# Clinical trial results:
# Randomised Controlled Trial of the efficacy and safety of an ICS/LABA reliever therapy regimen in asthma.

## Summary

| | |
|---|---|
| EudraCT number | 2015-002384-42 |
| Trial protocol | GB |
| Global end of trial date | 30 August 2018 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 23 April 2021 |
| First version publication date | 23 April 2021 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | MRINZ/15/A1 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | U1111-1170-2118 |
| Other trial identifiers | Global Sponsor: MRINZ/15/A1, ANZCTR: ACTRN12615000999538 |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | (1) THE CHANCELLOR MASTERS AND SCHOLARS OF THE OXFORD OF OXFORD |
| Sponsor organisation address | Oxford Offices, Wellington Square, Oxford, United Kingdom, OX1 2JD |
| Public contact | Magda Laskawiec-Szkonter, Oxford Respiratory Trials Unit (ORTU), 44 01865225205, magda.laskawiec@ouh.nhs.uk |
| Scientific contact | Magda Laskawiec-Szkonter, Oxford Respiratory Trials Unit (ORTU), 44 01865225205, magda.laskawiec@ouh.nhs.uk |
| Sponsor organisation name | Medical Research Institute of New Zealand |
| Sponsor organisation address | Level 7 CSB Building, Wellington Hospital, Riddiford Street, Newtown, Wellington, New Zealand, 6021 |
| Public contact | Richard Beasley, Medical Research Institute of New Zealand, 64 43890147, mark.holliday@mrinz.ac.nz |
| Scientific contact | Richard Beasley, Medical Research Institute of New Zealand, 64 43890147, mark.holliday@mrinz.ac.nz |

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 | No |

| | |
|---|---|
| 1901/2006 apply to this trial? | |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 31 January 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 August 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 August 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To compare the efficacy of ICS/LABA reliever therapy with SABA reliever therapy and with maintenance ICS and SABA reliever therapy in adult patients using SABA monotherapy (i.e. without any other asthma medication).

Protection of trial subjects:

The Data Safety Monitoring Committee was established to ensure independent safety review during the study. Participants were withdrawn from the study after experiencing 3 asthma exacerbations or 1 severe asthma exacerbation for the purpose of safety, to ensure they were able to receive the appropriate treatment outside of the randomised regimens.

Background therapy:

n/a

Evidence for comparator:

Comparators were selected based on their use in clinical practice driven by international guidelines (the Global Initiative for Asthma). Short acting beta agonist (SABA) taken as required for relief of symptoms was recommended step 1 and maintenance inhaled corticosteroids plus SABA as required recommended as step 2 treatment at the time the trial was initiated.

| | |
|---|---|
| Actual start date of recruitment | 01 January 2016 |
| 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: 52 |
| Country: Number of subjects enrolled | Australia: 26 |
| Country: Number of subjects enrolled | New Zealand: 553 |
| Country: Number of subjects enrolled | Italy: 44 |
| Worldwide total number of subjects | 675 |
| EEA total number of subjects | 96 |

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) | 641 |
| From 65 to 84 years | 34 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited from sites in New Zealand, Australia, Italy and the United Kingdom. The recruitment period ran from first patient first visit (FPFV) on 17/03/2016 to last patient first visit (LPFV) on 29/08/2017 worldwide.

### Pre-assignment

Screening details:

Participants were screened according to the protocol inclusion/ exclusion criteria. Participants that were randomised but subsequently were found to be ineligible (incorrectly randomised) are not included as part of the baseline or analysis sets (n=7), based on a modified intention to treat approach.

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 675 |
| Number of subjects completed | 668 |

### Pre-assignment subject non-completion reasons

| | |
|---|---|
| Reason: Number of subjects | Protocol deviation: 7 |

### Period 1

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

Blinding implementation details:

n/a

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | SABA reliever therapy |

Arm description:

salbutamol MDI 100µg, 2 inhalations for relief of symptoms as required.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | salbutamol |
| Investigational medicinal product code | |
| Other name | Ventolin |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

salbutamol metered dose inhaler 100µg, 2 inhalations for relief of symptoms as required.

| | |
|---|---|
| **Arm title** | ICS/LABA reliever therapy |

Arm description:

budesonide/formoterol Turbuhaler 200/6µg, one inhalation for relief of symptoms as required.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | budesonide/formoterol |
| Investigational medicinal product code | |
| Other name | Symbicort |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

budesonide/formoterol Turbuhaler 200/6µg, one inhalation for relief of symptoms as required.

| **Arm title** | Maintenance ICS and SABA reliever therapy |
|---|---|

Arm description:

budesonide Turbuhaler 200µg, 1 inhalation twice daily and salbutamol MDI 100µg 2 inhalations for relief of symptoms as required.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | budesonide Turbuhaler 200µg, 1 inhalation twice daily |
| Investigational medicinal product code | |
| Other name | Pulmicort |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

budesonide Turbuhaler 200µg, 1 inhalation twice daily

| | |
|---|---|
| Investigational medicinal product name | salbutamol MDI 100µg 2 inhalations for relief of symptoms as required. |
| Investigational medicinal product code | |
| Other name | Ventolin |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

salbutamol MDI 100µg 2 inhalations for relief of symptoms as required.

| **Number of subjects in period 1[1]** | SABA reliever therapy | ICS/LABA reliever therapy | Maintenance ICS and SABA reliever therapy |
|---|---|---|---|
| Started | 223 | 220 | 225 |
| Completed | 151 | 163 | 153 |
| Not completed | 72 | 57 | 72 |
| Adverse event, serious fatal | - | 1 | 1 |
| incorrectly withdrawn in error | - | 1 | 2 |
| Physician decision | 1 | 1 | - |
| Consent withdrawn by subject | 24 | 32 | 33 |
| randomised in error, ineligible | 3 | 2 | 1 |
| Adverse event, non-fatal | - | 2 | 10 |
| Pregnancy | 2 | 5 | 1 |
| Lost to follow-up | 5 | 1 | 2 |
| Lack of efficacy | 37 | 12 | 22 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 675 participants were randomised however 7 were found to have not met the eligibility criteria after they had been randomised (randomised in error). 668 participants were therefore included

in the analysis dataset, including within the baseline reporting datataset, as part of a modified intention to treat approach.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | SABA reliever therapy |
| Reporting group description: | |
| salbutamol MDI 100µg, 2 inhalations for relief of symptoms as required. | |
| Reporting group title | ICS/LABA reliever therapy |
| Reporting group description: | |
| budesonide/formoterol Turbuhaler 200/6µg, one inhalation for relief of symptoms as required. | |
| Reporting group title | Maintenance ICS and SABA reliever therapy |
| Reporting group description: | |
| budesonide Turbuhaler 200µg, 1 inhalation twice daily and salbutamol MDI 100µg 2 inhalations for relief of symptoms as required. | |

| Reporting group values | SABA reliever therapy | ICS/LABA reliever therapy | Maintenance ICS and SABA reliever therapy |
|---|---|---|---|
| Number of subjects | 223 | 220 | 225 |
| Age categorical<br>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) | 214 | 210 | 215 |
| From 65-84 years | 9 | 10 | 10 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 35.8 | 36 | 34.9 |
| standard deviation | ± 14 | ± 14.1 | ± 14.3 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 113 | 122 | 129 |
| Male | 110 | 98 | 96 |
| Current Smoker<br>Units: Subjects | | | |
| Smoker | 24 | 18 | 22 |
| Non-smoker | 199 | 202 | 203 |
| No. of severe exacerbations in the previous 12 months<br>Units: Subjects | | | |
| Zero | 203 | 208 | 208 |
| One | 20 | 12 | 15 |
| Two | 0 | 0 | 2 |

| | | | |
|---|---|---|---|
| Patient-reported SABA use in the 4 weeks before enrollment | | | |
| Units: No. occasions per week | | | |
| arithmetic mean | 3.4 | 3.8 | 3.2 |
| standard deviation | ± 3.3 | ± 3.5 | ± 3.0 |
| No. of hospital admissions for asthma at any time before enrollment | | | |
| Units: Mean per participant | | | |
| arithmetic mean | 0.3 | 0.3 | 0.3 |
| standard deviation | ± 0.9 | ± 1.3 | ± 0.9 |
| Asthma Control Questionnaire-5 score | | | |
| Units: Score | | | |
| arithmetic mean | 1.1 | 1.1 | 1.1 |
| standard deviation | ± 0.7 | ± 0.7 | ± 0.7 |
| On-treatment Forced Expired Volume in 1 Second | | | |
| Units: % of predicted value | | | |
| arithmetic mean | 89.2 | 89.8 | 90.3 |
| standard deviation | ± 13.7 | ± 14.1 | ± 13.6 |
| Fractional Exhaled Nitric Oxide | | | |
| Units: parts per billion | | | |
| median | 40 | 37 | 38 |
| full range (min-max) | 5 to 235 | 3 to 300 | 5 to 200 |
| Periostin | | | |
| Units: ng/ml | | | |
| arithmetic mean | 69.3 | 70.8 | 70.6 |
| standard deviation | ± 28.9 | ± 27 | ± 27.8 |
| Blood eosinophil count | | | |
| Units: x10^9 per litre | | | |
| arithmetic mean | 0.3 | 0.3 | 0.3 |
| standard deviation | ± 0.2 | ± 0.2 | ± 0.2 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 668 | | |
| 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) | 639 | | |
| From 65-84 years | 29 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

| | | | |
|---|---|---|---|
| Gender categorical<br>Units: Subjects | | | |
| Female | 364 | | |
| Male | 304 | | |
| Current Smoker<br>Units: Subjects | | | |
| Smoker | 64 | | |
| Non-smoker | 604 | | |
| No. of severe exacerbations in the previous 12 months<br>Units: Subjects | | | |
| Zero | 619 | | |
| One | 47 | | |
| Two | 2 | | |
| Patient-reported SABA use in the 4 weeks before enrollment<br>Units: No. occasions per week | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| No. of hospital admissions for asthma at any time before enrollment<br>Units: Mean per participant | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Asthma Control Questionnaire-5 score<br>Units: Score | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| On-treatment Forced Expired Volume in 1 Second<br>Units: % of predicted value | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Fractional Exhaled Nitric Oxide<br>Units: parts per billion | | | |
| median | | | |
| full range (min-max) | - | | |
| Periostin<br>Units: ng/ml | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Blood eosinophil count<br>Units: x10^9 per litre | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | SABA reliever therapy |
| Reporting group description: | |
| salbutamol MDI 100µg, 2 inhalations for relief of symptoms as required. | |
| Reporting group title | ICS/LABA reliever therapy |
| Reporting group description: | |
| budesonide/formoterol Turbuhaler 200/6µg, one inhalation for relief of symptoms as required. | |
| Reporting group title | Maintenance ICS and SABA reliever therapy |
| Reporting group description: | |
| budesonide Turbuhaler 200µg, 1 inhalation twice daily and salbutamol MDI 100µg 2 inhalations for relief of symptoms as required. | |

### Primary: Annualized rate of asthma exacerbations per patient

| | |
|---|---|
| End point title | Annualized rate of asthma exacerbations per patient |
| End point description: | |

| | |
|---|---|
| End point type | Primary |
| End point timeframe: | |
| Overall study period | |

| End point values | SABA reliever therapy | ICS/LABA reliever therapy | Maintenance ICS and SABA reliever therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 223 | 220 | 225 | |
| Units: Rate of exacerbations | | | | |
| number (not applicable) | 0.40 | 0.195 | 0.175 | |

### Statistical analyses

| Statistical analysis title | Relative rate exacerbations ICS/LABA vs SABA |
|---|---|
| Comparison groups | SABA reliever therapy v ICS/LABA reliever therapy |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [1] |
| Method | Poisson regression |
| Parameter estimate | Relative Rate |
| Point estimate | 0.49 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.33 |
| upper limit | 0.72 |

Notes:

[1] - Overall test for a difference in rates by treatment: Chi-square 21.1 on 2 DF; P<0.001

| | |
|---|---|
| **Statistical analysis title** | Relative rate exacerbations ICS/LABA vs ICS+SABA |
| Comparison groups | Maintenance ICS and SABA reliever therapy v ICS/LABA reliever therapy |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.65 |
| Method | Poisson regression |
| Parameter estimate | Relative rate |
| Point estimate | 1.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.79 |

## Secondary: Time to first exacerbation

| | |
|---|---|
| End point title | Time to first exacerbation |

End point description:

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

End point timeframe:

Overall study period

| **End point values** | SABA reliever therapy | ICS/LABA reliever therapy | Maintenance ICS and SABA reliever therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 223 | 220 | 225 | |
| Units: Exacerbations | 74 | 37 | 32 | |

## Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Time to first exacerbation ICS/LABA vs SABA only |
| Comparison groups | SABA reliever therapy v ICS/LABA reliever therapy |

| | |
|---|---|
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Log rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.29 |
| upper limit | 0.73 |

| | |
|---|---|
| **Statistical analysis title** | Time to first exacerbation ICS/LABA vs ICS+SABA |
| Comparison groups | ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.79 |
| Method | Log rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.55 |
| upper limit | 1.57 |

**Secondary: Time to first severe exacerbation**

| | |
|---|---|
| End point title | Time to first severe exacerbation |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Overall study period | |

| **End point values** | SABA reliever therapy | ICS/LABA reliever therapy | Maintenance ICS and SABA reliever therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 223 | 220 | 225 | |
| Units: exacerbtions | 23 | 9 | 21 | |

**Statistical analyses**

| **Statistical analysis title** | Time to severe exacerbation ICS/LABA vs SABA only |
|---|---|
| Comparison groups | SABA reliever therapy v ICS/LABA reliever therapy |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.014 |
| Method | Log rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.38 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.18 |
| upper limit | 0.82 |

| **Statistical analysis title** | Time to severe exacerbation ICS/LABA vs ICS+SABA |
|---|---|
| Comparison groups | ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.026 |
| Method | Log rank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.19 |
| upper limit | 0.9 |

| **Secondary: Number of severe exacerbations** | |
|---|---|
| End point title | Number of severe exacerbations |
| End point description: | |

| End point type | Secondary |
|---|---|
| End point timeframe: | |
| Overall study period | |

| End point values | SABA reliever therapy | ICS/LABA reliever therapy | Maintenance ICS and SABA reliever therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 223 | 220 | 225 | |
| Units: Severe Exacerbations | 23 | 9 | 21 | |

**Statistical analyses**

| Statistical analysis title | Relative risk sev. exacerbations ICS/LABA vs SABA |
|---|---|
| Comparison groups | SABA reliever therapy v ICS/LABA reliever therapy |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.019 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.18 |
| upper limit | 0.86 |

| Statistical analysis title | Relative risk sev. exac ICS/LABA vs ICS+SABA |
|---|---|
| Comparison groups | ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.038 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.44 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 0.96 |

## Secondary: Asthma Control Questionnaire-5 Score

| End point title | Asthma Control Questionnaire-5 Score |
|---|---|

End point description:

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

End point timeframe:

Overall study period

| End point values | SABA reliever therapy | ICS/LABA reliever therapy | Maintenance ICS and SABA reliever therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 222 | 220 | 225 | |
| Units: Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 1 | 1.1 (± 0.7) | 1.1 (± 0.7) | 1.1 (± 0.7) | |
| Visit 2 | 1.0 (± 0.7) | 0.9 (± 0.6) | 0.8 (± 0.7) | |
| Visit 3 | 1.0 (± 0.8) | 0.8 (± 0.6) | 0.7 (± 0.6) | |
| Visit 4 | 0.9 (± 0.7) | 0.8 (± 0.6) | 0.7 (± 0.7) | |
| Visit 5 | 0.9 (± 0.9) | 0.8 (± 0.7) | 0.6 (± 0.7) | |
| Visit 6 | 0.8 (± 0.8) | 0.8 (± 0.7) | 0.6 (± 0.8) | |
| Visit 7 | 0.9 (± 0.9) | 0.8 (± 0.7) | 0.7 (± 0.8) | |

### Statistical analyses

| Statistical analysis title | Mean difference in ACQ-5 ICS/LABA vs SABA only |
|---|---|

Statistical analysis description:

main effects averaged over all visits

| Comparison groups | SABA reliever therapy v ICS/LABA reliever therapy |
|---|---|
| Number of subjects included in analysis | 442 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 [2] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.24 |
| upper limit | -0.06 |

Notes:

[2] - Overall P<0.001 for treatment effect

| Statistical analysis title | Mean difference in ACQ-5 ICS/LABA vs ICS+SABA |
|---|---|

| | |
|---|---|
| Statistical analysis description: | |
| Main effects analysis averaged over all visits | |
| Comparison groups | ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 [3] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.05 |
| upper limit | 0.23 |

Notes:

[3] - Overall P<0.001 for treatment effect

## Secondary: Forced Expired Volume in 1 second (FEV1)

| | |
|---|---|
| End point title | Forced Expired Volume in 1 second (FEV1) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Overall study period | |

| End point values | SABA reliever therapy | ICS/LABA reliever therapy | Maintenance ICS and SABA reliever therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 223 | 218 | 225 | |
| Units: Litres | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 1 | 3.30 (± 0.76) | 3.30 (± 0.87) | 3.30 (± 0.87) | |
| Visit 2 | 3.33 (± 0.77) | 3.37 (± 0.85) | 3.36 (± 0.88) | |
| Visit 3 | 3.35 (± 0.78) | 3.36 (± 0.89) | 3.38 (± 0.88) | |
| Visit 4 | 3.33 (± 0.78) | 3.32 (± 0.84) | 3.35 (± 0.88) | |
| Visit 5 | 3.32 (± 0.74) | 3.30 (± 0.85) | 3.33 (± 0.88) | |
| Visit 6 | 3.30 (± 0.72) | 3.30 (± 0.87) | 3.34 (± 0.91) | |
| Visit 7 | 3.23 (± 0.71) | 3.28 (± 0.84) | 3.31 (± 0.89) | |

## Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Mean difference in FEV1 (L) ICS/LABA vs SABA only |

| | |
|---|---|
| Statistical analysis description: | |
| Main effects analysis averaged over all visits | |
| Comparison groups | SABA reliever therapy v ICS/LABA reliever therapy |
| Number of subjects included in analysis | 441 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1 [4] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.006 |
| upper limit | 0.07 |

Notes:

[4] - Overall P=0.20 for treatment effect

| **Statistical analysis title** | Mean difference in FEV1 (L) ICS/LABA vs ICS+SABA |
|---|---|
| Statistical analysis description: | |
| Main effects analysis averaged over all visits | |
| Comparison groups | ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.85 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.004 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.03 |
| upper limit | 0.04 |

## Secondary: Fraction of exhaled nitric oxide (FeNO)

| | |
|---|---|
| End point title | Fraction of exhaled nitric oxide (FeNO) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Overall study period | |

| End point values | SABA reliever therapy | ICS/LABA reliever therapy | Maintenance ICS and SABA reliever therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 223 | 220 | 225 | |
| Units: parts per billion | | | | |
| log mean (standard deviation) | | | | |
| Visit 1 | 3.69 (± 0.83) | 3.56 (± 0.88) | 3.66 (± 0.84) | |
| Visit 3 | 3.7 (± 0.8) | 3.36 (± 0.78) | 3.2 (± 0.65) | |
| Visit 7 | 3.61 (± 0.77) | 3.32 (± 0.78) | 3.29 (± 0.74) | |

**Statistical analyses**

| Statistical analysis title | Difference in log FeNO ICS/LABA vs SABA only V3 |
|---|---|
| Comparison groups | SABA reliever therapy v ICS/LABA reliever therapy |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | ratio of geometric means |
| Point estimate | 0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 0.87 |

| Statistical analysis title | Difference in log FeNO ICS/LABA vs ICS+SABA V3 |
|---|---|
| Comparison groups | ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | ratio of geometric means |
| Point estimate | 1.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.15 |
| upper limit | 1.4 |

| Statistical analysis title | Difference in log FeNO ICS/LABA vs SABA only V7 |
|---|---|
| Comparison groups | SABA reliever therapy v ICS/LABA reliever therapy |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | ratio of geometric means |
| Point estimate | 0.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 0.91 |

| Statistical analysis title | Difference in log FeNO ICS/LABA vs ICS+SABA V7 |
|---|---|
| Comparison groups | ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.022 |
| Method | Mixed models analysis |
| Parameter estimate | ratio of geometric means |
| Point estimate | 1.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.02 |
| upper limit | 1.25 |

## Secondary: Mean inhaled corticosteroid dose per day

| End point title | Mean inhaled corticosteroid dose per day[5] |
|---|---|

End point description:

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

End point timeframe:

overall study period

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The SABA only arm did not take regular maintenance inhaled corticosteroid therefore no data is available for this outcome for that group.

| End point values | ICS/LABA reliever therapy | Maintenance ICS and SABA reliever therapy | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 220 | 225 | | |
| Units: microgram(s) | | | | |
| arithmetic mean (standard deviation) | 1.07 (± 109) | 222 (± 113) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Total systemic corticosteroid exposure use per year

| End point title | Total systemic corticosteroid exposure use per year |
|---|---|

End point description:

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

End point timeframe:

overall study period

| End point values | SABA reliever therapy | ICS/LABA reliever therapy | Maintenance ICS and SABA reliever therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 223 | 220 | 225 | |
| Units: milligram(s) | | | | |
| arithmetic mean (standard deviation) | 17.4 (± 59.8) | 71.4 (± 72.1) | 152.3 (± 97.1) | |

## Statistical analyses

| Statistical analysis title | Total systemic steroid exposure ICS/LABA vs SABA |
|---|---|
| Comparison groups | SABA reliever therapy v ICS/LABA reliever therapy |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Hodges-Lehmann estimator |
| Point estimate | 41.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 34.4 |
| upper limit | 48.4 |

| Statistical analysis title | Total systemic steroid exp. ICS/LABA vs ICS+SABA |
|---|---|
| Comparison groups | ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Hodges-Lehmann estimator |
| Point estimate | -84.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -104 |
| upper limit | -64.8 |

## Secondary: Proportion of participants withdrawn due to treatment failure

| End point title | Proportion of participants withdrawn due to treatment failure |
|---|---|

End point description:

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

End point timeframe:

Overall study period

| End point values | SABA reliever therapy | ICS/LABA reliever therapy | Maintenance ICS and SABA reliever therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 223 | 220 | 225 | |
| Units: Participants | | | | |
| One Severe Exacerbation | 23 | 9 | 21 | |
| Three Exacerbations | 3 | 3 | 1 | |
| Randomised treatment modified by healthcare provid | 11 | 0 | 0 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Global Initiative for Asthma Question Category

| End point title | Global Initiative for Asthma Question Category |
|---|---|

End point description:

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

End point timeframe:

Overall study period

| **End point values** | SABA reliever therapy | ICS/LABA reliever therapy | Maintenance ICS and SABA reliever therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 223 | 220 | 225 | |
| Units: GINA Category | | | | |
| Visit 1 Well controlled | 54 | 44 | 54 | |
| Visit 1 Partly controlled | 121 | 123 | 108 | |
| Visit 1 Uncontrolled | 48 | 53 | 63 | |
| Visit 2 Well controlled | 60 | 38 | 79 | |
| Visit 2 Partly controlled | 95 | 127 | 101 | |
| Visit 2 Uncontrolled | 50 | 43 | 26 | |
| Visit 3 Well controlled | 57 | 53 | 95 | |
| Visit 3 Partly controlled | 95 | 109 | 82 | |
| Visit 3 Uncontrolled | 49 | 25 | 26 | |
| Visit 4 Well controlled | 53 | 58 | 85 | |
| Visit 4 Partly controlled | 90 | 95 | 78 | |
| Visit 4 Uncontrolled | 39 | 30 | 19 | |
| Visit 5 Well controlled | 71 | 56 | 82 | |
| Visit 5 Partly controlled | 68 | 87 | 69 | |
| Visit 5 Uncontrolled | 35 | 31 | 20 | |
| Visit 6 Well controlled | 58 | 62 | 74 | |
| Visit 6 Partly controlled | 77 | 78 | 56 | |
| Visit 6 Uncontrolled | 28 | 30 | 25 | |
| Visit 7 Well controlled | 72 | 69 | 87 | |
| Visit 7 Partly controlled | 77 | 97 | 74 | |
| Visit 7 Uncontrolled | 48 | 31 | 36 | |

## Statistical analyses

| **Statistical analysis title** | GINA level of control ICS/LABA vs SABA Visit 2 |
|---|---|

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 2

| Comparison groups | ICS/LABA reliever therapy v SABA reliever therapy |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.42 [6] |
| Method | Mixed models analysis |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 1.32 |

Notes:

[6] - Time by treatment interaction not statistically significant, P=0.23

| **Statistical analysis title** | GINA level of control ICS/LABA vs SABA Visit 3 |
|---|---|

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 3

| | |
|---|---|
| Comparison groups | SABA reliever therapy v ICS/LABA reliever therapy |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.67 [7] |
| Method | Mixed models analysis |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 1.78 |

Notes:

[7] - Time by treatment interaction not statistically significant, P=0.23

| **Statistical analysis title** | GINA level of control ICS/LABA vs SABA Visit 4 |
|---|---|

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 4

| | |
|---|---|
| Comparison groups | SABA reliever therapy v ICS/LABA reliever therapy |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.24 [8] |
| Method | Mixed models analysis |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.35 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.82 |
| upper limit | 2.2 |

Notes:

[8] - Time by treatment interaction not statistically significant, P=0.23

| **Statistical analysis title** | GINA level of control ICS/LABA vs SABA Visit 5 |
|---|---|

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 5

| | |
|---|---|
| Comparison groups | SABA reliever therapy v ICS/LABA reliever therapy |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5 [9] |
| Method | Mixed models analysis |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 1.39 |

Notes:

[9] - Time by treatment interaction not statistically significant, P=0.23

| **Statistical analysis title** | GINA level of control ICS/LABA vs SABA Visit 6 |
|---|---|

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 6

| | |
|---|---|
| Comparison groups | SABA reliever therapy v ICS/LABA reliever therapy |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.68 [10] |
| Method | Mixed models analysis |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.86 |

Notes:

[10] - Time by treatment interaction not statistically significant, P=0.23

| **Statistical analysis title** | GINA level of control ICS/LABA vs SABA Visit 7 |
|---|---|

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 7

| | |
|---|---|
| Comparison groups | SABA reliever therapy v ICS/LABA reliever therapy |
| Number of subjects included in analysis | 443 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.32 [11] |
| Method | Mixed models analysis |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 2.05 |

Notes:

[11] - Time by treatment interaction not statistically significant, P=0.23

| **Statistical analysis title** | GINA level of control ICS/LABA vs ICS+SABA Visit 2 |
|---|---|

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 2

| | |
|---|---|
| Comparison groups | ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [12] |
| Method | Mixed models analysis |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.26 |
| upper limit | 0.65 |

Notes:

[12] - Time by treatment interaction not statistically significant, P=0.23

| **Statistical analysis title** | GINA level of control ICS/LABA vs ICS+SABA Visit 3 |
|---|---|

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 3

| | |
|---|---|
| Comparison groups | ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy |

| | |
|---|---|
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [13] |
| Method | Mixed models analysis |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.25 |
| upper limit | 0.64 |

Notes:

[13] - Time by treatment interaction not statistically significant, P=0.23

| **Statistical analysis title** | GINA level of control ICS/LABA vs ICS+SABA Visit 4 |
|---|---|

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 4

| | |
|---|---|
| Comparison groups | ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.004 [14] |
| Method | Mixed models analysis |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.29 |
| upper limit | 0.79 |

Notes:

[14] - Time by treatment interaction not statistically significant, P=0.23

| **Statistical analysis title** | GINA level of control ICS/LABA vs ICS+SABA Visit 5 |
|---|---|

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 5

| | |
|---|---|
| Comparison groups | ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 [15] |
| Method | Mixed models analysis |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.46 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.28 |
| upper limit | 0.77 |

Notes:

[15] - Time by treatment interaction not statistically significant, P=0.23

| **Statistical analysis title** | GINA level of control ICS/LABA vs ICS+SABA Visit 6 |
|---|---|

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 6

| | |
|---|---|
| Comparison groups | ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1 [16] |
| Method | Mixed models analysis |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.38 |
| upper limit | 1.09 |

Notes:

[16] - Time by treatment interaction not statistically significant, P=0.23

| **Statistical analysis title** | GINA level of control ICS/LABA vs ICS+SABA Visit 7 |
|---|---|

Statistical analysis description:

Comparison of ordinal odds of association with GINA overall level of control (generalized linear mixed model) without baseline GINA control as a co-variate and with a time by treatment interaction, at Visit 7

| | |
|---|---|
| Comparison groups | ICS/LABA reliever therapy v Maintenance ICS and SABA reliever therapy |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.28 [17] |
| Method | Mixed models analysis |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.48 |
| upper limit | 1.24 |

Notes:

[17] - Time by treatment interaction not statistically significant, P=0.23

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Overall study period

Adverse event reporting additional description:

Adverse events were collected at each visit via participant self-report, investigator assessment and investigator review of the participant completed asthma management plans/ logbooks containing healthcare utilisation and asthma related events.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Safety Analysis Dataset |

Reporting group description:

Dataset includes all participants that were randomised, including those who were randomised incorrectly (those who were randomised and subsequently found to not meet the eligibility criteria).

| Serious adverse events | Safety Analysis Dataset | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 23 / 675 (3.41%) | | |
| number of deaths (all causes) | 2 | | |
| number of deaths resulting from adverse events | 2 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Intraductal proliferative breast lesion | | | |
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastatic malignant melanoma | | | |
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Road traffic accident | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cardiac disorders | | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery dissection | | | |
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Pregnancy | | | |
| subjects affected / exposed | 2 / 675 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eating disorder | | | |
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Completed suicide | | | |
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic sinusitis | | | |
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower respiratory tract infection viral | | | |
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 675 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 2 / 675 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 2 %

| **Non-serious adverse events** | Safety Analysis Dataset | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 549 / 675 (81.33%) | | |
| Injury, poisoning and procedural complications | | | |
| Ligament sprain | | | |
| subjects affected / exposed | 21 / 675 (3.11%) | | |
| occurrences (all) | 23 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 38 / 675 (5.63%) | | |
| occurrences (all) | 49 | | |
| Migraine | | | |
| subjects affected / exposed | 14 / 675 (2.07%) | | |
| occurrences (all) | 14 | | |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 27 / 675 (4.00%) | | |
| occurrences (all) | 28 | | |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Toothache | | | |
| subjects affected / exposed | 14 / 675 (2.07%) | | |
| occurrences (all) | 14 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 89 / 675 (13.19%) | | |
| occurrences (all) | 99 | | |
| Cough | | | |
| subjects affected / exposed | 36 / 675 (5.33%) | | |
| occurrences (all) | 37 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 22 / 675 (3.26%) | | |
| occurrences (all) | 23 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 19 / 675 (2.81%) | | |
| occurrences (all) | 19 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 23 / 675 (3.41%) | | |
| occurrences (all) | 24 | | |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 221 / 675 (32.74%) | | |
| occurrences (all) | 305 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 128 / 675 (18.96%) | | |
| occurrences (all) | 163 | | |
| Influenza | | | |
| subjects affected / exposed | 62 / 675 (9.19%) | | |
| occurrences (all) | 72 | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 52 / 675 (7.70%) | | |
| occurrences (all) | 57 | | |
| Respiratory tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 28 / 675 (4.15%) | | |
| occurrences (all) | 33 | | |
| Sinusitis | | | |
| subjects affected / exposed | 26 / 675 (3.85%) | | |
| occurrences (all) | 35 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 20 / 675 (2.96%) | | |
| occurrences (all) | 25 | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 19 / 675 (2.81%) | | |
| occurrences (all) | 22 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 06 October 2016 | Protocol Amendment v3.0 to v4.0 due to request by MHRA:<br>Addition of exclusion criterion 14;<br>14. Any known or suspected contraindications to the Investigational Medicinal Products or excipients<br>Update to wording in 7.2.3.;<br>7.2.3. In the case of safety concerns arising during the study, the Sponsor and Investigators may deviate from the protocol only in cases where appropriate urgent safety measures are warranted to protect the trial participants against any immediate hazard to their health or safety. The Global Sponsor must be informed of any cases where the protocol is not adhered to and the reasons for non-adherence, as soon as possible. Non-adherence will be reported to the appropriate ethics committees and regulatory authorities in line with local requirements. |
| 30 August 2018 | Protocol Amendment v4.0 to v5.0. The MHRA approval date for this amendment was 13/09/2018 however this cannot be entered into the system as it prevents form validation due to approval date being subsequent to global end date.<br>Change of definition for exacerbation of asthma (removal of "use" and replacement with "prescription"):<br>Exacerbation of Asthma:<br>Worsening asthma resulting in the prescription of systemic corticosteroids, such as a course of oral prednisone for any duration and/or…<br>Severe Asthma Exacerbation:<br>a. The prescription of systemic corticosteroids for at least 3 days because of asthma, or…<br>Addition of sensitivity analysis:<br>Severe exacerbation sensitivity analysis<br>Wherever severe exacerbations are analysed a separate sensitivity analysis will be performed using the interpretation of the definition of a severe exacerbation that has been used in the PRACTICAL41 study; i.e.: self-reported use of corticosteroids for 3 or more days because of asthma, rather than prescription of systemic corticosteroid for at least 3 days because of asthma.<br>Addition of reference to the PRACTICAL trial:<br>41. Fingleton J, et al. Description of the protocol for the PRACTICAL study: a randomised controlled trial of the efficacy and safety of ICS/LABA reliever therapy in asthma. BMJ Open Respiratory Research 2017;4:e000217. DOI: 10.1136 /bmjresp-2017-000217 |

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/31112386