



Clinical trial results:

Efficacy and safety of Salmeterol/Fluticasone MDI HEXAL versus Seretide™ Evohaler™ in adolescent and adult patients with moderate-to-severe persistent asthma: A 12-week, multicenter, randomized, double-blind, double-dummy, parallel group study

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2007-005235-29 |
| Trial protocol | HU CZ PL |
| Global end of trial date | 27 April 2009 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 |
| This version publication date | 24 March 2016 |
| First version publication date | 06 February 2016 |
| Version creation reason | • Correction of full data set Information about Article 46 was not correct |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | 2007-41-DOS-3 |
|-----------------------|---------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | HEXAL AG |
| Sponsor organisation address | Industriestraße 25, Holzkirchen, Germany, 83607 |
| Public contact | Head of Clinical Research Department, Hexal AG, 0049 80249080, |
| Scientific contact | Head of Clinical Research Department, Hexal AG, 0049 80249080, |

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 | 07 August 2009 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 April 2009 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 April 2009 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to evaluate the long-term efficacy and safety of Salmeterol/Fluticasone MDI HEXAL compared to Seretide Evohaler in adolescent and adult patients suffering from moderate-to-severe persistent asthma.

Protection of trial subjects:

Safety assessments included adverse events (AEs), physical examination, ECG, vital signs and clinical laboratory data. This study was conducted in accordance with International Conference on Harmonisation of Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements.

Background therapy:

-

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 13 October 2008 |
| 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 | Czech Republic: 29 |
| Country: Number of subjects enrolled | Hungary: 49 |
| Country: Number of subjects enrolled | Poland: 175 |
| Country: Number of subjects enrolled | Romania: 40 |
| Country: Number of subjects enrolled | Ukraine: 279 |
| Worldwide total number of subjects | 572 |
| EEA total number of subjects | 293 |

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) | 94 |
| Adults (18-64 years) | 477 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Double-blind, double-dummy, multicenter, multinational, randomized parallel group study in adolescent and adult patients suffering from moderate-to-severe asthma

Pre-assignment

Screening details:

A total number of 610 patients were screened and 572 patients were randomized. A 2-week run-in period followed by a 12-week blinded treatment period. The screening visit (Visit -1) was followed by a 2-week run-in period during which all asthma treatments except reliever medication were to be stopped.

Pre-assignment period milestones

| | |
|------------------------------|--------------------|
| Number of subjects started | 610 ^[1] |
| Number of subjects completed | 572 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|-------------------------------------|
| Reason: Number of subjects | Adverse event, non-fatal: 1 |
| Reason: Number of subjects | Adverse event, serious non-fatal: 1 |
| Reason: Number of subjects | Consent withdrawn by subject: 4 |
| Reason: Number of subjects | Physician decision: 1 |
| Reason: Number of subjects | Pregnancy: 1 |
| Reason: Number of subjects | Lost to follow-up: 3 |
| Reason: Number of subjects | Ineligibility: 24 |
| Reason: Number of subjects | Sponsor decision: 3 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 38 Patients dropped out according to protocol.

Period 1

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

Arms

| | |
|--|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Salmeterol/Fluticasone MDI HEXAL |
| Investigational medicinal product code | |
| Other name | NA |
| Pharmaceutical forms | Pressurised inhalation |
| Routes of administration | Inhalation use |

Dosage and administration details:

Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg of salmeterol/fluticasone per actuation), 2x2 actuations per day

| | |
|---|---|
| Arm title | Seretide 50 Evohaler |
| Arm description: - | |
| Arm type | Active comparator |
| Investigational medicinal product name | Seretide 50 |
| Investigational medicinal product code | |
| Other name | NA |
| Pharmaceutical forms | Pressurised inhalation |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Seretide 50 Evohaler (25 µg/50 µg per actuation), 2x2 actuations per day | |
| Arm title | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Salmeterol/Fluticasone MDI HEXAL |
| Investigational medicinal product code | |
| Other name | NA |
| Pharmaceutical forms | Pressurised inhalation |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg of salmeterol/fluticasone per actuation), 2x2 actuations per day | |
| Arm title | Seretide 250 Evohaler |
| Arm description: - | |
| Arm type | Active comparator |
| Investigational medicinal product name | Seretide 250 |
| Investigational medicinal product code | |
| Other name | NA |
| Pharmaceutical forms | Pressurised inhalation |
| Routes of administration | Inhalation use |
| Dosage and administration details: | |
| Seretide 250 Evohaler (25 µg/250 µg per actuation), 2x2 actuations per day | |

| Number of subjects in period 1 | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) | Seretide 50 Evohaler | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) |
|---------------------------------------|--|----------------------|---|
| Started | 195 | 192 | 96 |
| Completed | 185 | 180 | 91 |
| Not completed | 10 | 12 | 5 |
| Consent withdrawn by subject | 4 | 8 | 4 |
| Envelope opened | - | 1 | - |
| Adverse event, non-fatal | 1 | 1 | - |
| Lost to follow-up | 3 | - | 1 |
| Sponsor decision | 1 | 1 | - |
| Protocol deviation | 1 | - | - |
| Lack of efficacy | - | 1 | - |

| Number of subjects in period 1 | Seretide 250 Evohaler |
|---------------------------------------|--------------------------|
| Started | 89 |
| Completed | 81 |
| Not completed | 8 |
| Consent withdrawn by subject | 5 |
| Envelope opened | - |
| Adverse event, non-fatal | 2 |
| Lost to follow-up | 1 |
| Sponsor decision | - |
| Protocol deviation | - |
| Lack of efficacy | - |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---|
| Reporting group title | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) |
| Reporting group description: - | |
| Reporting group title | Seretide 50 Evohaler |
| Reporting group description: - | |
| Reporting group title | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) |
| Reporting group description: - | |
| Reporting group title | Seretide 250 Evohaler |
| Reporting group description: - | |

| Reporting group values | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) | Seretide 50 Evohaler | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) |
|--|--|----------------------|---|
| Number of subjects | 195 | 192 | 96 |
| Age Categorical | | | |
| Age Categorical Characteristic | | | |
| Units: Subjects | | | |
| In Utero | 0 | 0 | 0 |
| Preterm newborn- gestational age < 37 wk | 0 | 0 | 0 |
| Newborns (0-27days) | 0 | 0 | 0 |
| Infants and toddlers (28days – 23months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 year) | 30 | 34 | 18 |
| From 18 - 64 years | 164 | 158 | 78 |
| From 65 – 84 years | 1 | 0 | 0 |
| Over 85 years | 0 | 0 | 0 |
| Age Continuous | | | |
| Age Continuous Characteristic | | | |
| Units: Years | | | |
| arithmetic mean | 39.9 | 41 | 40 |
| standard deviation | ± 15.8 | ± 17.2 | ± 17.3 |
| Gender Categorical | | | |
| Gender Categorical Characteristic | | | |
| Units: Subjects | | | |
| Female | 118 | 115 | 55 |
| Male | 77 | 77 | 41 |

| Reporting group values | Seretide 250 Evohaler | Total | |
|--|-----------------------|-------|--|
| Number of subjects | 89 | 572 | |
| Age Categorical | | | |
| Age Categorical Characteristic | | | |
| Units: Subjects | | | |
| In Utero | 0 | 0 | |
| Preterm newborn- gestational age < 37 wk | 0 | 0 | |
| Newborns (0-27days) | 0 | 0 | |

| | | | |
|--|--------|-----|--|
| Infants and toddlers (28days – 23months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 year) | 12 | 94 | |
| From 18 - 64 years | 77 | 477 | |
| From 65 – 84 years | 0 | 1 | |
| Over 85 years | 0 | 0 | |
| Age Continuous | | | |
| Age Continuous Characteristic | | | |
| Units: Years | | | |
| arithmetic mean | 39.3 | | |
| standard deviation | ± 16.3 | - | |
| Gender Categorical | | | |
| Gender Categorical Characteristic | | | |
| Units: Subjects | | | |
| Female | 49 | 337 | |
| Male | 40 | 235 | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) |
| Reporting group description: - | |
| Reporting group title | Seretide 50 Evohaler |
| Reporting group description: - | |
| Reporting group title | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) |
| Reporting group description: - | |
| Reporting group title | Seretide 250 Evohaler |
| Reporting group description: - | |
| Subject analysis set title | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - Safety Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The analysis consist of all patients who - were randomized - received at least one dose of IP | |
| Subject analysis set title | Seretide 50 Evohaler - Safety Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The analysis consist of all patients who - were randomized - received at least one dose of IP | |
| Subject analysis set title | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - Safety Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The analysis consist of all patients who - were randomized - received at least one dose of IP | |
| Subject analysis set title | Seretide 250 Evohaler - Safety Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The analysis consist of all patients who - were randomized - received at least one dose of IP | |
| Subject analysis set title | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The analysis consist of all patients who - are included in the Safety analysis set - had FEV1 data after the baseline visit | |
| Subject analysis set title | Seretide 50 Evohaler - FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The analysis consist of all patients who - are included in the Safety analysis set - had FEV1 data after the baseline visit | |
| Subject analysis set title | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The analysis consist of all patients who - are included in the Safety analysis set - had FEV1 data after the baseline visit | |
| Subject analysis set title | Seretide 250 Evohaler - FAS |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The analysis consist of all patients who
- are included in the Safety analysis set
- had FEV1 data after the baseline visit

| | |
|----------------------------|--|
| Subject analysis set title | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - PPS |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The analysis consist of all patients who
- are included in the FA set
- completed the study
- had no major protocol violations

| | |
|----------------------------|----------------------------|
| Subject analysis set title | Seretide 50 Evohaler - PPS |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The analysis consist of all patients who
- are included in the FA set
- completed the study
- had no major protocol violations

| | |
|----------------------------|---|
| Subject analysis set title | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - PPS |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The analysis consist of all patients who
- are included in the FA set
- completed the study
- had no major protocol violations

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | Seretide 250 Evohaler - PPS |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The analysis consist of all patients who
- are included in the FA set
- completed the study
- had no major protocol violations

Primary: The mean change in FEV1 from baseline to the end of 12-week study period (Visit 6)

| | |
|-----------------|--|
| End point title | The mean change in FEV1 from baseline to the end of 12-week study period (Visit 6) |
|-----------------|--|

End point description:

The change from baseline at the end of the 12-week treatment period. Missing values of the primary endpoint 'change in FEV1' were replaced using the last-value-carried-forward strategy as follows: in case if both pre-dose FEV1 values were missing at Visit 6/ET, the last value observed under treatment before Visit 6/ET was imputed as Visit 6/ET value. If there is no such last value under treatment, no imputation was made. If there is only one assessment of FEV1 pre-dose values at Visit 0 or Visit 6/ET is done, the available value was used for analysis.

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

End point timeframe:

From baseline (Visit 0) to end of 12 weeks study period (Visit 6)

| End point values | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - FAS | Seretide 50 Evohaler - FAS | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - FAS | Seretide 250 Evohaler - FAS |
|-----------------------------|--|----------------------------|---|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 192 | 190 | 95 | 88 |
| Units: Litre | | | | |

| arithmetic mean (standard deviation) | | | | |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Baseline, FEV1 | 2.218 (± 0.544) | 2.127 (± 0.521) | 2.158 (± 0.597) | 2.221 (± 0.548) |
| Endpoint, FEV1 | 2.595 (± 0.814) | 2.57 (± 0.791) | 2.574 (± 0.884) | 2.742 (± 0.762) |
| Change from Baseline | 0.377 (± 0.472) | 0.443 (± 0.475) | 0.416 (± 0.477) | 0.522 (± 0.486) |

| End point values | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - PPS | Seretide 50 Evohaler - PPS | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - PPS | Seretide 250 Evohaler - PPS |
|--------------------------------------|--|----------------------------|---|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 183 | 177 | 89 | 81 |
| Units: Litre | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline, FEV1 | 2.226 (± 0.545) | 2.127 (± 0.513) | 2.154 (± 0.576) | 2.239 (± 0.54) |
| Endpoint, FEV1 | 2.611 (± 0.808) | 2.541 (± 0.765) | 2.587 (± 0.858) | 2.752 (± 0.768) |
| Change from Baseline | 0.385 (± 0.47) | 0.414 (± 0.458) | 0.433 (± 0.478) | 0.512 (± 0.491) |

Statistical analyses

| Statistical analysis title | Statistical analysis 1: ANCOVA |
|---|---|
| Statistical analysis description: | |
| An Analysis of Covariance (ANCOVA) using treatment and centre as factors and baseline FEV1 and age as co-variables. | |
| The first null hypothesis was that with respect to the change from baseline FEV1 (mean of the 2 pre-dose values at Visit 0) the test formulation is inferior to the reference formulation (the difference in means, $\mu_{\text{test}} - \mu_{\text{ref}}$ is smaller than -200mL) in favour of the alternative hypothesis that the test product is equivalent to or better than the reference product. | |
| Comparison groups | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - FAS v Seretide 50 Evohaler - FAS |
| Number of subjects included in analysis | 382 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.9739 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.080611 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 1-sided |
| lower limit | -0.161974 |

| Statistical analysis title | Statistical analysis 2: ANCOVA |
|----------------------------|--------------------------------|
|----------------------------|--------------------------------|

Statistical analysis description:

An Analysis of Covariance (ANCOVA) using treatment and centre as factors and baseline FEV1 and age as co-variables.

The first null hypothesis was that with respect to the change from baseline FEV1 (mean of the 2 pre-dose values at Visit 0) the test formulation is inferior to the reference formulation (the difference in means, $\mu_{\text{test}} - \mu_{\text{ref}}$ is smaller than -200mL) in favour of the alternative hypothesis that the test product is equivalent to or better than the reference product.

| | |
|---|---|
| Comparison groups | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - PPS v Seretide 50 Evohaler - PPS |
| Number of subjects included in analysis | 360 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.9104 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.056504 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 1-sided |
| lower limit | -0.139088 |

Statistical analysis title

Statistical analysis 3: ANCOVA

Statistical analysis description:

An Analysis of Covariance (ANCOVA) using treatment and centre as factors and baseline FEV1 and age as co-variables.

The first null hypothesis was that with respect to the change from baseline FEV1 (mean of the 2 pre-dose values at Visit 0) the test formulation is inferior to the reference formulation (the difference in means, $\mu_{\text{test}} - \mu_{\text{ref}}$ is smaller than -200mL) in favour of the alternative hypothesis that the test product is equivalent to or better than the reference product.

| | |
|---|---|
| Comparison groups | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - FAS v Seretide 250 Evohaler - FAS |
| Number of subjects included in analysis | 183 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.9489 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.102292 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 1-sided |
| lower limit | -0.225175 |

Statistical analysis title

Statistical analysis 4: ANCOVA

Statistical analysis description:

An Analysis of Covariance (ANCOVA) using treatment and centre as factors and baseline FEV1 and age as co-variables.

The first null hypothesis was that with respect to the change from baseline FEV1 (mean of the 2 pre-dose values at Visit 0) the test formulation is inferior to the reference formulation (the difference in means, $\mu_{\text{test}} - \mu_{\text{ref}}$ is smaller than -200mL) in favour of the alternative hypothesis that the test product is equivalent to or better than the reference product.

| | |
|---|---|
| Comparison groups | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - PPS v Seretide 250 Evohaler - PPS |
| Number of subjects included in analysis | 170 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.8427 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.066329 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 1-sided |
| lower limit | -0.196239 |

Primary: AUC(0–12)/12 at the end of 12-week study period (Visit 6) relative to baseline

| | |
|--|--|
| End point title | AUC(0–12)/12 at the end of 12-week study period (Visit 6) relative to baseline |
| End point description: The area under the 12-hour serial FEV1 curve (AUC0-12) at the end of the 12-week treatment period (Visit 6) relative to baseline FEV1 (mean of the 2 pre-dose values at Visit 0). Missing values of the second primary endpoint 'FEV1 AUC(0-12)' were replaced using linear interpolation. | |
| End point type | Primary |
| End point timeframe: From baseline (Visit 0) to end of 12 weeks study period (Visit 6) | |

| End point values | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - FAS | Seretide 50 Evohaler - FAS | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - FAS | Seretide 250 Evohaler - FAS |
|---|--|----------------------------|---|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 192 | 190 | 95 | 88 |
| Units: Litre | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline, FEV1 | 2.218 (± 0.544) | 2.127 (± 0.521) | 2.158 (± 0.597) | 2.221 (± 0.548) |
| AUC(0–12)/12 (L) at V6/ET | 2.733 (± 0.825) | 2.702 (± 0.813) | 2.682 (± 0.868) | 2.896 (± 0.849) |
| Ratio of AUC(0–12)/12 and Baseline | 1.225 (± 0.21) | 1.262 (± 0.227) | 1.246 (± 0.221) | 1.303 (± 0.229) |
| Log of Ratio of AUC(0–12)/12 and Baseline | 0.189 (± 0.165) | 0.217 (± 0.179) | 0.205 (± 0.168) | 0.25 (± 0.17) |

| End point values | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - | Seretide 50 Evohaler - PPS | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - | Seretide 250 Evohaler - PPS |
|------------------|--|----------------------------|---|-----------------------------|
|------------------|--|----------------------------|---|-----------------------------|

| | PPS | | PPS | |
|---|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 183 | 177 | 89 | 81 |
| Units: Litre | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline, FEV1 | 2.226 (± 0.545) | 2.127 (± 0.513) | 2.154 (± 0.576) | 2.239 (± 0.54) |
| AUC(0–12)/12 (L) at V6/ET | 2.732 (± 0.829) | 2.677 (± 0.792) | 2.693 (± 0.865) | 2.899 (± 0.854) |
| Ratio of AUC(0–12)/12 and Baseline | 1.223 (± 0.209) | 1.255 (± 0.223) | 1.248 (± 0.222) | 1.299 (± 0.228) |
| Log of Ratio of AUC(0–12)/12 and Baseline | 0.187 (± 0.165) | 0.212 (± 0.177) | 0.207 (± 0.169) | 0.247 (± 0.169) |

Statistical analyses

| Statistical analysis title | Statistical analysis 5: ANCOVA |
|--|---|
| Statistical analysis description: | |
| Analysis of Covariance (ANCOVA) using treatment and centre as factors and log transformed baseline FEV1 and age as co-variables. | |
| The second null hypothesis was that with respect to the FEV1 AUC(0-12) after 12 weeks of treatment relative to baseline FEV1 the test formulation is inferior to the reference formulation (the ratio in means, $\mu_{\text{test}}/\mu_{\text{ref}}$, is smaller than 80%) in favour of the alternative hypothesis that the test formulation is equivalent to or better than the reference formulation. | |
| Comparison groups | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - FAS v Seretide 50 Evohaler - FAS |
| Number of subjects included in analysis | 382 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.9818 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.968004 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 1-sided |
| lower limit | 0.938962 |

| Statistical analysis title | Statistical analysis 6: ANCOVA |
|--|---|
| Statistical analysis description: | |
| Analysis of Covariance (ANCOVA) using treatment and centre as factors and log transformed baseline FEV1 and age as co-variables. | |
| The second null hypothesis was that with respect to the FEV1 AUC(0-12) after 12 weeks of treatment relative to baseline FEV1 the test formulation is inferior to the reference formulation (the ratio in means, $\mu_{\text{test}}/\mu_{\text{ref}}$, is smaller than 80%) in favour of the alternative hypothesis that the test formulation is equivalent to or better than the reference formulation. | |
| Comparison groups | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - PPS v Seretide 50 Evohaler - PPS |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 360 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.9721 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.970518 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 1-sided |
| lower limit | 0.941211 |

| | |
|-----------------------------------|--------------------------------|
| Statistical analysis title | Statistical analysis 7: ANCOVA |
|-----------------------------------|--------------------------------|

Statistical analysis description:

Analysis of Covariance (ANCOVA) using treatment and centre as factors and log transformed baseline FEV1 and age as co-variables.

The second null hypothesis was that with respect to the FEV1 AUC(0-12) after 12 weeks of treatment relative to baseline FEV1 the test formulation is inferior to the reference formulation (the ratio in means, $\mu_{\text{test}}/\mu_{\text{ref}}$, is smaller than 80%) in favour of the alternative hypothesis that the test formulation is equivalent to or better than the reference formulation.

| | |
|---|---|
| Comparison groups | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - FAS v Seretide 250 Evohaler - FAS |
| Number of subjects included in analysis | 183 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.9822 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.952911 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 1-sided |
| lower limit | 0.911031 |

| | |
|-----------------------------------|--------------------------------|
| Statistical analysis title | Statistical analysis 8: ANCOVA |
|-----------------------------------|--------------------------------|

Statistical analysis description:

Analysis of Covariance (ANCOVA) using treatment and centre as factors and log transformed baseline FEV1 and age as co-variables.

The second null hypothesis was that with respect to the FEV1 AUC(0-12) after 12 weeks of treatment relative to baseline FEV1 the test formulation is inferior to the reference formulation (the ratio in means, $\mu_{\text{test}}/\mu_{\text{ref}}$, is smaller than 80%) in favour of the alternative hypothesis that the test formulation is equivalent to or better than the reference formulation.

| | |
|-------------------|---|
| Comparison groups | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - PPS v Seretide 250 Evohaler - PPS |
|-------------------|---|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 170 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.9621 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.960046 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 1-sided |
| lower limit | 0.917738 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first intake of investigational product (IP) till the 28 days after the last intake of IP

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 11.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - Safety Set |
|-----------------------|---|

Reporting group description: -

| | |
|-----------------------|------------------------------------|
| Reporting group title | Seretide 250 Evohaler - Safety Set |
|-----------------------|------------------------------------|

Reporting group description: -

| | |
|-----------------------|--|
| Reporting group title | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - Safety Set |
|-----------------------|--|

Reporting group description: -

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Seretide 50 Evohaler - Safety Set |
|-----------------------|-----------------------------------|

Reporting group description: -

| Serious adverse events | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - Safety Set | Seretide 250 Evohaler - Safety Set | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - Safety Set |
|---|---|------------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | Seretide 50 Evohaler - Safety Set | | |
|---|-----------------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Salmeterol/Fluticasone MDI HEXAL (25 µg/50 µg) - Safety Set | Seretide 250 Evohaler - Safety Set | Salmeterol/Fluticasone MDI HEXAL (25 µg/250 µg) - Safety Set |
|--|---|------------------------------------|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 60 / 195 (30.77%) | 24 / 89 (26.97%) | 22 / 96 (22.92%) |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chills | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 1 / 96 (1.04%) |
| occurrences (all) | 0 | 0 | 1 |
| Oedema | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 1 / 89 (1.12%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 1 / 89 (1.12%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 3 / 195 (1.54%) | 1 / 89 (1.12%) | 2 / 96 (2.08%) |
| occurrences (all) | 3 | 1 | 2 |
| Dysphonia | | | |
| subjects affected / exposed | 7 / 195 (3.59%) | 3 / 89 (3.37%) | 3 / 96 (3.13%) |
| occurrences (all) | 7 | 3 | 3 |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 1 / 96 (1.04%) |
| occurrences (all) | 1 | 0 | 1 |
| Pharyngolaryngeal pain | | | |
| subjects affected / exposed | 2 / 195 (1.03%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 2 / 89 (2.25%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Sneezing | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Wheezing | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Nervousness | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 1 / 89 (1.12%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 2 / 89 (2.25%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cortisol free urine increased | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Electrocardiogram t wave inversion | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 2 / 195 (1.03%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 1 / 96 (1.04%) |
| occurrences (all) | 0 | 0 | 1 |
| Fibula fracture | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hand fracture | | | |

| | | | |
|--------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Joint sprain | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 1 / 89 (1.12%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Extrasystoles | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Supraventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 1 / 96 (1.04%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 4 / 195 (2.05%) | 1 / 89 (1.12%) | 1 / 96 (1.04%) |
| occurrences (all) | 4 | 1 | 3 |
| Intercostal neuralgia | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tremor | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 1 / 89 (1.12%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 1 / 96 (1.04%) |
| occurrences (all) | 1 | 0 | 1 |
| Gastrointestinal disorders | | | |

| | | | |
|---|-----------------|----------------|----------------|
| Cheilitis | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 1 / 89 (1.12%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 1 / 96 (1.04%) |
| occurrences (all) | 0 | 0 | 1 |
| Duodenitis | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 1 / 96 (1.04%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Photodermatosis | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 1 / 96 (1.04%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 1 / 89 (1.12%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Endocrine disorders | | | |
| Toxic nodular goitre | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|------------------------------|-----------------|----------------|----------------|
| Back pain | | | |
| subjects affected / exposed | 3 / 195 (1.54%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Limb discomfort | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 1 / 89 (1.12%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 1 / 89 (1.12%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Acute sinusitis | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 1 / 89 (1.12%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Acute tonsillitis | | | |
| subjects affected / exposed | 2 / 195 (1.03%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 195 (2.05%) | 1 / 89 (1.12%) | 1 / 96 (1.04%) |
| occurrences (all) | 4 | 1 | 1 |
| Candidiasis | | | |
| subjects affected / exposed | 2 / 195 (1.03%) | 2 / 89 (2.25%) | 0 / 96 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Cystitis | | | |

| | | | |
|-----------------------------------|------------------|----------------|----------------|
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 1 / 96 (1.04%) |
| occurrences (all) | 0 | 0 | 1 |
| Influenza | | | |
| subjects affected / exposed | 4 / 195 (2.05%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 1 / 89 (1.12%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 10 / 195 (5.13%) | 0 / 89 (0.00%) | 3 / 96 (3.13%) |
| occurrences (all) | 10 | 0 | 3 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal candidiasis | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 4 / 89 (4.49%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 12 / 195 (6.15%) | 5 / 89 (5.62%) | 6 / 96 (6.25%) |
| occurrences (all) | 14 | 5 | 7 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 7 / 195 (3.59%) | 2 / 89 (2.25%) | 5 / 96 (5.21%) |
| occurrences (all) | 9 | 2 | 6 |
| Rhinitis | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 2 / 195 (1.03%) | 0 / 89 (0.00%) | 2 / 96 (2.08%) |
| occurrences (all) | 2 | 0 | 2 |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 1 / 89 (1.12%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tracheobronchitis | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 1 / 96 (1.04%) |
| occurrences (all) | 0 | 0 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 195 (1.03%) | 1 / 89 (1.12%) | 2 / 96 (2.08%) |
| occurrences (all) | 2 | 1 | 2 |
| Viral infection | | | |
| subjects affected / exposed | 1 / 195 (0.51%) | 0 / 89 (0.00%) | 1 / 96 (1.04%) |
| occurrences (all) | 1 | 0 | 1 |
| Viral rhinitis | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 0 / 96 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 195 (0.00%) | 0 / 89 (0.00%) | 1 / 96 (1.04%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|--------------------------------------|--|--|
| Non-serious adverse events | Seretide 50 Evohaler - Safety Set | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 41 / 192 (21.35%) | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Chills | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oedema | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 2 / 192 (1.04%) | | |
| occurrences (all) | 2 | | |
| Dysphonia | | | |
| subjects affected / exposed | 2 / 192 (1.04%) | | |
| occurrences (all) | 3 | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Pharyngolaryngeal pain | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sneezing | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Wheezing | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Nervousness | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Alanine aminotransferase increased | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cortisol free urine increased | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Electrocardiogram t wave inversion | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Weight increased | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Joint sprain | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Extrasystoles | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Supraventricular extrasystoles | | | |

| | | | |
|--|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 192 (0.00%) 0 | | |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Headache | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 3 | | |
| Intercostal neuralgia | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tremor | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Cheilitis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Duodenitis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastritis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Toothache | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Photodermatosis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Endocrine disorders | | | |
| Toxic nodular goitre | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Limb discomfort | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 3 | | |
| Muscular weakness | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Acute sinusitis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Acute tonsillitis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Candidiasis | | | |
| subjects affected / exposed | 2 / 192 (1.04%) | | |
| occurrences (all) | 2 | | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 7 / 192 (3.65%) | | |
| occurrences (all) | 8 | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |

| | | | |
|-----------------------------------|------------------|--|--|
| Oral herpes | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Oropharyngeal candidiasis | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Paronychia | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 3 / 192 (1.56%) | | |
| occurrences (all) | 3 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 12 / 192 (6.25%) | | |
| occurrences (all) | 12 | | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 6 / 192 (3.13%) | | |
| occurrences (all) | 6 | | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tracheobronchitis | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 192 (1.56%) | | |
| occurrences (all) | 3 | | |

| | | | |
|---|-----------------|--|--|
| Viral infection | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Viral rhinitis | | | |
| subjects affected / exposed | 1 / 192 (0.52%) | | |
| occurrences (all) | 1 | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 192 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported