



## Clinical trial results:

**Double-blind, double-dummy, multi-center, randomized parallel group study to demonstrate therapeutic equivalence of Salmeterol/Fluticasone**

**DPI HEXAL versus**

**Seretide™ 100 Accuhaler™ over a period of 12 weeks in pediatric patients with persistent moderate asthma**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2007-005630-36   |
| Trial protocol           | LT PL            |
| Global end of trial date | 22 February 2010 |

### Results information

|                                |                                                                         |
|--------------------------------|-------------------------------------------------------------------------|
| Result version number          | v2 (current)                                                            |
| This version publication date  | 24 March 2016                                                           |
| First version publication date | 05 August 2015                                                          |
| Version creation reason        | • Correction of full data set<br>Information about article 46 was wrong |

### Trial information

#### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | 2006-57-DPI-2 |
|-----------------------|---------------|

#### 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? | Yes |

Notes:

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**Results analysis stage**

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|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 26 November 2010 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 22 February 2010 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 22 February 2010 |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

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Main objective of the trial:

The objective of this study was to evaluate the long-term efficacy and safety of Salmeterol/Fluticasone DPI HEXAL compared to Seretide™ 100 Accuhaler™ in pediatric patients suffering from persistent moderate 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                          | 22 July 2009 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |               |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Lithuania: 34 |
| Country: Number of subjects enrolled | Poland: 71    |
| Country: Number of subjects enrolled | Romania: 13   |
| Country: Number of subjects enrolled | Ukraine: 100  |
| Worldwide total number of subjects   | 218           |
| EEA total number of subjects         | 118           |

Notes:

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**Subjects enrolled per age group**

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|                                           |     |
|-------------------------------------------|-----|
| 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)                     | 218 |

|                           |   |
|---------------------------|---|
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years)      | 0 |
| From 65 to 84 years       | 0 |
| 85 years and over         | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Double-blind, double-dummy, multi-center, randomized, parallel group study in pediatric patients with persistent moderate asthma.

### Pre-assignment

Screening details:

A total number of 229 patients were screened and 218 patients were randomized. The study consisted of a 2-week run-in wash-out period and a 12-week blinded treatment period. A screening visit (Visit -1) was followed by a 2-week run-in wash-out period during which all asthma treatments except reliever medication were to be stopped.

### Pre-assignment period milestones

|                              |                    |
|------------------------------|--------------------|
| Number of subjects started   | 229 <sup>[1]</sup> |
| Number of subjects completed | 218                |

### Pre-assignment subject non-completion reasons

|                            |                                 |
|----------------------------|---------------------------------|
| Reason: Number of subjects | Consent withdrawn by subject: 2 |
| Reason: Number of subjects | Ineligibility: 8                |
| Reason: Number of subjects | Other reason: 1                 |

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: 11 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                              |
| <b>Arm title</b>             | Salmeterol/Fluticasone DPI HEXAL |

Arm description: -

|                                        |                                  |
|----------------------------------------|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Salmeterol/Fluticasone DPI HEXAL |
| Investigational medicinal product code |                                  |
| Other name                             | NA                               |
| Pharmaceutical forms                   | Pressurised inhalation           |
| Routes of administration               | Inhalation use                   |

Dosage and administration details:

Salmeterol/Fluticasone DPI HEXAL (50 µg salmeterol/100 µg fluticasone per actuation), one actuation two times per day

|                    |                        |
|--------------------|------------------------|
| <b>Arm title</b>   | Seretide 100 Accuhaler |
| Arm description: - |                        |
| Arm type           | Active comparator      |

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Seretide 100 Accuhaler |
| Investigational medicinal product code |                        |
| Other name                             | NA                     |
| Pharmaceutical forms                   | Pressurised inhalation |
| Routes of administration               | Inhalation use         |

Dosage and administration details:

Seretide 100 Accuhaler (50 µg salmeterol/100 µg fluticasone per actuation), one actuation two times per day

| <b>Number of subjects in period 1</b> | <b>Salmeterol/Fluticasone DPI HEXAL</b> | <b>Seretide 100 Accuhaler</b> |
|---------------------------------------|-----------------------------------------|-------------------------------|
| Started                               | 110                                     | 108                           |
| Completed                             | 108                                     | 106                           |
| Not completed                         | 2                                       | 2                             |
| Consent withdrawn by subject          | 1                                       | 1                             |
| Lost to follow-up                     | 1                                       | -                             |
| Protocol deviation                    | -                                       | 1                             |

## Baseline characteristics

### Reporting groups

|                                |                                  |
|--------------------------------|----------------------------------|
| Reporting group title          | Salmeterol/Fluticasone DPI HEXAL |
| Reporting group description: - |                                  |
| Reporting group title          | Seretide 100 Accuhaler           |
| Reporting group description: - |                                  |

| Reporting group values                   | Salmeterol/Fluticasone DPI HEXAL | Seretide 100 Accuhaler | Total |
|------------------------------------------|----------------------------------|------------------------|-------|
| Number of subjects                       | 110                              | 108                    | 218   |
| 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)                    | 110                              | 108                    | 218   |
| Adolescents (12-17 year)                 | 0                                | 0                      | 0     |
| From 18 - 64 years                       | 0                                | 0                      | 0     |
| From 65 – 84 years                       | 0                                | 0                      | 0     |
| Over 85 years                            | 0                                | 0                      | 0     |
| Age Continuous                           |                                  |                        |       |
| Age Continuous Characteristic            |                                  |                        |       |
| Units: Years                             |                                  |                        |       |
| arithmetic mean                          | 8.1                              | 8.5                    |       |
| standard deviation                       | ± 2                              | ± 1.8                  | -     |
| Gender Categorical                       |                                  |                        |       |
| Gender Categorical Characteristic        |                                  |                        |       |
| Units: Subjects                          |                                  |                        |       |
| Female                                   | 38                               | 39                     | 77    |
| Male                                     | 72                               | 69                     | 141   |

## End points

### End points reporting groups

|                                                                                                                                                                           |                                                            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| Reporting group title                                                                                                                                                     | Salmeterol/Fluticasone DPI HEXAL                           |
| Reporting group description: -                                                                                                                                            |                                                            |
| Reporting group title                                                                                                                                                     | Seretide 100 Accuhaler                                     |
| Reporting group description: -                                                                                                                                            |                                                            |
| Subject analysis set title                                                                                                                                                | Salmeterol/Fluticasone DPI HEXAL (6-11 years) - Safety Set |
| Subject analysis set type                                                                                                                                                 | Safety analysis                                            |
| Subject analysis set description:<br>The analysis set consists of all patients who were randomized and received at least one dose of IP.                                  |                                                            |
| Subject analysis set title                                                                                                                                                | Seretide 100 Accuhaler (4-5 years) - Safety Set            |
| Subject analysis set type                                                                                                                                                 | Safety analysis                                            |
| Subject analysis set description:<br>The analysis set consists of all patients who were randomized and received at least one dose of IP.                                  |                                                            |
| Subject analysis set title                                                                                                                                                | Salmeterol/Fluticasone DPI HEXAL (4-5 years) - Safety Set  |
| Subject analysis set type                                                                                                                                                 | Safety analysis                                            |
| Subject analysis set description:<br>The analysis set consists of all patients who were randomized and received at least one dose of IP.                                  |                                                            |
| Subject analysis set title                                                                                                                                                | Seretide 100 Accuhaler (4-5 years) - FAS                   |
| Subject analysis set type                                                                                                                                                 | Full analysis                                              |
| Subject analysis set description:<br>The analysis set consists of all patients who were included in the Safety Set and had clinic FEV1 data after the baseline visit.     |                                                            |
| Subject analysis set title                                                                                                                                                | Salmeterol/Fluticasone DPI HEXAL (6-11 years) - FAS        |
| Subject analysis set type                                                                                                                                                 | Full analysis                                              |
| Subject analysis set description:<br>The analysis set consists of all patients who were included in the Safety Set and had clinic FEV1 data after the baseline visit.     |                                                            |
| Subject analysis set title                                                                                                                                                | Seretide 100 Accuhaler (6-11 years) - Safety Set           |
| Subject analysis set type                                                                                                                                                 | Safety analysis                                            |
| Subject analysis set description:<br>The analysis set consists of all patients who were randomized and received at least one dose of IP.                                  |                                                            |
| Subject analysis set title                                                                                                                                                | Salmeterol/Fluticasone DPI HEXAL (4-5 years) - FAS         |
| Subject analysis set type                                                                                                                                                 | Full analysis                                              |
| Subject analysis set description:<br>The analysis set consists of all patients who were included in the SS and had clinic FEV1 data after the baseline visit.             |                                                            |
| Subject analysis set title                                                                                                                                                | Salmeterol/Fluticasone DPI HEXAL (6-11 years) - PPS        |
| Subject analysis set type                                                                                                                                                 | Per protocol                                               |
| Subject analysis set description:<br>The analysis set consists of all patients who were included in the FAS and completed the study and had no major protocol violations. |                                                            |
| Subject analysis set title                                                                                                                                                | Seretide 100 Accuhaler (6-11 years) - FAS                  |
| Subject analysis set type                                                                                                                                                 | Full analysis                                              |
| Subject analysis set description:<br>The analysis set consists of all patients who were included in the Safety Set and had clinic FEV1 data after the baseline visit.     |                                                            |
| Subject analysis set title                                                                                                                                                | Seretide 100 Accuhaler (6-11 years) - PPS                  |
| Subject analysis set type                                                                                                                                                 | Per protocol                                               |
| Subject analysis set description:<br>The analysis set consists of all patients who were included in the FAS and completed the study and had                               |                                                            |

**Primary: Relative Change in FEV1 from baseline to the end of treatment period**

|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | Relative Change in FEV1 from baseline to the end of treatment period |
|-----------------|----------------------------------------------------------------------|

End point description:

The change in FEV1 from baseline at the end of the 12-week treatment period. Missing values of the primary endpoint 'relative change in FEV1' were replaced using the last-value carried-forward strategy as follows: in case if both pre-dose FEV1 values was 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:

End of 12 weeks treatment period

| End point values                     | Salmeterol/Fluticasone DPI HEXAL (6-11 years) - PPS | Seretide 100 Accuhaler (6-11 years) - PPS |  |  |
|--------------------------------------|-----------------------------------------------------|-------------------------------------------|--|--|
| Subject group type                   | Subject analysis set                                | Subject analysis set                      |  |  |
| Number of subjects analysed          | 96                                                  | 98                                        |  |  |
| Units: Litre                         |                                                     |                                           |  |  |
| arithmetic mean (standard deviation) |                                                     |                                           |  |  |
| Baseline, FEV1                       | 1.377 (± 0.296)                                     | 1.402 (± 0.275)                           |  |  |
| Endpoint, FEV1                       | 1.853 (± 0.439)                                     | 1.865 (± 0.4)                             |  |  |
| Relative Change from Baseline (%)    | 35.4 (± 21.37)                                      | 33.9 (± 19.97)                            |  |  |

**Statistical analyses**

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

An Analysis of Covariance (ANCOVA) using treatment and centre as factors and baseline FEV1 (mean of the 2 pre-dose values at Visit 0) and age as co-variables was performed on the change.

|                                         |                                                                                                 |
|-----------------------------------------|-------------------------------------------------------------------------------------------------|
| Comparison groups                       | Salmeterol/Fluticasone DPI HEXAL (6-11 years) - PPS v Seretide 100 Accuhaler (6-11 years) - PPS |
| Number of subjects included in analysis | 194                                                                                             |
| Analysis specification                  | Pre-specified                                                                                   |
| Analysis type                           | non-inferiority                                                                                 |
| P-value                                 | = 0.646                                                                                         |
| Method                                  | ANCOVA                                                                                          |
| Parameter estimate                      | Mean Difference                                                                                 |
| Point estimate                          | 0.011932                                                                                        |

|                     |           |
|---------------------|-----------|
| Confidence interval |           |
| level               | 95 %      |
| sides               | 2-sided   |
| lower limit         | -0.039171 |
| upper limit         | 0.063036  |

**Primary: The area under the 4-hour serial FEV1 curve (AUC0-4) at the end of the 12-week treatment period (Visit 6) relative to the mean FEV1 value at Visit 6 pre-inhalation**

|                 |                                                                                                                                                                     |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | The area under the 4-hour serial FEV1 curve (AUC0-4) at the end of the 12-week treatment period (Visit 6) relative to the mean FEV1 value at Visit 6 pre-inhalation |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The area under the 4-hour serial FEV1 curve

(AUC0-4) at the end of the 12-week treatment period (Visit 6) relative to the mean FEV1 value at Visit 6 pre-inhalation. Missing values of the second primary endpoint 'FEV1 AUC(0-4)' were replaced using linear interpolation.

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

End point timeframe:

At the end of the double blind treatment period

|                                                |                                                     |                                           |  |  |
|------------------------------------------------|-----------------------------------------------------|-------------------------------------------|--|--|
| <b>End point values</b>                        | Salmeterol/Fluticasone DPI HEXAL (6-11 years) - PPS | Seretide 100 Accuhaler (6-11 years) - PPS |  |  |
| Subject group type                             | Subject analysis set                                | Subject analysis set                      |  |  |
| Number of subjects analysed                    | 96                                                  | 98                                        |  |  |
| Units: Litre                                   |                                                     |                                           |  |  |
| arithmetic mean (standard deviation)           |                                                     |                                           |  |  |
| FEV1 pre-IP Inhalation                         | 1.853 (± 0.439)                                     | 1.865 (± 0.4)                             |  |  |
| AUC(0-4)/4 (L) at V6/ET                        | 1.92 (± 0.45)                                       | 1.959 (± 0.423)                           |  |  |
| Ratio of AUC(0-4)/4 and FEV1 pre-IP Inhalation | 1.039 (± 0.059)                                     | 1.052 (± 0.081)                           |  |  |

**Statistical analyses**

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

An Analysis of Covariance (ANCOVA) was performed using treatment and centre as factors, age and log transformed pre-inhalation FEV1 as co-variables.

|                   |                                                                                                 |
|-------------------|-------------------------------------------------------------------------------------------------|
| Comparison groups | Salmeterol/Fluticasone DPI HEXAL (6-11 years) - PPS v Seretide 100 Accuhaler (6-11 years) - PPS |
|-------------------|-------------------------------------------------------------------------------------------------|

|                                         |                 |
|-----------------------------------------|-----------------|
| Number of subjects included in analysis | 194             |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | non-inferiority |
| P-value                                 | = 0.142         |
| Method                                  | ANCOVA          |
| Parameter estimate                      | Ratio           |
| Point estimate                          | 0.987814        |
| Confidence interval                     |                 |
| level                                   | 95 %            |
| sides                                   | 2-sided         |
| lower limit                             | 0.971726        |
| upper limit                             | 1.004169        |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first intake of investigational product (IP) till the patient's last study visit.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 12.1 |
|--------------------|------|

### Reporting groups

|                       |                                                           |
|-----------------------|-----------------------------------------------------------|
| Reporting group title | Salmeterol/Fluticasone DPI HEXAL (4-5 years) - Safety Set |
|-----------------------|-----------------------------------------------------------|

Reporting group description: -

|                       |                                                 |
|-----------------------|-------------------------------------------------|
| Reporting group title | Seretide 100 Accuhaler (4-5 years) - Safety Set |
|-----------------------|-------------------------------------------------|

Reporting group description: -

|                       |                                                  |
|-----------------------|--------------------------------------------------|
| Reporting group title | Seretide 100 Accuhaler (6-11 years) - Safety Set |
|-----------------------|--------------------------------------------------|

Reporting group description: -

|                       |                                                            |
|-----------------------|------------------------------------------------------------|
| Reporting group title | Salmeterol/Fluticasone DPI HEXAL (6-11 years) - Safety Set |
|-----------------------|------------------------------------------------------------|

Reporting group description: -

| <b>Serious adverse events</b>                     | Salmeterol/Fluticasone DPI HEXAL (4-5 years) - Safety Set | Seretide 100 Accuhaler (4-5 years) - Safety Set | Seretide 100 Accuhaler (6-11 years) - Safety Set |
|---------------------------------------------------|-----------------------------------------------------------|-------------------------------------------------|--------------------------------------------------|
| Total subjects affected by serious adverse events |                                                           |                                                 |                                                  |
| subjects affected / exposed                       | 0 / 10 (0.00%)                                            | 0 / 6 (0.00%)                                   | 2 / 102 (1.96%)                                  |
| number of deaths (all causes)                     | 0                                                         | 0                                               | 0                                                |
| number of deaths resulting from adverse events    | 0                                                         | 0                                               | 0                                                |
| Respiratory, thoracic and mediastinal disorders   |                                                           |                                                 |                                                  |
| Asthma                                            |                                                           |                                                 |                                                  |
| subjects affected / exposed                       | 0 / 10 (0.00%)                                            | 0 / 6 (0.00%)                                   | 1 / 102 (0.98%)                                  |
| occurrences causally related to treatment / all   | 0 / 0                                                     | 0 / 0                                           | 0 / 1                                            |
| deaths causally related to treatment / all        | 0 / 0                                                     | 0 / 0                                           | 0 / 0                                            |
| Respiratory failure                               |                                                           |                                                 |                                                  |
| subjects affected / exposed                       | 0 / 10 (0.00%)                                            | 0 / 6 (0.00%)                                   | 1 / 102 (0.98%)                                  |
| occurrences causally related to treatment / all   | 0 / 0                                                     | 0 / 0                                           | 0 / 1                                            |
| deaths causally related to treatment / all        | 0 / 0                                                     | 0 / 0                                           | 0 / 0                                            |
| Infections and infestations                       |                                                           |                                                 |                                                  |
| Respiratory tract infection                       |                                                           |                                                 |                                                  |
| subjects affected / exposed                       | 0 / 10 (0.00%)                                            | 0 / 6 (0.00%)                                   | 1 / 102 (0.98%)                                  |
| occurrences causally related to treatment / all   | 0 / 0                                                     | 0 / 0                                           | 0 / 1                                            |
| deaths causally related to treatment / all        | 0 / 0                                                     | 0 / 0                                           | 0 / 0                                            |

|                                                                  |                |               |                 |
|------------------------------------------------------------------|----------------|---------------|-----------------|
| Respiratory tract infection viral<br>subjects affected / exposed | 0 / 10 (0.00%) | 0 / 6 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to<br>treatment / all               | 0 / 0          | 0 / 0         | 0 / 1           |
| deaths causally related to<br>treatment / all                    | 0 / 0          | 0 / 0         | 0 / 0           |

|                                                   |                                                            |  |  |
|---------------------------------------------------|------------------------------------------------------------|--|--|
| <b>Serious adverse events</b>                     | Salmeterol/Fluticasone DPI HEXAL (6-11 years) - Safety Set |  |  |
| Total subjects affected by serious adverse events |                                                            |  |  |
| subjects affected / exposed                       | 0 / 100 (0.00%)                                            |  |  |
| number of deaths (all causes)                     | 0                                                          |  |  |
| number of deaths resulting from adverse events    | 0                                                          |  |  |
| Respiratory, thoracic and mediastinal disorders   |                                                            |  |  |
| Asthma                                            |                                                            |  |  |
| subjects affected / exposed                       | 0 / 100 (0.00%)                                            |  |  |
| occurrences causally related to treatment / all   | 0 / 0                                                      |  |  |
| deaths causally related to treatment / all        | 0 / 0                                                      |  |  |
| Respiratory failure                               |                                                            |  |  |
| subjects affected / exposed                       | 0 / 100 (0.00%)                                            |  |  |
| occurrences causally related to treatment / all   | 0 / 0                                                      |  |  |
| deaths causally related to treatment / all        | 0 / 0                                                      |  |  |
| Infections and infestations                       |                                                            |  |  |
| Respiratory tract infection                       |                                                            |  |  |
| subjects affected / exposed                       | 0 / 100 (0.00%)                                            |  |  |
| occurrences causally related to treatment / all   | 0 / 0                                                      |  |  |
| deaths causally related to treatment / all        | 0 / 0                                                      |  |  |
| Respiratory tract infection viral                 |                                                            |  |  |
| subjects affected / exposed                       | 0 / 100 (0.00%)                                            |  |  |
| occurrences causally related to treatment / all   | 0 / 0                                                      |  |  |
| deaths causally related to treatment / all        | 0 / 0                                                      |  |  |

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

| <b>Non-serious adverse events</b>                                                                                         | <b>Salmeterol/Fluticasone DPI HEXAL (4-5 years) - Safety Set</b> | <b>Seretide 100 Accuhaler (4-5 years) - Safety Set</b> | <b>Seretide 100 Accuhaler (6-11 years) - Safety Set</b> |
|---------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|--------------------------------------------------------|---------------------------------------------------------|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed                                      | 4 / 10 (40.00%)                                                  | 4 / 6 (66.67%)                                         | 39 / 102 (38.24%)                                       |
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 10 (0.00%)<br>0                                              | 0 / 6 (0.00%)<br>0                                     | 1 / 102 (0.98%)<br>1                                    |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                                                      | 0 / 10 (0.00%)<br>0                                              | 0 / 6 (0.00%)<br>0                                     | 1 / 102 (0.98%)<br>1                                    |
| Injury, poisoning and procedural complications<br>Traumatic arthritis<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0                                              | 0 / 6 (0.00%)<br>0                                     | 1 / 102 (0.98%)<br>1                                    |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 10 (0.00%)<br>0                                              | 1 / 6 (16.67%)<br>1                                    | 1 / 102 (0.98%)<br>3                                    |
| General disorders and administration site conditions<br>Pyrexia<br>subjects affected / exposed<br>occurrences (all)       | 0 / 10 (0.00%)<br>0                                              | 1 / 6 (16.67%)<br>1                                    | 0 / 102 (0.00%)<br>0                                    |
| Gastrointestinal disorders<br>Constipation<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 10 (0.00%)<br>0                                              | 0 / 6 (0.00%)<br>0                                     | 0 / 102 (0.00%)<br>0                                    |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                                             | 0 / 10 (0.00%)<br>0                                              | 0 / 6 (0.00%)<br>0                                     | 0 / 102 (0.00%)<br>0                                    |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)                                                             | 1 / 10 (10.00%)<br>1                                             | 1 / 6 (16.67%)<br>1                                    | 1 / 102 (0.98%)<br>1                                    |
| Gastritis<br>subjects affected / exposed<br>occurrences (all)                                                             | 1 / 10 (10.00%)<br>1                                             | 0 / 6 (0.00%)<br>0                                     | 0 / 102 (0.00%)<br>0                                    |
| Gastrointestinal disorder                                                                                                 |                                                                  |                                                        |                                                         |

|                                                                                                                           |                     |                     |                      |
|---------------------------------------------------------------------------------------------------------------------------|---------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                                                          | 0 / 10 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 1 / 102 (0.98%)<br>1 |
| Toothache<br>subjects affected / exposed<br>occurrences (all)                                                             | 0 / 10 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 102 (0.00%)<br>0 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                                              | 0 / 10 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 102 (0.00%)<br>0 |
| Respiratory, thoracic and mediastinal disorders<br>Asthma<br>subjects affected / exposed<br>occurrences (all)             | 0 / 10 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 102 (0.00%)<br>0 |
| Cough<br>subjects affected / exposed<br>occurrences (all)                                                                 | 0 / 10 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 102 (0.00%)<br>0 |
| Nasal septum deviation<br>subjects affected / exposed<br>occurrences (all)                                                | 0 / 10 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 102 (0.00%)<br>0 |
| Dysphonia<br>subjects affected / exposed<br>occurrences (all)                                                             | 0 / 10 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 1 / 102 (0.98%)<br>1 |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 10 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 | 0 / 102 (0.00%)<br>0 |
| Musculoskeletal and connective tissue disorders<br>Growth retardation<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 102 (0.00%)<br>0 |
| Jaw cyst<br>subjects affected / exposed<br>occurrences (all)                                                              | 0 / 10 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 1 / 102 (0.98%)<br>1 |
| Infections and infestations<br>Acute tonsillitis<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 10 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 102 (0.00%)<br>0 |

|                                   |                 |                |                 |
|-----------------------------------|-----------------|----------------|-----------------|
| Bronchitis                        |                 |                |                 |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 0 / 6 (0.00%)  | 0 / 102 (0.00%) |
| occurrences (all)                 | 0               | 0              | 0               |
| Bronchopneumonia                  |                 |                |                 |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 0 / 6 (0.00%)  | 1 / 102 (0.98%) |
| occurrences (all)                 | 0               | 0              | 1               |
| Ear lobe infection                |                 |                |                 |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 0 / 6 (0.00%)  | 0 / 102 (0.00%) |
| occurrences (all)                 | 0               | 0              | 0               |
| Herpes dermatitis                 |                 |                |                 |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 0 / 6 (0.00%)  | 0 / 102 (0.00%) |
| occurrences (all)                 | 0               | 0              | 0               |
| Influenza                         |                 |                |                 |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 0 / 6 (0.00%)  | 3 / 102 (2.94%) |
| occurrences (all)                 | 0               | 0              | 3               |
| Nasopharyngitis                   |                 |                |                 |
| subjects affected / exposed       | 1 / 10 (10.00%) | 0 / 6 (0.00%)  | 3 / 102 (2.94%) |
| occurrences (all)                 | 1               | 0              | 4               |
| Laryngitis                        |                 |                |                 |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 0 / 6 (0.00%)  | 0 / 102 (0.00%) |
| occurrences (all)                 | 0               | 0              | 0               |
| Pharyngitis                       |                 |                |                 |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 1 / 6 (16.67%) | 9 / 102 (8.82%) |
| occurrences (all)                 | 0               | 1              | 9               |
| Respiratory tract infection       |                 |                |                 |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 0 / 6 (0.00%)  | 4 / 102 (3.92%) |
| occurrences (all)                 | 0               | 0              | 5               |
| Respiratory tract infection viral |                 |                |                 |
| subjects affected / exposed       | 1 / 10 (10.00%) | 1 / 6 (16.67%) | 9 / 102 (8.82%) |
| occurrences (all)                 | 1               | 1              | 9               |
| Rhinitis                          |                 |                |                 |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 0 / 6 (0.00%)  | 4 / 102 (3.92%) |
| occurrences (all)                 | 0               | 0              | 4               |
| Sinusitis                         |                 |                |                 |
| subjects affected / exposed       | 0 / 10 (0.00%)  | 0 / 6 (0.00%)  | 0 / 102 (0.00%) |
| occurrences (all)                 | 0               | 0              | 0               |

|                                         |                 |                |                 |
|-----------------------------------------|-----------------|----------------|-----------------|
| Skin infection                          |                 |                |                 |
| subjects affected / exposed             | 0 / 10 (0.00%)  | 0 / 6 (0.00%)  | 1 / 102 (0.98%) |
| occurrences (all)                       | 0               | 0              | 1               |
| Tracheitis                              |                 |                |                 |
| subjects affected / exposed             | 0 / 10 (0.00%)  | 0 / 6 (0.00%)  | 0 / 102 (0.00%) |
| occurrences (all)                       | 0               | 0              | 0               |
| Upper respiratory tract infection       |                 |                |                 |
| subjects affected / exposed             | 1 / 10 (10.00%) | 1 / 6 (16.67%) | 3 / 102 (2.94%) |
| occurrences (all)                       | 1               | 1              | 3               |
| Urinary tract infection                 |                 |                |                 |
| subjects affected / exposed             | 0 / 10 (0.00%)  | 0 / 6 (0.00%)  | 0 / 102 (0.00%) |
| occurrences (all)                       | 0               | 0              | 0               |
| Varicella                               |                 |                |                 |
| subjects affected / exposed             | 0 / 10 (0.00%)  | 1 / 6 (16.67%) | 0 / 102 (0.00%) |
| occurrences (all)                       | 0               | 1              | 0               |
| Viral rhinitis                          |                 |                |                 |
| subjects affected / exposed             | 0 / 10 (0.00%)  | 0 / 6 (0.00%)  | 2 / 102 (1.96%) |
| occurrences (all)                       | 0               | 0              | 2               |
| Viral upper respiratory tract infection |                 |                |                 |
| subjects affected / exposed             | 0 / 10 (0.00%)  | 0 / 6 (0.00%)  | 4 / 102 (3.92%) |
| occurrences (all)                       | 0               | 0              | 5               |

|                                                       |                                                            |  |  |
|-------------------------------------------------------|------------------------------------------------------------|--|--|
| <b>Non-serious adverse events</b>                     | Salmeterol/Fluticasone DPI HEXAL (6-11 years) - Safety Set |  |  |
| Total subjects affected by non-serious adverse events |                                                            |  |  |
| subjects affected / exposed                           | 48 / 100 (48.00%)                                          |  |  |
| Investigations                                        |                                                            |  |  |
| Alanine aminotransferase increased                    |                                                            |  |  |
| subjects affected / exposed                           | 0 / 100 (0.00%)                                            |  |  |
| occurrences (all)                                     | 0                                                          |  |  |
| Weight increased                                      |                                                            |  |  |
| subjects affected / exposed                           | 0 / 100 (0.00%)                                            |  |  |
| occurrences (all)                                     | 0                                                          |  |  |
| Injury, poisoning and procedural complications        |                                                            |  |  |
| Traumatic arthritis                                   |                                                            |  |  |
| subjects affected / exposed                           | 0 / 100 (0.00%)                                            |  |  |
| occurrences (all)                                     | 0                                                          |  |  |

|                                                      |                 |  |  |
|------------------------------------------------------|-----------------|--|--|
| Nervous system disorders                             |                 |  |  |
| Headache                                             |                 |  |  |
| subjects affected / exposed                          | 0 / 100 (0.00%) |  |  |
| occurrences (all)                                    | 0               |  |  |
| General disorders and administration site conditions |                 |  |  |
| Pyrexia                                              |                 |  |  |
| subjects affected / exposed                          | 3 / 100 (3.00%) |  |  |
| occurrences (all)                                    | 4               |  |  |
| Gastrointestinal disorders                           |                 |  |  |
| Constipation                                         |                 |  |  |
| subjects affected / exposed                          | 1 / 100 (1.00%) |  |  |
| occurrences (all)                                    | 1               |  |  |
| Diarrhoea                                            |                 |  |  |
| subjects affected / exposed                          | 1 / 100 (1.00%) |  |  |
| occurrences (all)                                    | 1               |  |  |
| Dyspepsia                                            |                 |  |  |
| subjects affected / exposed                          | 2 / 100 (2.00%) |  |  |
| occurrences (all)                                    | 4               |  |  |
| Gastritis                                            |                 |  |  |
| subjects affected / exposed                          | 0 / 100 (0.00%) |  |  |
| occurrences (all)                                    | 0               |  |  |
| Gastrointestinal disorder                            |                 |  |  |
| subjects affected / exposed                          | 1 / 100 (1.00%) |  |  |
| occurrences (all)                                    | 1               |  |  |
| Toothache                                            |                 |  |  |
| subjects affected / exposed                          | 1 / 100 (1.00%) |  |  |
| occurrences (all)                                    | 1               |  |  |
| Vomiting                                             |                 |  |  |
| subjects affected / exposed                          | 1 / 100 (1.00%) |  |  |
| occurrences (all)                                    | 1               |  |  |
| Respiratory, thoracic and mediastinal disorders      |                 |  |  |
| Asthma                                               |                 |  |  |
| subjects affected / exposed                          | 3 / 100 (3.00%) |  |  |
| occurrences (all)                                    | 3               |  |  |
| Cough                                                |                 |  |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                 |  |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nasal septum deviation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dysphonia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                                                                                                                                                                                                                    | <p>2 / 100 (2.00%)</p> <p>2</p> <p>1 / 100 (1.00%)</p> <p>1</p> <p>2 / 100 (2.00%)</p> <p>2</p>                                                                 |  |  |
| <p>Skin and subcutaneous tissue disorders</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                                                                                                                                                                                                                                                                                                                                 | <p>0 / 100 (0.00%)</p> <p>0</p>                                                                                                                                 |  |  |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Growth retardation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Jaw cyst</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                                                                                                                                                                                                                              | <p>3 / 100 (3.00%)</p> <p>3</p> <p>0 / 100 (0.00%)</p> <p>0</p>                                                                                                 |  |  |
| <p>Infections and infestations</p> <p>Acute tonsillitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Bronchitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Bronchopneumonia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Ear lobe infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Herpes dermatitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Influenza</p> | <p>1 / 100 (1.00%)</p> <p>1</p> <p>2 / 100 (2.00%)</p> <p>2</p> <p>0 / 100 (0.00%)</p> <p>0</p> <p>1 / 100 (1.00%)</p> <p>1</p> <p>1 / 100 (1.00%)</p> <p>1</p> |  |  |

|                                   |                 |  |  |
|-----------------------------------|-----------------|--|--|
| subjects affected / exposed       | 3 / 100 (3.00%) |  |  |
| occurrences (all)                 | 3               |  |  |
| Nasopharyngitis                   |                 |  |  |
| subjects affected / exposed       | 7 / 100 (7.00%) |  |  |
| occurrences (all)                 | 7               |  |  |
| Laryngitis                        |                 |  |  |
| subjects affected / exposed       | 1 / 100 (1.00%) |  |  |
| occurrences (all)                 | 1               |  |  |
| Pharyngitis                       |                 |  |  |
| subjects affected / exposed       | 5 / 100 (5.00%) |  |  |
| occurrences (all)                 | 5               |  |  |
| Respiratory tract infection       |                 |  |  |
| subjects affected / exposed       | 8 / 100 (8.00%) |  |  |
| occurrences (all)                 | 11              |  |  |
| Respiratory tract infection viral |                 |  |  |
| subjects affected / exposed       | 6 / 100 (6.00%) |  |  |
| occurrences (all)                 | 6               |  |  |
| Rhinitis                          |                 |  |  |
| subjects affected / exposed       | 5 / 100 (5.00%) |  |  |
| occurrences (all)                 | 6               |  |  |
| Sinusitis                         |                 |  |  |
| subjects affected / exposed       | 1 / 100 (1.00%) |  |  |
| occurrences (all)                 | 1               |  |  |
| Skin infection                    |                 |  |  |
| subjects affected / exposed       | 0 / 100 (0.00%) |  |  |
| occurrences (all)                 | 0               |  |  |
| Tracheitis                        |                 |  |  |
| subjects affected / exposed       | 1 / 100 (1.00%) |  |  |
| occurrences (all)                 | 1               |  |  |
| Upper respiratory tract infection |                 |  |  |
| subjects affected / exposed       | 2 / 100 (2.00%) |  |  |
| occurrences (all)                 | 3               |  |  |
| Urinary tract infection           |                 |  |  |
| subjects affected / exposed       | 2 / 100 (2.00%) |  |  |
| occurrences (all)                 | 2               |  |  |
| Varicella                         |                 |  |  |

|                                         |                 |  |  |
|-----------------------------------------|-----------------|--|--|
| subjects affected / exposed             | 1 / 100 (1.00%) |  |  |
| occurrences (all)                       | 1               |  |  |
| Viral rhinitis                          |                 |  |  |
| subjects affected / exposed             | 3 / 100 (3.00%) |  |  |
| occurrences (all)                       | 4               |  |  |
| Viral upper respiratory tract infection |                 |  |  |
| subjects affected / exposed             | 2 / 100 (2.00%) |  |  |
| occurrences (all)                       | 2               |  |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported