



## Clinical trial results:

### A Multicenter, Double-Blind, Randomized, Cross-Over Design Study to Evaluate the Effect of Montelukast vs. Salmeterol on the Inhibition of Exercise-Induced Bronchoconstriction in Asthmatic Patients Aged 6-14 Years.

#### Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2004-004709-53          |
| Trial protocol           | EE ES IT Outside EU/EEA |
| Global end of trial date | 14 November 2008        |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 27 April 2016 |
| First version publication date | 15 July 2015  |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | MK-0476-911 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |                                    |
|------------------------------------|------------------------------------|
| ISRCTN number                      | -                                  |
| ClinicalTrials.gov id (NCT number) | NCT00127166                        |
| WHO universal trial number (UTN)   | -                                  |
| Other trial identifiers            | Merck Protocol Number: MK-0476-911 |

Notes:

##### Sponsors

|                              |                                                                                              |
|------------------------------|----------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Merck Sharp & Dohme Corp.                                                                    |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033                               |
| Public contact               | Clinical Trials Disclosure, Merck Sharp & Dohme Corp.,<br>ClinicalTrialsDisclosure@merck.com |
| Scientific contact           | Clinical Trials Disclosure, Merck Sharp & Dohme Corp.,<br>ClinicalTrialsDisclosure@merck.com |

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                       | 14 November 2008 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 14 November 2008 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 14 November 2008 |
| 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 purpose of this study is to determine the effect of four weeks of treatment with two investigational drugs (oral versus inhaled administration) plus an inhaled medication in the treatment of airway constriction brought on by exercise in participants with asthma.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

The following additional measure defined for this individual study was in place for the protection of trial subjects: salbutamol was to be used throughout all periods on an "as needed" basis for rescue.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 07 December 2005 |
| 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 | Spain: 2     |
| Country: Number of subjects enrolled | Estonia: 17  |
| Country: Number of subjects enrolled | Italy: 13    |
| Country: Number of subjects enrolled | Brazil: 41   |
| Country: Number of subjects enrolled | Colombia: 25 |
| Country: Number of subjects enrolled | Croatia: 3   |
| Country: Number of subjects enrolled | Greece: 11   |
| Country: Number of subjects enrolled | Mexico: 8    |
| Country: Number of subjects enrolled | Peru: 20     |
| Country: Number of subjects enrolled | Poland: 14   |
| Worldwide total number of subjects   | 154          |
| EEA total number of subjects         | 60           |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| 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)                     | 112 |
| Adolescents (12-17 years)                 | 42  |
| Adults (18-64 years)                      | 0   |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

For randomization, participants fulfilled the following criteria: 1. Forced Expiratory Volume in one second (FEV1)  $\geq 70\%$  predicted while withholding beta ( $\beta$ )-agonist for at least 6 hours 2. Exercise-induced bronchoconstriction (EIB) showing FEV1  $\geq 15\%$  reduction from baseline while on inhaled corticosteroids demonstrated twice during the run-in period

### Period 1

|                              |                         |
|------------------------------|-------------------------|
| Period 1 title               | Period I                |
| 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>             | Montelukast / Salmeterol |

Arm description:

Period I- Montelukast 5 mg oral tablet once daily and salmeterol matching placebo dry powder inhaler (DPI) twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- Montelukast matching placebo oral tablet once daily and salmeterol DPI 50 mcg twice daily for 4 weeks. Inhaled fluticasone 100 mcg twice daily throughout the study.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Montelukast sodium |
| Investigational medicinal product code |                    |
| Other name                             | MK-0476            |
| Pharmaceutical forms                   | Chewable tablet    |
| Routes of administration               | Oral use           |

Dosage and administration details:

Montelukast 5 mg oral tablet once daily

|                                        |                             |
|----------------------------------------|-----------------------------|
| Investigational medicinal product name | Salmeterol matching placebo |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Inhalation powder           |
| Routes of administration               | Inhalation use              |

Dosage and administration details:

Matching placebo to salmeterol dry powder for inhalation administered twice daily

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Fluticasone propionate |
| Investigational medicinal product code |                        |
| Other name                             | Flixotide Evohaler     |
| Pharmaceutical forms                   | Inhalation powder      |
| Routes of administration               | Inhalation use         |

Dosage and administration details:

Fluticasone (50 mcg per actuation) 100 mcg inhaled twice daily

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | Salmeterol / Montelukast |
|------------------|--------------------------|

Arm description:

Period I- Montelukast matching placebo oral tablet once daily and salmeterol DPI 50 mcg twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching

placebo). Period II- Montelukast 5 mg oral tablet once daily and salmeterol matching placebo DPI twice daily for 4 weeks. Inhaled fluticasone 100 mcg twice daily throughout the study.

|                                        |                      |
|----------------------------------------|----------------------|
| Arm type                               | Experimental         |
| Investigational medicinal product name | Salmeterol xinafoate |
| Investigational medicinal product code |                      |
| Other name                             | Serevent Accuhaler   |
| Pharmaceutical forms                   | Inhalation powder    |
| Routes of administration               | Inhalation use       |

Dosage and administration details:

Salmeterol 50 mcg dry powder per actuation inhaled twice daily

|                                        |                              |
|----------------------------------------|------------------------------|
| Investigational medicinal product name | Montelukast matching placebo |
| Investigational medicinal product code |                              |
| Other name                             |                              |
| Pharmaceutical forms                   | Chewable tablet              |
| Routes of administration               | Oral use                     |

Dosage and administration details:

Matching placebo to montelukast oral tablet administered once daily

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Fluticasone propionate |
| Investigational medicinal product code |                        |
| Other name                             | Flixotide Evohaler     |
| Pharmaceutical forms                   | Inhalation powder      |
| Routes of administration               | Inhalation use         |

Dosage and administration details:

Fluticasone (50 mcg per actuation) 100 mcg inhaled twice daily

| Number of subjects in period 1              | Montelukast / Salmeterol | Salmeterol / Montelukast |
|---------------------------------------------|--------------------------|--------------------------|
| Started                                     | 78                       | 76                       |
| Completed                                   | 75                       | 74                       |
| Not completed                               | 3                        | 2                        |
| Consent withdrawn by subject                | 2                        | -                        |
| Participant did not meet inclusion criteria | 1                        | -                        |
| Protocol deviation                          | -                        | 2                        |

## Period 2

|                              |                         |
|------------------------------|-------------------------|
| Period 2 title               | Washout Period          |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Single blind            |
| Roles blinded                | Subject                 |

## Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                                                                                                                                                                                                                                                                                                                                                                                                 |                              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| <b>Arm title</b>                                                                                                                                                                                                                                                                                                                                                                                | Montelukast / Salmeterol     |
| Arm description:                                                                                                                                                                                                                                                                                                                                                                                |                              |
| Period I- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study. |                              |
| Arm type                                                                                                                                                                                                                                                                                                                                                                                        | Experimental                 |
| Investigational medicinal product name                                                                                                                                                                                                                                                                                                                                                          | Fluticasone propionate       |
| Investigational medicinal product code                                                                                                                                                                                                                                                                                                                                                          |                              |
| Other name                                                                                                                                                                                                                                                                                                                                                                                      | Flixotide Evohaler           |
| Pharmaceutical forms                                                                                                                                                                                                                                                                                                                                                                            | Inhalation powder            |
| Routes of administration                                                                                                                                                                                                                                                                                                                                                                        | Inhalation use               |
| Dosage and administration details:                                                                                                                                                                                                                                                                                                                                                              |                              |
| Fluticasone (50 mcg per actuation) 100 mcg inhaled twice daily                                                                                                                                                                                                                                                                                                                                  |                              |
| Investigational medicinal product name                                                                                                                                                                                                                                                                                                                                                          | Salmeterol matching placebo  |
| Investigational medicinal product code                                                                                                                                                                                                                                                                                                                                                          |                              |
| Other name                                                                                                                                                                                                                                                                                                                                                                                      |                              |
| Pharmaceutical forms                                                                                                                                                                                                                                                                                                                                                                            | Inhalation powder            |
| Routes of administration                                                                                                                                                                                                                                                                                                                                                                        | Inhalation use               |
| Dosage and administration details:                                                                                                                                                                                                                                                                                                                                                              |                              |
| Matching placebo to salmeterol dry powder for inhalation administered twice daily                                                                                                                                                                                                                                                                                                               |                              |
| Investigational medicinal product name                                                                                                                                                                                                                                                                                                                                                          | Montelukast matching placebo |
| Investigational medicinal product code                                                                                                                                                                                                                                                                                                                                                          |                              |
| Other name                                                                                                                                                                                                                                                                                                                                                                                      |                              |
| Pharmaceutical forms                                                                                                                                                                                                                                                                                                                                                                            | Chewable tablet              |
| Routes of administration                                                                                                                                                                                                                                                                                                                                                                        | Oral use                     |
| Dosage and administration details:                                                                                                                                                                                                                                                                                                                                                              |                              |
| Matching placebo to montelukast oral tablet administered once daily                                                                                                                                                                                                                                                                                                                             |                              |
| <b>Arm title</b>                                                                                                                                                                                                                                                                                                                                                                                | Salmeterol / Montelukast     |
| Arm description:                                                                                                                                                                                                                                                                                                                                                                                |                              |
| Period I- Montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study. |                              |
| Arm type                                                                                                                                                                                                                                                                                                                                                                                        | Experimental                 |
| Investigational medicinal product name                                                                                                                                                                                                                                                                                                                                                          | Fluticasone propionate       |
| Investigational medicinal product code                                                                                                                                                                                                                                                                                                                                                          |                              |
| Other name                                                                                                                                                                                                                                                                                                                                                                                      | Flixotide Evohaler           |
| Pharmaceutical forms                                                                                                                                                                                                                                                                                                                                                                            | Inhalation powder            |
| Routes of administration                                                                                                                                                                                                                                                                                                                                                                        | Inhalation use               |
| Dosage and administration details:                                                                                                                                                                                                                                                                                                                                                              |                              |
| Fluticasone (50 mcg per actuation) 100 mcg inhaled twice daily                                                                                                                                                                                                                                                                                                                                  |                              |
| Investigational medicinal product name                                                                                                                                                                                                                                                                                                                                                          | Salmeterol matching placebo  |
| Investigational medicinal product code                                                                                                                                                                                                                                                                                                                                                          |                              |
| Other name                                                                                                                                                                                                                                                                                                                                                                                      |                              |
| Pharmaceutical forms                                                                                                                                                                                                                                                                                                                                                                            | Inhalation powder            |
| Routes of administration                                                                                                                                                                                                                                                                                                                                                                        | Inhalation use               |
| Dosage and administration details:                                                                                                                                                                                                                                                                                                                                                              |                              |
| Matching placebo to salmeterol dry powder for inhalation administered twice daily                                                                                                                                                                                                                                                                                                               |                              |
| Investigational medicinal product name                                                                                                                                                                                                                                                                                                                                                          | Montelukast matching placebo |
| Investigational medicinal product code                                                                                                                                                                                                                                                                                                                                                          |                              |
| Other name                                                                                                                                                                                                                                                                                                                                                                                      |                              |
| Pharmaceutical forms                                                                                                                                                                                                                                                                                                                                                                            | Chewable tablet              |

|                          |          |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

Matching placebo to montelukast oral tablet administered once daily

| Number of subjects in period 2              | Montelukast / Salmeterol | Salmeterol / Montelukast |
|---------------------------------------------|--------------------------|--------------------------|
| Started                                     | 75                       | 74                       |
| Completed                                   | 75                       | 73                       |
| Not completed                               | 0                        | 1                        |
| Participant did not meet inclusion criteria | -                        | 1                        |

### Period 3

|                              |                         |
|------------------------------|-------------------------|
| Period 3 title               | Period II               |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Double blind            |
| Roles blinded                | Subject, Investigator   |

### Arms

|                              |                          |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes                      |
| Arm title                    | Montelukast / Salmeterol |

Arm description:

Period I- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study.

|                                        |                              |
|----------------------------------------|------------------------------|
| Arm type                               | Experimental                 |
| Investigational medicinal product name | Montelukast matching placebo |
| Investigational medicinal product code |                              |
| Other name                             |                              |
| Pharmaceutical forms                   | Chewable tablet              |
| Routes of administration               | Oral use                     |

Dosage and administration details:

Matching placebo to montelukast oral tablet administered once daily

|                                        |                      |
|----------------------------------------|----------------------|
| Investigational medicinal product name | Salmeterol xinafoate |
| Investigational medicinal product code |                      |
| Other name                             | Serevent Accuhaler   |
| Pharmaceutical forms                   | Inhalation powder    |
| Routes of administration               | Inhalation use       |

Dosage and administration details:

Salmeterol 50 mcg dry powder per actuation inhaled twice daily

|                                                                |                          |
|----------------------------------------------------------------|--------------------------|
| Investigational medicinal product name                         | Fluticasone propionate   |
| Investigational medicinal product code                         |                          |
| Other name                                                     | Flixotide Evohaler       |
| Pharmaceutical forms                                           | Inhalation powder        |
| Routes of administration                                       | Inhalation use           |
| Dosage and administration details:                             |                          |
| Fluticasone (50 mcg per actuation) 100 mcg inhaled twice daily |                          |
| <b>Arm title</b>                                               | Salmeterol / Montelukast |

**Arm description:**

Period I- Montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Montelukast sodium |
| Investigational medicinal product code |                    |
| Other name                             | MK-0476            |
| Pharmaceutical forms                   | Chewable tablet    |
| Routes of administration               | Oral use           |

**Dosage and administration details:**

Montelukast 5 mg oral tablet once daily

|                                        |                             |
|----------------------------------------|-----------------------------|
| Investigational medicinal product name | Salmeterol matching placebo |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Inhalation powder           |
| Routes of administration               | Inhalation use              |

**Dosage and administration details:**

Matching placebo to salmeterol dry powder inhaler administered twice daily

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Fluticasone propionate |
| Investigational medicinal product code |                        |
| Other name                             | Flixotide Evohaler     |
| Pharmaceutical forms                   | Inhalation powder      |
| Routes of administration               | Inhalation use         |

**Dosage and administration details:**

Fluticasone (50 mcg per actuation) 100 mcg inhaled twice daily

| <b>Number of subjects in period 3</b>           | Montelukast / Salmeterol | Salmeterol / Montelukast |
|-------------------------------------------------|--------------------------|--------------------------|
| Started                                         | 75                       | 73                       |
| Completed                                       | 72                       | 73                       |
| Not completed                                   | 3                        | 0                        |
| Consent withdrawn by subject                    | 2                        | -                        |
| Participant did not perform last visit exercise | 1                        | -                        |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                      |                          |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                | Montelukast / Salmeterol |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                         |                          |
| Period I- Montelukast 5 mg oral tablet once daily and salmeterol matching placebo dry powder inhaler (DPI) twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- Montelukast matching placebo oral tablet once daily and salmeterol DPI 50 mcg twice daily for 4 weeks. Inhaled fluticasone 100 mcg twice daily throughout the study. |                          |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                | Salmeterol / Montelukast |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                         |                          |
| Period I- Montelukast matching placebo oral tablet once daily and salmeterol DPI 50 mcg twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- Montelukast 5 mg oral tablet once daily and salmeterol matching placebo DPI twice daily for 4 weeks. Inhaled fluticasone 100 mcg twice daily throughout the study.                      |                          |

| Reporting group values                                                                                                 | Montelukast / Salmeterol | Salmeterol / Montelukast | Total |
|------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|-------|
| Number of subjects                                                                                                     | 78                       | 76                       | 154   |
| Age categorical                                                                                                        |                          |                          |       |
| Units: Subjects                                                                                                        |                          |                          |       |
| Age continuous                                                                                                         |                          |                          |       |
| Units: years                                                                                                           |                          |                          |       |
| arithmetic mean                                                                                                        | 10.2                     | 9.8                      |       |
| standard deviation                                                                                                     | ± 2                      | ± 2                      | -     |
| Gender categorical                                                                                                     |                          |                          |       |
| Units: Subjects                                                                                                        |                          |                          |       |
| Female                                                                                                                 | 35                       | 30                       | 65    |
| Male                                                                                                                   | 43                       | 46                       | 89    |
| Race                                                                                                                   |                          |                          |       |
| Units: Subjects                                                                                                        |                          |                          |       |
| Asian                                                                                                                  | 1                        | 0                        | 1     |
| Black                                                                                                                  | 11                       | 7                        | 18    |
| White                                                                                                                  | 38                       | 41                       | 79    |
| Hispanic                                                                                                               | 15                       | 18                       | 33    |
| Multiracial                                                                                                            | 13                       | 10                       | 23    |
| Area under the curve from 0 to 20 minutes (AUC(0-20))                                                                  |                          |                          |       |
| Area Under the Curve for percent-change from pre-exercise baseline FEV1 in liters, from 0 to 20 minutes (AUC(0-20))    |                          |                          |       |
| Units: Percent times minutes                                                                                           |                          |                          |       |
| arithmetic mean                                                                                                        | 320.08                   | 317.74                   |       |
| standard deviation                                                                                                     | ± 208.62                 | ± 165.71                 | -     |
| Avg %-change from pre-exercise baseline FEV1 after 1st β-agonist use & Prior to 2nd β-agonist use                      |                          |                          |       |
| Average (avg) percent (%) -change from pre-exercise baseline FEV1 after 1st β-agonist use & prior to 2nd β-agonist use |                          |                          |       |
| Units: Percent change from baseline                                                                                    |                          |                          |       |
| arithmetic mean                                                                                                        | 1.36                     | 4.78                     |       |
| standard deviation                                                                                                     | ± 10.99                  | ± 10.92                  | -     |

|                                                                                                                                                       |                  |                   |   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|-------------------|---|
| Maximum FEV1 Percent Predicted<br>Units: Percent of predicted value<br>arithmetic mean<br>standard deviation                                          | 99.88<br>± 32.45 | 100.54<br>± 15.61 | - |
| Maximum Percent Fall in FEV1 After Exercise<br>Units: Percent change from baseline<br>arithmetic mean<br>standard deviation                           | 24.77<br>± 10.25 | 25.42<br>± 9.04   | - |
| Time to recovery                                                                                                                                      |                  |                   |   |
| Population includes participants who returned to within 5% of the baseline FEV1 value. Montelukast / Salmeterol, n=71; Salmeterol / Montelukast, n=70 |                  |                   |   |
| Units: Minutes<br>arithmetic mean<br>standard deviation                                                                                               | 23.53<br>± 10.53 | 21.51<br>± 8.3    | - |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                | Montelukast / Salmeterol |
| Reporting group description:<br>Period I- Montelukast 5 mg oral tablet once daily and salmeterol matching placebo dry powder inhaler (DPI) twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- Montelukast matching placebo oral tablet once daily and salmeterol DPI 50 mcg twice daily for 4 weeks. Inhaled fluticasone 100 mcg twice daily throughout the study. |                          |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                | Salmeterol / Montelukast |
| Reporting group description:<br>Period I- Montelukast matching placebo oral tablet once daily and salmeterol DPI 50 mcg twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- Montelukast 5 mg oral tablet once daily and salmeterol matching placebo DPI twice daily for 4 weeks. Inhaled fluticasone 100 mcg twice daily throughout the study.                      |                          |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                | Montelukast / Salmeterol |
| Reporting group description:<br>Period I- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study.                      |                          |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                | Salmeterol / Montelukast |
| Reporting group description:<br>Period I- Montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study.                      |                          |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                | Montelukast / Salmeterol |
| Reporting group description:<br>Period I- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study.                      |                          |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                | Salmeterol / Montelukast |
| Reporting group description:<br>Period I- Montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks followed by a 2-week washout period (salmeterol matching placebo + montelukast matching placebo). Period II- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study.                      |                          |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                           | Montelukast              |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                            | Full analysis            |
| Subject analysis set description:<br>The primary efficacy analysis was based on the full analysis set (FAS) population which included all randomized participants who took at least one dose of post randomization study drug and had a measurement for analysis available in both treatment periods of the cross-over design.                                                                                                                       |                          |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                           | Salmeterol               |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                            | Full analysis            |
| Subject analysis set description:<br>The primary efficacy analysis was based on the full analysis set (FAS) population which included all randomized participants who took at least one dose of post randomization study drug and had a measurement for analysis available in both treatment periods of the cross-over design.                                                                                                                       |                          |

**Primary: Maximum post-exercise percent fall in FEV1**

|                 |                                            |
|-----------------|--------------------------------------------|
| End point title | Maximum post-exercise percent fall in FEV1 |
|-----------------|--------------------------------------------|

End point description:

The effect of four weeks of treatment with oral montelukast plus inhaled fluticasone, and inhaled salmeterol plus inhaled fluticasone on EIB as measured by the maximum post-exercise percent fall (relative to pre-exercise baseline) in FEV1.

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

End point timeframe:

4 weeks (Weeks 0 to 4 or Weeks 6 to 10)

| End point values                             | Montelukast           | Salmeterol             |  |  |
|----------------------------------------------|-----------------------|------------------------|--|--|
| Subject group type                           | Subject analysis set  | Subject analysis set   |  |  |
| Number of subjects analysed                  | 144                   | 144                    |  |  |
| Units: Percent change from baseline          |                       |                        |  |  |
| least squares mean (confidence interval 95%) | 10.57 (8.86 to 12.27) | 13.82 (12.11 to 15.52) |  |  |

**Statistical analyses**

|                            |                                  |
|----------------------------|----------------------------------|
| Statistical analysis title | Difference in least squares mean |
|----------------------------|----------------------------------|

Statistical analysis description:

There were a total of 144 participants included in this analysis (cross-over design).

|                   |                          |
|-------------------|--------------------------|
| Comparison groups | Montelukast v Salmeterol |
|-------------------|--------------------------|

|                                         |     |
|-----------------------------------------|-----|
| Number of subjects included in analysis | 288 |
|-----------------------------------------|-----|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |       |
|---------------|-------|
| Analysis type | other |
|---------------|-------|

|         |                        |
|---------|------------------------|
| P-value | = 0.009 <sup>[1]</sup> |
|---------|------------------------|

|        |       |
|--------|-------|
| Method | ANOVA |
|--------|-------|

|                    |                               |
|--------------------|-------------------------------|
| Parameter estimate | Least squares mean difference |
|--------------------|-------------------------------|

|                |       |
|----------------|-------|
| Point estimate | -3.25 |
|----------------|-------|

Confidence interval

|       |      |
|-------|------|
| level | 95 % |
|-------|------|

|       |         |
|-------|---------|
| sides | 2-sided |
|-------|---------|

|             |       |
|-------------|-------|
| lower limit | -5.66 |
|-------------|-------|

|             |       |
|-------------|-------|
| upper limit | -0.84 |
|-------------|-------|

Notes:

[1] - Model terms: participant, treatment and period. The treatment test is adjusted for period.

**Secondary: Area under the curve for percent-change from pre-exercise baseline FEV1 in liters, from 0 to 20 Minutes (AUC(0-20))**

|                 |                                                                                                                     |
|-----------------|---------------------------------------------------------------------------------------------------------------------|
| End point title | Area under the curve for percent-change from pre-exercise baseline FEV1 in liters, from 0 to 20 Minutes (AUC(0-20)) |
|-----------------|---------------------------------------------------------------------------------------------------------------------|

End point description:

The effect of a four-week treatment course of oral montelukast plus inhaled fluticasone, compared to inhaled salmeterol plus inhaled fluticasone, on the extent and severity of EIB as measured by the area under the curve from 0 to 20 minutes (AUC0-20) for FEV1 percent change from pre-exercise baseline.

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

End point timeframe:

4 weeks (Weeks 0 to 4 or Weeks 6 to 10)

| End point values                             | Montelukast              | Salmeterol                |  |  |
|----------------------------------------------|--------------------------|---------------------------|--|--|
| Subject group type                           | Subject analysis set     | Subject analysis set      |  |  |
| Number of subjects analysed                  | 144                      | 144                       |  |  |
| Units: Percent times minutes                 |                          |                           |  |  |
| least squares mean (confidence interval 95%) | 116.04 (89.95 to 142.24) | 168.75 (142.56 to 194.95) |  |  |

## Statistical analyses

| Statistical analysis title                                                                                                 | Difference in least squares mean |
|----------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| Statistical analysis description:<br>There were a total of 144 participants included in this analysis (cross-over design). |                                  |
| Comparison groups                                                                                                          | Montelukast v Salmeterol         |
| Number of subjects included in analysis                                                                                    | 288                              |
| Analysis specification                                                                                                     | Pre-specified                    |
| Analysis type                                                                                                              | other                            |
| P-value                                                                                                                    | = 0.006 <sup>[2]</sup>           |
| Method                                                                                                                     | ANOVA                            |
| Parameter estimate                                                                                                         | Least squares mean difference    |
| Point estimate                                                                                                             | -52.71                           |
| Confidence interval                                                                                                        |                                  |
| level                                                                                                                      | 95 %                             |
| sides                                                                                                                      | 2-sided                          |
| lower limit                                                                                                                | -89.76                           |
| upper limit                                                                                                                | -15.66                           |

Notes:

[2] - Model terms: participant, treatment and period. The treatment test is adjusted for period.

## Secondary: Maximum FEV1 percent predicted following first $\beta$ -agonist use

|                                                                                                                                                                                                                                                                                                                      |                                                                     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                      | Maximum FEV1 percent predicted following first $\beta$ -agonist use |
| End point description:<br>The effect of a four-week treatment course of oral montelukast plus inhaled fluticasone, compared to inhaled salmeterol plus inhaled fluticasone, on short-acting $\beta$ -agonist bronchodilation as measured by the maximum FEV1 percent predicted following first $\beta$ -agonist use. |                                                                     |
| End point type                                                                                                                                                                                                                                                                                                       | Secondary                                                           |
| End point timeframe:<br>4 weeks (Weeks 0 to 4 or Weeks 6 to 10)                                                                                                                                                                                                                                                      |                                                                     |

| End point values                             | Montelukast               | Salmeterol              |  |  |
|----------------------------------------------|---------------------------|-------------------------|--|--|
| Subject group type                           | Subject analysis set      | Subject analysis set    |  |  |
| Number of subjects analysed                  | 144                       | 144                     |  |  |
| Units: Percent of predicted value            |                           |                         |  |  |
| least squares mean (confidence interval 95%) | 104.03 (102.83 to 105.23) | 99.92 (98.72 to 101.12) |  |  |

## Statistical analyses

| Statistical analysis title                                                            | Difference in least squares mean |
|---------------------------------------------------------------------------------------|----------------------------------|
| Statistical analysis description:                                                     |                                  |
| There were a total of 144 participants included in this analysis (cross-over design). |                                  |
| Comparison groups                                                                     | Montelukast v Salmeterol         |
| Number of subjects included in analysis                                               | 288                              |
| Analysis specification                                                                | Pre-specified                    |
| Analysis type                                                                         | other                            |
| P-value                                                                               | < 0.001 <sup>[3]</sup>           |
| Method                                                                                | ANCOVA                           |
| Parameter estimate                                                                    | Least squares mean difference    |
| Point estimate                                                                        | 4.11                             |
| Confidence interval                                                                   |                                  |
| level                                                                                 | 95 %                             |
| sides                                                                                 | 2-sided                          |
| lower limit                                                                           | 2.58                             |
| upper limit                                                                           | 5.64                             |

Notes:

[3] - Terms: participant, treatment, period & covariate for FEV1 %-predicted at pre-exercise baseline.

## Secondary: Time to recovery to within 5 percent of baseline FEV1

| End point title                                                                                                                                                                                                                                                                                                              | Time to recovery to within 5 percent of baseline FEV1 |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| End point description:                                                                                                                                                                                                                                                                                                       |                                                       |
| The effect of a four-week treatment course of oral montelukast plus inhaled fluticasone, compared to inhaled salmeterol plus inhaled fluticasone, on the extent and severity of EIB as measured by the time to recovery (to within 5 percent of the pre-exercise baseline FEV1) following a standardized exercise challenge. |                                                       |
| End point type                                                                                                                                                                                                                                                                                                               | Secondary                                             |
| End point timeframe:                                                                                                                                                                                                                                                                                                         |                                                       |
| 4 weeks (Weeks 0 to 4 or Weeks 6 to 10)                                                                                                                                                                                                                                                                                      |                                                       |

| End point values                      | Montelukast          | Salmeterol            |  |  |
|---------------------------------------|----------------------|-----------------------|--|--|
| Subject group type                    | Subject analysis set | Subject analysis set  |  |  |
| Number of subjects analysed           | 144                  | 144                   |  |  |
| Units: minutes                        |                      |                       |  |  |
| median (inter-quartile range (Q1-Q3)) | 5.9 (0 to 19.12)     | 11.1 (0.065 to 22.94) |  |  |

## Statistical analyses

|                                                                                                                            |                                               |
|----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b>                                                                                          | Comparison between montelukast vs. salmeterol |
| Statistical analysis description:<br>There were a total of 144 participants included in this analysis (cross-over design). |                                               |
| Comparison groups                                                                                                          | Montelukast v Salmeterol                      |
| Number of subjects included in analysis                                                                                    | 288                                           |
| Analysis specification                                                                                                     | Pre-specified                                 |
| Analysis type                                                                                                              | other <sup>[4]</sup>                          |
| P-value                                                                                                                    | = 0.035 <sup>[5]</sup>                        |
| Method                                                                                                                     | Cox proportional hazard model                 |
| Parameter estimate                                                                                                         | Hazard ratio (HR)                             |
| Point estimate                                                                                                             | 1.26                                          |
| Confidence interval                                                                                                        |                                               |
| level                                                                                                                      | 95 %                                          |
| sides                                                                                                                      | 2-sided                                       |
| lower limit                                                                                                                | 1.02                                          |
| upper limit                                                                                                                | 1.55                                          |

Notes:

[4] - A robust estimate of the variance of the treatment effect was calculated using the marginal approach introduced by Wei, Lin and Weissfeld (WLW model).

[5] - Model terms: treatment and period.

## Secondary: Average percent-change in FEV1 after first $\beta$ -agonist use and prior to second $\beta$ -agonist use

|                                                                                                                                                                                                                                                                                                                                               |                                                                                                          |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                               | Average percent-change in FEV1 after first $\beta$ -agonist use and prior to second $\beta$ -agonist use |
| End point description:<br>The effect of a four-week treatment course of oral montelukast plus inhaled fluticasone, compared to inhaled salmeterol plus inhaled fluticasone, on the extent and severity of EIB as measured by the average percent change in FEV1 after first $\beta$ -agonist intake and prior to second $\beta$ -agonist use. |                                                                                                          |
| End point type                                                                                                                                                                                                                                                                                                                                | Secondary                                                                                                |
| End point timeframe:<br>4 weeks (Weeks 0 to 4 or Weeks 6 to 10)                                                                                                                                                                                                                                                                               |                                                                                                          |

|                                              |                      |                      |  |  |
|----------------------------------------------|----------------------|----------------------|--|--|
| <b>End point values</b>                      | Montelukast          | Salmeterol           |  |  |
| Subject group type                           | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed                  | 144                  | 144                  |  |  |
| Units: Percent change from baseline          |                      |                      |  |  |
| least squares mean (confidence interval 95%) | 6.51 (5.44 to 7.59)  | 2.72 (1.64 to 3.79)  |  |  |

## Statistical analyses

|                                                                                                                            |                                  |
|----------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| <b>Statistical analysis title</b>                                                                                          | Difference in least squares mean |
| Statistical analysis description:<br>There were a total of 144 participants included in this analysis (cross-over design). |                                  |
| Comparison groups                                                                                                          | Montelukast v Salmeterol         |
| Number of subjects included in analysis                                                                                    | 288                              |
| Analysis specification                                                                                                     | Pre-specified                    |
| Analysis type                                                                                                              | other                            |
| P-value                                                                                                                    | < 0.001 <sup>[6]</sup>           |
| Method                                                                                                                     | ANOVA                            |
| Parameter estimate                                                                                                         | Least squares mean difference    |
| Point estimate                                                                                                             | 3.8                              |
| Confidence interval                                                                                                        |                                  |
| level                                                                                                                      | 95 %                             |
| sides                                                                                                                      | 2-sided                          |
| lower limit                                                                                                                | 2.28                             |
| upper limit                                                                                                                | 5.32                             |

Notes:

[6] - Model terms: participant, treatment and period. The treatment test is adjusted for period.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 12 weeks (including 2 weeks following last dose of study drug)

Adverse event reporting additional description:

Of 154 participants enrolled, only 150 took at least 1 dose of each treatment (tx); 78 were in Montelukast (M) /Salmeterol (S) sequence (seq) and 76 in S/M seq. 4 participants in M/S seq only took 1st tx; so 78 took M & 74 took S. 4 different participants in S/M seq only took 1st tx; so 76 took S & 72 took M. Total 150 pts took M and 150 took S.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 11.1 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Montelukast |
|-----------------------|-------------|

Reporting group description:

Period I- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks. Period II- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study.

|                       |            |
|-----------------------|------------|
| Reporting group title | Salmeterol |
|-----------------------|------------|

Reporting group description:

Period I- Montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks. Period II- Montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks. Inhaled Fluticasone 100 mcg twice daily throughout the study.

| Serious adverse events                            | Montelukast     | Salmeterol      |  |
|---------------------------------------------------|-----------------|-----------------|--|
| Total subjects affected by serious adverse events |                 |                 |  |
| subjects affected / exposed                       | 1 / 150 (0.67%) | 1 / 150 (0.67%) |  |
| number of deaths (all causes)                     | 0               | 0               |  |
| number of deaths resulting from adverse events    |                 |                 |  |
| Injury, poisoning and procedural complications    |                 |                 |  |
| Accidental overdose                               |                 |                 |  |
| subjects affected / exposed                       | 0 / 150 (0.00%) | 1 / 150 (0.67%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Overdose                                          |                 |                 |  |
| subjects affected / exposed                       | 1 / 150 (0.67%) | 0 / 150 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Montelukast       | Salmeterol        |  |
|-------------------------------------------------------|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 27 / 150 (18.00%) | 21 / 150 (14.00%) |  |
| Injury, poisoning and procedural complications        |                   |                   |  |
| Ear injury                                            |                   |                   |  |
| subjects affected / exposed                           | 1 / 150 (0.67%)   | 0 / 150 (0.00%)   |  |
| occurrences (all)                                     | 1                 | 0                 |  |
| Fall                                                  |                   |                   |  |
| subjects affected / exposed                           | 1 / 150 (0.67%)   | 0 / 150 (0.00%)   |  |
| occurrences (all)                                     | 1                 | 0                 |  |
| Limb injury                                           |                   |                   |  |
| subjects affected / exposed                           | 1 / 150 (0.67%)   | 1 / 150 (0.67%)   |  |
| occurrences (all)                                     | 1                 | 1                 |  |
| Skin injury                                           |                   |                   |  |
| subjects affected / exposed                           | 1 / 150 (0.67%)   | 0 / 150 (0.00%)   |  |
| occurrences (all)                                     | 1                 | 0                 |  |
| Wound                                                 |                   |                   |  |
| subjects affected / exposed                           | 0 / 150 (0.00%)   | 1 / 150 (0.67%)   |  |
| occurrences (all)                                     | 0                 | 1                 |  |
| Nervous system disorders                              |                   |                   |  |
| Headache                                              |                   |                   |  |
| subjects affected / exposed                           | 2 / 150 (1.33%)   | 0 / 150 (0.00%)   |  |
| occurrences (all)                                     | 2                 | 0                 |  |
| General disorders and administration site conditions  |                   |                   |  |
| Pyrexia                                               |                   |                   |  |
| subjects affected / exposed                           | 0 / 150 (0.00%)   | 2 / 150 (1.33%)   |  |
| occurrences (all)                                     | 0                 | 2                 |  |
| Immune system disorders                               |                   |                   |  |
| Allergy to plants                                     |                   |                   |  |
| subjects affected / exposed                           | 0 / 150 (0.00%)   | 1 / 150 (0.67%)   |  |
| occurrences (all)                                     | 0                 | 1                 |  |
| Eye disorders                                         |                   |                   |  |
| Conjunctivitis                                        |                   |                   |  |

|                                                                             |                      |                      |  |
|-----------------------------------------------------------------------------|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                            | 1 / 150 (0.67%)<br>1 | 0 / 150 (0.00%)<br>0 |  |
| Conjunctivitis allergic<br>subjects affected / exposed<br>occurrences (all) | 0 / 150 (0.00%)<br>0 | 1 / 150 (0.67%)<br>1 |  |
| Gastrointestinal disorders                                                  |                      |                      |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)               | 2 / 150 (1.33%)<br>2 | 0 / 150 (0.00%)<br>0 |  |
| Toothache<br>subjects affected / exposed<br>occurrences (all)               | 0 / 150 (0.00%)<br>0 | 1 / 150 (0.67%)<br>1 |  |
| Reproductive system and breast disorders                                    |                      |                      |  |
| Menstruation delayed<br>subjects affected / exposed<br>occurrences (all)    | 0 / 150 (0.00%)<br>0 | 1 / 150 (0.67%)<br>1 |  |
| Respiratory, thoracic and mediastinal disorders                             |                      |                      |  |
| Asthma<br>subjects affected / exposed<br>occurrences (all)                  | 4 / 150 (2.67%)<br>4 | 4 / 150 (2.67%)<br>4 |  |
| Bronchospasm<br>subjects affected / exposed<br>occurrences (all)            | 1 / 150 (0.67%)<br>1 | 0 / 150 (0.00%)<br>0 |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)        | 1 / 150 (0.67%)<br>1 | 0 / 150 (0.00%)<br>0 |  |
| Wheezing<br>subjects affected / exposed<br>occurrences (all)                | 1 / 150 (0.67%)<br>1 | 0 / 150 (0.00%)<br>0 |  |
| Skin and subcutaneous tissue disorders                                      |                      |                      |  |
| Dermatitis atopic<br>subjects affected / exposed<br>occurrences (all)       | 1 / 150 (0.67%)<br>1 | 0 / 150 (0.00%)<br>0 |  |
| Eczema<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 150 (0.67%)<br>1 | 1 / 150 (0.67%)<br>1 |  |

|                                   |                 |                 |  |
|-----------------------------------|-----------------|-----------------|--|
| Skin lesion                       |                 |                 |  |
| subjects affected / exposed       | 0 / 150 (0.00%) | 1 / 150 (0.67%) |  |
| occurrences (all)                 | 0               | 1               |  |
| Infections and infestations       |                 |                 |  |
| Candidiasis                       |                 |                 |  |
| subjects affected / exposed       | 1 / 150 (0.67%) | 0 / 150 (0.00%) |  |
| occurrences (all)                 | 1               | 0               |  |
| Ear infection                     |                 |                 |  |
| subjects affected / exposed       | 1 / 150 (0.67%) | 0 / 150 (0.00%) |  |
| occurrences (all)                 | 1               | 0               |  |
| Influenza                         |                 |                 |  |
| subjects affected / exposed       | 1 / 150 (0.67%) | 1 / 150 (0.67%) |  |
| occurrences (all)                 | 1               | 1               |  |
| Nasopharyngitis                   |                 |                 |  |
| subjects affected / exposed       | 2 / 150 (1.33%) | 1 / 150 (0.67%) |  |
| occurrences (all)                 | 2               | 1               |  |
| Pertussis                         |                 |                 |  |
| subjects affected / exposed       | 2 / 150 (1.33%) | 0 / 150 (0.00%) |  |
| occurrences (all)                 | 2               | 0               |  |
| Pharyngitis                       |                 |                 |  |
| subjects affected / exposed       | 5 / 150 (3.33%) | 3 / 150 (2.00%) |  |
| occurrences (all)                 | 5               | 3               |  |
| Pneumonia                         |                 |                 |  |
| subjects affected / exposed       | 0 / 150 (0.00%) | 1 / 150 (0.67%) |  |
| occurrences (all)                 | 0               | 1               |  |
| Respiratory tract infection       |                 |                 |  |
| subjects affected / exposed       | 0 / 150 (0.00%) | 1 / 150 (0.67%) |  |
| occurrences (all)                 | 0               | 1               |  |
| Respiratory tract infection viral |                 |                 |  |
| subjects affected / exposed       | 1 / 150 (0.67%) | 0 / 150 (0.00%) |  |
| occurrences (all)                 | 1               | 0               |  |
| Tonsillitis                       |                 |                 |  |
| subjects affected / exposed       | 3 / 150 (2.00%) | 2 / 150 (1.33%) |  |
| occurrences (all)                 | 3               | 2               |  |
| Upper respiratory tract infection |                 |                 |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 150 (0.67%) | 1 / 150 (0.67%) |  |
| occurrences (all)           | 1               | 1               |  |
| Viral infection             |                 |                 |  |
| subjects affected / exposed | 0 / 150 (0.00%) | 2 / 150 (1.33%) |  |
| occurrences (all)           | 0               | 2               |  |
| Viral pharyngitis           |                 |                 |  |
| subjects affected / exposed | 1 / 150 (0.67%) | 0 / 150 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Viral rhinitis              |                 |                 |  |
| subjects affected / exposed | 1 / 150 (0.67%) | 0 / 150 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                              |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 13 August 2005  | Amendment 1: Primary reason for the amendment was to update the salmeterol dosage to salmeterol/matching placebo drug powder inhaler (DPI) formulation 50 mcg/puff, one puff twice daily, total dose of 100 mcg/day. Use of spacer device with salmeterol was deleted. |
| 16 January 2007 | Amendment 2: Primary reason for the amendment was that participants must demonstrate exercise induced bronchoconstriction with post-exercise decline in FEV1 of 15 % (change from 20 %).                                                                               |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported