



## Clinical trial results:

**A repeat-dose, open-label, 2-session study to assess the systemic exposure to, and pharmacodynamics of, fluticasone propionate HFA inhalation aerosol 88 mcg administered twice-daily for 28 days delivered via an MDI and valved holding chamber with facemask to subjects ages 6 months to <12 months who have experienced 2 or more wheezing episodes in the preceding 6 months**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-004884-35 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 12 April 2007  |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 22 January 2017 |
| First version publication date | 22 January 2017 |

### Trial information

#### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | FAS106533 |
|-----------------------|-----------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |                                                            |
|------------------------------|------------------------------------------------------------|
| Sponsor organisation name    | GlaxoSmithKline                                            |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom, |
| Public contact               | GSK Response Center, GlaxoSmithKline, 1 866-435-7343,      |
| Scientific contact           | GSK Response Center, GlaxoSmithKline, 1 866-435-7343,      |

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**

|                                                      |               |
|------------------------------------------------------|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 19 July 2007  |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 12 April 2007 |
| Was the trial ended prematurely?                     | No            |

Notes:

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**General information about the trial**

Main objective of the trial:

To determine the effect of administration of FP HFA MDI 88 mcg BID on 12 h serum cortisol in pediatric subjects, ages 6 months to <12 months, who have experienced 2 or more wheezing episodes in the preceding 6 months.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

|                                                           |                |
|-----------------------------------------------------------|----------------|
| Actual start date of recruitment                          | 30 August 2006 |
| 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 | United States: 23 |
| Worldwide total number of subjects   | 23                |
| EEA total number of subjects         | 0                 |

Notes:

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**Subjects enrolled per age group**

|                                           |    |
|-------------------------------------------|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 23 |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

This was an open-label, repeat-dose, 2-session study to assess the systemic exposure to, and pharmacodynamics of, fluticasone propionate hydrofluoroalkane (FP HFA) inhalation administered twice-daily, via an metered-dose inhaler (MDI), to participants, aged 6 months to <12 months, who had experienced 2 wheezing episodes in the preceding 6 months.

### Pre-assignment

Screening details:

The study consisted of 2 sessions followed by a follow-up call. The total duration of the study was approximately 8 weeks.

### Period 1

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

### Arms

|           |               |
|-----------|---------------|
| Arm title | Overall Study |
|-----------|---------------|

Arm description:

Placebo twice daily (BID) for 14 days followed by FP HFA 44 microgram (mcg) BID for 28 days

|                                        |                                                     |
|----------------------------------------|-----------------------------------------------------|
| Arm type                               | Experimental                                        |
| Investigational medicinal product name | Fluticasone propionate (FP) hydrofluoroalkane (HFA) |
| Investigational medicinal product code |                                                     |
| Other name                             |                                                     |
| Pharmaceutical forms                   | Inhalation solution                                 |
| Routes of administration               | Inhalation use                                      |

Dosage and administration details:

This consists of a white to off-white suspension of FP (micronized) in a liquefied HFA propellant. A metered dose inhaler (MDI) is a small hand held pressurized canister device that contains both medications, in this case, FP, and a propellant. In Session 2, it was administered at 44 mcg (two inhalations BID given 30 seconds apart for 28 days) using a Aerochamber Plus with an infant mask

|                                        |                     |
|----------------------------------------|---------------------|
| Investigational medicinal product name | Placebo HFA         |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Inhalation solution |
| Routes of administration               | Inhalation use      |

Dosage and administration details:

This consists of a liquefied HFA propellant (placebo). An MDI is a small hand held pressurized canister device that contains both medications, in this case, FP, and a propellant. In Session 1, two inhalations were administered BID 30 seconds apart for 14 days, using a Aerochamber Plus with an infant mask

| <b>Number of subjects in period 1</b> | Overall Study |
|---------------------------------------|---------------|
| Started                               | 23            |
| Completed Session 1                   | 21            |
| Completed                             | 18            |
| Not completed                         | 5             |
| Consent withdrawn by subject          | 2             |
| Adverse event, non-fatal              | 1             |
| Medication not administered           | 1             |
| Lost to follow-up                     | 1             |

## Baseline characteristics

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description:

In

Session 1, participants received two inhalations of placebo HFA BID 30 seconds apart from Day 1 to 14, via a MDI and a valved holding chamber (AeroChamber Plus) with infant mask. In Session 2, participants received 2 inhalations of 44 mcg FP HFA BID 30 seconds apart from Day 1 to 28, via a MDI and a valved holding chamber (AeroChamber Plus) with infant mask. Doses were given at about the same time of day approximately 12 hours apart.

| Reporting group values                                                  | Overall Study | Total |  |
|-------------------------------------------------------------------------|---------------|-------|--|
| Number of subjects                                                      | 23            | 23    |  |
| Age categorical<br>Units: Subjects                                      |               |       |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 9.4<br>± 1.59 | -     |  |
| Gender categorical<br>Units:                                            |               |       |  |
| Male                                                                    | 18            | 18    |  |
| Female                                                                  | 5             | 5     |  |
| Race, Customized<br>Units: Subjects                                     |               |       |  |
| African American/African Heritage                                       | 8             | 8     |  |
| White-Arabic/North African Heritage                                     | 1             | 1     |  |
| White-White/Caucasian/European Heritage                                 | 12            | 12    |  |
| Mixed Race                                                              | 2             | 2     |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                    |                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Reporting group title                                                                                                                                                                                                                                              | Overall Study       |
| Reporting group description:                                                                                                                                                                                                                                       |                     |
| Placebo twice daily (BID) for 14 days followed by FP HFA 44 microgram (mcg) BID for 28 days                                                                                                                                                                        |                     |
| Subject analysis set title                                                                                                                                                                                                                                         | Placebo HFA         |
| Subject analysis set type                                                                                                                                                                                                                                          | Sub-group analysis  |
| Subject analysis set description:                                                                                                                                                                                                                                  |                     |
| In Session 1, participants received two inhalations of placebo HFA BID 30 seconds apart from Day 1 to 14, via a MDI and a valved holding chamber (AeroChamber Plus) with infant mask.                                                                              |                     |
| Subject analysis set title                                                                                                                                                                                                                                         | FP HFA 44 microgram |
| Subject analysis set type                                                                                                                                                                                                                                          | Sub-group analysis  |
| Subject analysis set description:                                                                                                                                                                                                                                  |                     |
| In Session 2, participants received 2 inhalations of 44 mcg FP HFA BID 30 seconds apart from Day 1 to 28, via a MDI and a valved holding chamber (AeroChamber Plus) with infant mask. Doses were given at about the same time of day approximately 12 hours apart. |                     |

### Primary: Weighted mean serum cortisol over 0 to 12 hours (h) (0-12 h) post dose

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Weighted mean serum cortisol over 0 to 12 hours (h) (0-12 h) post dose |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                        |
| Blood samples of participants were collected at the following time points: 0, 2, 4, 8, and 12 hour following the morning dose on Day 14 of Session 1 and Day 28 of Session 2. The primary outcome compared serum cortisol weighted mean(0-12h) between treatments after 28 days of FP HFA MDI 88 mcg with 14 days of placebo, obtained from the repeated measures analysis. . Only those participants available at the specified time points were analyzed. Pharmacodynamic (PD) Population: all participants in the Safety Population (comprised of all participants who received at least one dose of placebo in session 1) who had serum cortisol results for session 1 Day 14 or session 2 Day 28 were included. |                                                                        |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Primary                                                                |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                        |
| Day 14 and Day 28                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                        |

| End point values                    | Placebo HFA          | FP HFA 44 microgram  |  |  |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type                  | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed         | 21 <sup>[1]</sup>    | 17 <sup>[2]</sup>    |  |  |
| Units: Nanomoles per liter (nmol/L) |                      |                      |  |  |
| geometric mean (standard error)     | 191.65 (± 0.108)     | 184.58 (± 0.12)      |  |  |

Notes:

[1] - PD Population

[2] - PD Population

### Statistical analyses

|                            |                                   |
|----------------------------|-----------------------------------|
| Statistical analysis title | Statistical Analysis - 1          |
| Comparison groups          | FP HFA 44 microgram v Placebo HFA |

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 38                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[3]</sup> |
| Parameter estimate                      | Ratio of geometric means       |
| Point estimate                          | 0.96                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0.71                           |
| upper limit                             | 1.31                           |

Notes:

[3] - Non-inferiority was demonstrated if the lower limit of the two-sided 95% confidence interval for the ratio of the geometric mean for the two treatment arms was greater than 0.7.

### Secondary: Minimum serum cortisol concentration (Cmin) over 0 to 12 h

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Minimum serum cortisol concentration (Cmin) over 0 to 12 h |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                            |
| Blood samples for serum cortisol were collected at the following timepoints: 0, 2, 4, 8, and 12 hour following the morning dose on Day 14 of Session 1 and Day 28 of Session 2. Cmin was derived from the serum cortisol concentration data. Any difference in systemic exposure of the two treatments was considered to also result in differences in serum cortisol concentrations. Only those participants available at the specified time points were analyzed. |                                                            |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Secondary                                                  |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                            |
| Day 14 and Day 28                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                            |

| End point values                         | Placebo HFA              | FP HFA 44 microgram  |  |  |
|------------------------------------------|--------------------------|----------------------|--|--|
| Subject group type                       | Subject analysis set     | Subject analysis set |  |  |
| Number of subjects analysed              | 17 <sup>[4]</sup>        | 14 <sup>[5]</sup>    |  |  |
| Units: nmol/L                            |                          |                      |  |  |
| geometric mean (confidence interval 95%) | 103.25 (74.47 to 143.15) | 91.56 (64 to 131)    |  |  |

Notes:

[4] - PD Population

[5] - PD Population

### Statistical analyses

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis - 1          |
| Comparison groups                       | Placebo HFA v FP HFA 44 microgram |
| Number of subjects included in analysis | 31                                |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | non-inferiority <sup>[6]</sup>    |
| Parameter estimate                      | Ratio of geometric means          |
| Point estimate                          | 0.887                             |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | 0.579                             |
| upper limit                             | 1.359                             |

Notes:

[6] - Non-inferiority was not demonstrated if the lower confidence limit was greater than 0.7

### Secondary: Maximum plasma concentration at steady-state (C<sub>max</sub>) for FP

|                 |                                                                         |
|-----------------|-------------------------------------------------------------------------|
| End point title | Maximum plasma concentration at steady-state (C <sub>max</sub> ) for FP |
|-----------------|-------------------------------------------------------------------------|

End point description:

Plasma FP samples were collected at the following times: 1 h post-dose following morning dose on Day 14 (Session 1) and 0, 1, 4, 8 and 12 h post-dose on Day 28 (Session 2) and analyzed for C<sub>max</sub> of FP in the blood. C<sub>max</sub> was used to estimate the time at which the activity of the drug was at its maximum. Pharmacokinetic (PK) Parameter Population: All participants in the PK Concentration Population (included all participants in the Safety Population who had PK results for Session 1 Day 14 or Session 2 Day 28) who had derived PK parameters for session 2 Day 28 were included.

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

End point timeframe:

Day 14 and Day 28

| End point values                         | FP HFA 44 microgram  |  |  |  |
|------------------------------------------|----------------------|--|--|--|
| Subject group type                       | Subject analysis set |  |  |  |
| Number of subjects analysed              | 17 <sup>[7]</sup>    |  |  |  |
| Units: Picogram/milliliter (pg/mL)       |                      |  |  |  |
| geometric mean (confidence interval 95%) | 24.6 (13.4 to 45)    |  |  |  |

Notes:

[7] - PK Parameter Population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area under the plasma concentration versus time curve within a dosing interval at steady-state (AUC<sub>[0-t]</sub>) for FP

|                 |                                                                                                                               |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------|
| End point title | Area under the plasma concentration versus time curve within a dosing interval at steady-state (AUC <sub>[0-t]</sub> ) for FP |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------|

End point description:

Plasma FP samples were collected at the following times: 1 h post-dose following morning dose on Day 14 (Session 1) and 0, 1, 4, 8 and 12 h post-dose on Day 28 (Session 2) and analyzed for AUC(0-t) of FP in the blood. AUC(0-t) is a measure of the plasma drug concentration from pre-dose to the last measurable concentration.

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

End point timeframe:

Day 14 and Day 28



|                                          |                      |  |  |  |
|------------------------------------------|----------------------|--|--|--|
| <b>End point values</b>                  | FP HFA 44 microgram  |  |  |  |
| Subject group type                       | Subject analysis set |  |  |  |
| Number of subjects analysed              | 17 <sup>[8]</sup>    |  |  |  |
| Units: Hours per picogram per milliliter |                      |  |  |  |
| geometric mean (confidence interval 95%) | 75 (33.8 to 166.3)   |  |  |  |

Notes:

[8] - PK Parameter Population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Reach Maximum Observed Plasma Concentration at steady state (tmaxss) for FP

|                 |                                                                                     |
|-----------------|-------------------------------------------------------------------------------------|
| End point title | Time to Reach Maximum Observed Plasma Concentration at steady state (tmaxss) for FP |
|-----------------|-------------------------------------------------------------------------------------|

End point description:

Plasma FP samples were collected at the following times: 1 h post-dose following morning dose on Day 14 (Session 1) and 0, 1, 4, 8 and 12 h post-dose on Day 28 (Session 2) and analyzed for tmax of FP in the blood. Tmax is a measure of the time required to reach the maximum concentration of the drug

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

End point timeframe:

Day 14 and Day 28

|                               |                      |  |  |  |
|-------------------------------|----------------------|--|--|--|
| <b>End point values</b>       | FP HFA 44 microgram  |  |  |  |
| Subject group type            | Subject analysis set |  |  |  |
| Number of subjects analysed   | 17 <sup>[9]</sup>    |  |  |  |
| Units: Hour (hr)              |                      |  |  |  |
| median (full range (min-max)) | 1 (0 to 4)           |  |  |  |

Notes:

[9] - PK parameter population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with any adverse events (AEs) and any serious adverse events (SAE) during the treatment period

|                 |                                                                                                                       |
|-----------------|-----------------------------------------------------------------------------------------------------------------------|
| End point title | Number of participants with any adverse events (AEs) and any serious adverse events (SAE) during the treatment period |
|-----------------|-----------------------------------------------------------------------------------------------------------------------|

End point description:

An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. SAEs assessed included medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, and is a significant medical event in the investigator's judgment. Safety Population: all participants who received at least one dose of placebo in session 1.

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

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End point timeframe:

Up to 4 weeks

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| End point values            | Placebo HFA          | FP HFA 44 microgram  |  |  |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type          | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed | 23 <sup>[10]</sup>   | 21 <sup>[11]</sup>   |  |  |
| Units: Participants         |                      |                      |  |  |
| number (not applicable)     |                      |                      |  |  |
| Any AE                      | 22                   | 19                   |  |  |
| Any SAE                     | 1                    | 0                    |  |  |

Notes:

[10] - Safety Population

[11] - Safety Population

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs were collected from the time a parent/guardian consents for their infant to participate in the study to the end of the the treatment period (approximately 8 weeks including screening and follow-up).

Adverse event reporting additional description:

SAEs and non-serious AEs were reported for the Safety Population, comprised all participants who received at least one dose of placebo in session 1.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 10.0 |
|--------------------|------|

### Reporting groups

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Fluticasone propionate HFA |
|-----------------------|----------------------------|

Reporting group description:

In Session 2, participants received 2 inhalations of 44 mcg FP HFA BID 30 seconds apart from Day 1 to 28, via a MDI and a valved holding chamber (AeroChamber Plus) with infant mask. Doses were given at about the same time of day approximately 12 hours apart.

|                       |             |
|-----------------------|-------------|
| Reporting group title | Placebo HFA |
|-----------------------|-------------|

Reporting group description:

In Session 1, participants received two inhalations of placebo HFA BID 30 seconds apart from Day 1 to 14, via a MDI and a valved holding chamber (AeroChamber Plus) with infant mask.

| Serious adverse events                            | Fluticasone propionate HFA | Placebo HFA    |  |
|---------------------------------------------------|----------------------------|----------------|--|
| Total subjects affected by serious adverse events |                            |                |  |
| subjects affected / exposed                       | 0 / 21 (0.00%)             | 1 / 23 (4.35%) |  |
| number of deaths (all causes)                     | 0                          | 0              |  |
| number of deaths resulting from adverse events    |                            |                |  |
| Infections and infestations                       |                            |                |  |
| Pyelonephritis                                    |                            |                |  |
| subjects affected / exposed                       | 0 / 21 (0.00%)             | 1 / 23 (4.35%) |  |
| occurrences causally related to treatment / all   | 0 / 0                      | 0 / 1          |  |
| deaths causally related to treatment / all        | 0 / 0                      | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events                            | Fluticasone propionate HFA | Placebo HFA      |  |
|-------------------------------------------------------|----------------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                            |                  |  |
| subjects affected / exposed                           | 19 / 21 (90.48%)           | 22 / 23 (95.65%) |  |

|                                                      |                  |                  |  |
|------------------------------------------------------|------------------|------------------|--|
| General disorders and administration site conditions |                  |                  |  |
| Pyrexia                                              |                  |                  |  |
| subjects affected / exposed                          | 6 / 21 (28.57%)  | 8 / 23 (34.78%)  |  |
| occurrences (all)                                    | 10               | 11               |  |
| Irritability                                         |                  |                  |  |
| subjects affected / exposed                          | 1 / 21 (4.76%)   | 1 / 23 (4.35%)   |  |
| occurrences (all)                                    | 1                | 1                |  |
| Ear and labyrinth disorders                          |                  |                  |  |
| Ear pain                                             |                  |                  |  |
| subjects affected / exposed                          | 1 / 21 (4.76%)   | 0 / 23 (0.00%)   |  |
| occurrences (all)                                    | 1                | 0                |  |
| Eye disorders                                        |                  |                  |  |
| Conjunctivitis                                       |                  |                  |  |
| subjects affected / exposed                          | 1 / 21 (4.76%)   | 1 / 23 (4.35%)   |  |
| occurrences (all)                                    | 1                | 1                |  |
| Gastrointestinal disorders                           |                  |                  |  |
| Diarrhoea                                            |                  |                  |  |
| subjects affected / exposed                          | 0 / 21 (0.00%)   | 2 / 23 (8.70%)   |  |
| occurrences (all)                                    | 0                | 2                |  |
| Teething                                             |                  |                  |  |
| subjects affected / exposed                          | 3 / 21 (14.29%)  | 1 / 23 (4.35%)   |  |
| occurrences (all)                                    | 4                | 1                |  |
| Vomiting                                             |                  |                  |  |
| subjects affected / exposed                          | 2 / 21 (9.52%)   | 1 / 23 (4.35%)   |  |
| occurrences (all)                                    | 2                | 1                |  |
| Respiratory, thoracic and mediastinal disorders      |                  |                  |  |
| Cough                                                |                  |                  |  |
| subjects affected / exposed                          | 14 / 21 (66.67%) | 17 / 23 (73.91%) |  |
| occurrences (all)                                    | 32               | 58               |  |
| Rhinorrhoea                                          |                  |                  |  |
| subjects affected / exposed                          | 13 / 21 (61.90%) | 15 / 23 (65.22%) |  |
| occurrences (all)                                    | 23               | 25               |  |
| Nasal congestion                                     |                  |                  |  |
| subjects affected / exposed                          | 6 / 21 (28.57%)  | 12 / 23 (52.17%) |  |
| occurrences (all)                                    | 12               | 16               |  |
| Wheezing                                             |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 8 / 21 (38.10%)  | 10 / 23 (43.48%) |  |
| occurrences (all)                               | 22               | 26               |  |
| Dyspnoea                                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 21 (4.76%)   | 3 / 23 (13.04%)  |  |
| occurrences (all)                               | 1                | 3                |  |
| Respiratory tract congestion                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 21 (4.76%)   | 1 / 23 (4.35%)   |  |
| occurrences (all)                               | 1                | 1                |  |
| Grunting                                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 21 (4.76%)   | 0 / 23 (0.00%)   |  |
| occurrences (all)                               | 1                | 0                |  |
| Sneezing                                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 21 (4.76%)   | 0 / 23 (0.00%)   |  |
| occurrences (all)                               | 1                | 0                |  |
| Psychiatric disorders                           |                  |                  |  |
| Middle insomnia                                 |                  |                  |  |
| subjects affected / exposed                     | 11 / 21 (52.38%) | 9 / 23 (39.13%)  |  |
| occurrences (all)                               | 17               | 27               |  |
| Crying                                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 21 (4.76%)   | 0 / 23 (0.00%)   |  |
| occurrences (all)                               | 1                | 0                |  |
| Musculoskeletal and connective tissue disorders |                  |                  |  |
| Muscular weakness                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 21 (4.76%)   | 0 / 23 (0.00%)   |  |
| occurrences (all)                               | 1                | 0                |  |
| Infections and infestations                     |                  |                  |  |
| Ear infection                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 21 (4.76%)   | 1 / 23 (4.35%)   |  |
| occurrences (all)                               | 1                | 1                |  |
| Nasopharyngitis                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 21 (4.76%)   | 1 / 23 (4.35%)   |  |
| occurrences (all)                               | 1                | 1                |  |
| Eye infection                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 21 (4.76%)   | 0 / 23 (0.00%)   |  |
| occurrences (all)                               | 1                | 0                |  |
| Influenza                                       |                  |                  |  |

|                                   |                |                |  |
|-----------------------------------|----------------|----------------|--|
| subjects affected / exposed       | 1 / 21 (4.76%) | 0 / 23 (0.00%) |  |
| occurrences (all)                 | 1              | 0              |  |
| Streptococcal sepsis              |                |                |  |
| subjects affected / exposed       | 1 / 21 (4.76%) | 0 / 23 (0.00%) |  |
| occurrences (all)                 | 1              | 0              |  |
| Upper respiratory tract infection |                |                |  |
| subjects affected / exposed       | 1 / 21 (4.76%) | 0 / 23 (0.00%) |  |
| occurrences (all)                 | 1              | 0              |  |
| Varicella                         |                |                |  |
| subjects affected / exposed       | 1 / 21 (4.76%) | 0 / 23 (0.00%) |  |
| occurrences (all)                 | 1              | 0              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                                                                                          |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 03 October 2006 | The purpose of this amendment is to make changes to the Rationale, Endpoints, Hypotheses, Study Design, Dose Rationale and Sample Size Assumptions sections of the protocol as well as include additional information to the Background Section of the protocol and remove section 10.2.2 which no longer applies to this protocol |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported