACATEROL | | |
|--|------------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 14 | | |
| Units: kPa/l | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| baseline | 1.63 (0.58 to 2.68) | 1.63 (0.58 to 2.68) | | |
| single | 0.76 (0.34 to 1.19) | 0.44 (0.25 to 0.63) | | |
| chronic | 0.68 (0.43 to 0.92) | 0.78 (0.48 to 1.09) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: RDR (%/mg)

| | |
|--|------------|
| End point title | RDR (%/mg) |
| End point description: Single (1 day) vs chronic (28 days) dosing | |
| End point type | Secondary |
| End point timeframe: 1- 28 days | |

| End point values | INDACATEROL | TIOTROPIUM + INDACATEROL | | |
|--|---------------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 14 | | |
| Units: %/mg | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| baseline | 0.037 (0.025 to 0.055) | 0.037 (0.025 to 0.055) | | |
| single | 0.011 (0.005 to 0.026) | 0.015 (0.008 to 0.029) | | |
| chronic | 0.037 (0.023 to 0.061) | 0.035 (0.018 to 0.07) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: FeNO (ppb)

| | |
|--|------------|
| End point title | FeNO (ppb) |
| End point description: Single (1 day) vs chronic (28 days) dosing | |
| End point type | Secondary |
| End point timeframe: 1- 28 days | |

| End point values | INDACATEROL | TIOTROPIUM + INDACATEROL | | |
|---|-----------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 14 | | |
| Units: ppb | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| baseline | 30 (20 to 45) | 30 (20 to 45) | | |
| single | 30 (20 to 44) | 32 (23 to 45) | | |
| chronic | 30 (20 to 45) | 29 (19 to 44) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Salbutamol Recovery (%.min)

| | |
|--|-----------------------------|
| End point title | Salbutamol Recovery (%.min) |
| End point description: | |
| Single (1 day) vs chronic (28 days) dosing | |
| End point type | Secondary |
| End point timeframe: | |
| 1- 28 days | |

| End point values | INDACATEROL | TIOTROPIUM + INDACATEROL | | |
|---|------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 14 | | |
| Units: %/min | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| baseline | 47 (-79 to 172) | 47 (-79 to 172) | | |
| single | 33 (-47 to 113) | 77 (19 to 136) | | |
| chronic | 259 (196 to 322) | 239 (177 to 300) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: ACQ-7

| | |
|--|-----------|
| End point title | ACQ-7 |
| End point description: | |
| Single (1 day) vs chronic (28 days) dosing | |
| End point type | Secondary |

End point timeframe:

1- 28 days

| End point values | INDACATEROL | TIOTROPIUM + INDACATEROL | | |
|--|------------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 14 | | |
| Units: units | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| baseline | 0.72 (0.48 to 0.95) | 0.72 (0.48 to 0.95) | | |
| chronic | 0.44 (0.24 to 0.63) | 0.5 (0.27 to 0.73) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were recorded from the time a participant consented to join the study until the last study visit.

Adverse event reporting additional description:

Subjects were asked about the occurrence of AEs at each study visit and received training on how to record AEs and concomitant medications. All AEs were recorded on subject-specific logs in the CRF.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 20 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Completed Subjects |
|-----------------------|--------------------|

Reporting group description: -

| Serious adverse events | Completed Subjects | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 14 (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 | Completed Subjects | | |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 14 (78.57%) | | |
| Investigations | | | |
| Delayed Recovery following Mannitol Challenge | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |
| Surgical and medical procedures | | | |
| Root Canal | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Headache | | | |

| | | | |
|--|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Feeling Shaky</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 14 (21.43%)</p> <p>4</p> <p>1 / 14 (7.14%)</p> <p>2</p> | | |
| <p>General disorders and administration site conditions</p> <p>Fatigue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hangover</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 14 (7.14%)</p> <p>1</p> <p>1 / 14 (7.14%)</p> <p>1</p> | | |
| <p>Blood and lymphatic system disorders</p> <p>Elevated INR</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 14 (7.14%)</p> <p>1</p> | | |
| <p>Immune system disorders</p> <p>Allergic reaction</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 14 (14.29%)</p> <p>2</p> | | |
| <p>Gastrointestinal disorders</p> <p>Nausea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 14 (7.14%)</p> <p>2</p> <p>1 / 14 (7.14%)</p> <p>2</p> <p>1 / 14 (7.14%)</p> <p>2</p> <p>2 / 14 (14.29%)</p> <p>2</p> | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Rhinovirus infection</p> | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 4 / 14 (28.57%) | | |
| occurrences (all) | 5 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 3 / 14 (21.43%) | | |
| occurrences (all) | 5 | | |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |
| Chest pain | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | | |
| occurrences (all) | 3 | | |
| Cough | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 2 | | |
| Rhinitis | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | | |
| occurrences (all) | 3 | | |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Foot Cramps | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 3 | | |
| Hand Cramps | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |
| Painful Finger Joint | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | | |
| occurrences (all) | 1 | | |
| Jaw Pain | | | |

| | | | |
|---|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | | |
| Metabolism and nutrition disorders Toothache subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 09 January 2014 | REC Amendment (AM01) Amendment to notify REC of changes made in response to MHRA's grounds for non-acceptance and right to amend request during initial application process. |
| 19 March 2015 | REC Amendment (AM02) Amendment for use of additional sources for patient recruitment. |
| 20 October 2015 | REC Amendment (AM03) Amendment for prospective approval of patient diaries and emergency contact card |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28665534>