



Clinical trial results: Efficacy of Intermittent Tiotropium in Early Childhood Wheezing Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2015-002985-22 |
| Trial protocol | FI |
| Global end of trial date | 18 November 2020 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 22 January 2023 |
| First version publication date | 22 January 2023 |

Trial information

Trial identification

| | |
|-----------------------|-------|
| Sponsor protocol code | TFS01 |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03199976 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Mika J. Mäkelä |
| Sponsor organisation address | P.O. Box 160, Helsinki, Finland, FIN-00029 HUS |
| Public contact | Paediatric Unit -- Trials, Department of Allergology, Helsinki University Hospital, +358 94711, |
| Scientific contact | Paediatric Unit -- Trials, Department of Allergology, Helsinki University Hospital, +358 94711, |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 14 May 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 November 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 November 2020 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary AIM of the study is

1) to find out the effect of intermittent tiotropium bromide and salbutamol as needed (TBS) versus intermittent fluticasone propionate and salbutamol as needed (FPS), or solely, salbutamol as needed (SA) on episode-free days in infants and toddlers with recurrent episodes of wheeze and/or shortness of breath.

Episode-free days are defined as those days during which there are no symptoms of wheeze and/or shortness of breath, no unscheduled medical visits for wheeze and/or shortness of breath, and no use of rescue or supplementary controller medications.

Protection of trial subjects:

Most of the study visits took place as part of routine outpatient control visits at the nearest hospital, and the study laboratory tests were taken as part of routine laboratory tests during the routine outpatient visits. Occurrence of drug-related adverse events was attempted to be minimized by including the conditions that may increase the risk for drug-related adverse events in the exclusion criteria.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 20 April 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Finland: 80 |
| Worldwide total number of subjects | 80 |
| EEA total number of subjects | 80 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 | 53 |

| | |
|---------------------------|----|
| months) | |
| Children (2-11 years) | 27 |
| 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:

The first patient was recruited to the study on April 20, 2016, and the last patient on December 16, 2019. All participants were recruited in the coordinating center, and the coordinating subinvestigator recruited 98% of the study subjects.

Pre-assignment

Screening details:

170 patients were screened for eligibility -- 4 of those did not meet inclusion criteria and 44 had at least 1 exclusion criterion. 122 children were considered eligible, and 80 of them were enrolled and randomized. Because the interventions were intermittent, the trial did not include a run-in period.

Period 1

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

Arms

| | |
|------------------------------|---------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Tiotropium Bromide & Salbutamol |

Arm description:

Inhaled tiotropium bromide 5 ug once a day, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed, and inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath

| | |
|--|---------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Spiriva Respimat |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

2.5 ug two doses once a day via an AeroChamber spacer device, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed

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

Dosage and administration details:

0.1 mg 2 doses 4 to 6 times a day via an AeroChamber spacer device as needed for wheeze and shortness of breath

| | |
|------------------|-------------------------------------|
| Arm title | Fluticasone Propionate & Salbutamol |
|------------------|-------------------------------------|

Arm description:

Inhaled fluticasone propionate 125 ug twice a day, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed, and inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

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

Dosage and administration details:

125 ug twice a day via a Babyhaler spacer device, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed

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

Dosage and administration details:

0.1 mg 2 doses 4 to 6 times a day via a Babyhaler spacer device as needed for wheeze and shortness of breath

| | |
|------------------|------------|
| Arm title | Salbutamol |
|------------------|------------|

Arm description:

Inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath

| | |
|--|---------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Ventoline Evohaler |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

0.1 mg 2 doses 4 to 6 times a day via a Babyhaler spacer device as needed for wheeze and shortness of breath

| Number of subjects in period 1 | Tiotropium Bromide & Salbutamol | Fluticasone Propionate & Salbutamol | Salbutamol |
|--------------------------------|---------------------------------|-------------------------------------|------------|
| | | | |
| Started | 27 | 25 | 28 |
| Completed | 23 | 18 | 14 |
| Not completed | 4 | 7 | 14 |
| Consent withdrawn by subject | 1 | - | - |
| Lost to follow-up | - | 1 | 1 |
| Lack of efficacy | 3 | 6 | 13 |

Baseline characteristics

Reporting groups

| | |
|--|-------------------------------------|
| Reporting group title | Tiotropium Bromide & Salbutamol |
| Reporting group description: Inhaled tiotropium bromide 5 ug once a day, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed, and inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath | |
| Reporting group title | Fluticasone Propionate & Salbutamol |
| Reporting group description: Inhaled fluticasone propionate 125 ug twice a day, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed, and inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath | |
| Reporting group title | Salbutamol |
| Reporting group description: Inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath | |

| Reporting group values | Tiotropium Bromide & Salbutamol | Fluticasone Propionate & Salbutamol | Salbutamol |
|---|---------------------------------|-------------------------------------|---------------|
| Number of subjects | 27 | 25 | 28 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: months | | | |
| arithmetic mean standard deviation | 21.4 ± 7.0 | 20.0 ± 6.8 | 22.1 ± 6.0 |
| Gender categorical Units: Subjects | | | |
| Female | 9 | 9 | 10 |
| Male | 18 | 16 | 18 |
| Allergic sensitization | | | |
| Defined as a specific IgE level of ≥ 0.70 kU/l to food allergens (i.e. milk, egg, wheat, soy bean, cod, peanut), a specific IgE level of ≥ 0.35 kU/l to aeroallergens (i.e. birch, timothy, mugwort, cat, dog, horse, Dermatophagoides pteronyssinus, Cladosporium herbarum), or in case there was no blood specimen drawn, as an earlier skin prick test result with a wheal diameter of ≥ 3 mm to aeroallergens. | | | |
| Units: Subjects | | | |
| Sensitized | 8 | 12 | 5 |
| Not sensitized | 19 | 13 | 23 |
| Short-course glucocorticoid treatment in previous 2 weeks | | | |
| Short-course glucocorticoid treatment in previous 2 weeks, i.e. per oral for 1 to 3 days, or inhaled for 1 | | | |

| | | | |
|---|--------|--------|--------|
| to 2 weeks. | | | |
| Units: Subjects | | | |
| Present | 3 | 10 | 8 |
| Not present | 24 | 15 | 20 |
| Physician-confirmed episodes of wheeze and/or shortness of breath | | | |
| Units: Number of episodes | | | |
| median | 2 | 3 | 3 |
| inter-quartile range (Q1-Q3) | 2 to 3 | 2 to 3 | 2 to 3 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 80 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: months | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 28 | | |
| Male | 52 | | |
| Allergic sensitization | | | |
| Defined as a specific IgE level of ≥ 0.70 kU/l to food allergens (i.e. milk, egg, wheat, soy bean, cod, peanut), a specific IgE level of ≥ 0.35 kU/l to aeroallergens (i.e. birch, timothy, mugwort, cat, dog, horse, Dermatophagoides pteronyssinus, Cladosporium herbarum), or in case there was no blood specimen drawn, as an earlier skin prick test result with a wheal diameter of ≥ 3 mm to aeroallergens. | | | |
| Units: Subjects | | | |
| Sensitized | 25 | | |
| Not sensitized | 55 | | |
| Short-course glucocorticoid treatment in previous 2 weeks | | | |
| Short-course glucocorticoid treatment in previous 2 weeks, i.e. per oral for 1 to 3 days, or inhaled for 1 to 2 weeks. | | | |
| Units: Subjects | | | |
| Present | 21 | | |
| Not present | 59 | | |
| Physician-confirmed episodes of wheeze and/or shortness of breath | | | |
| Units: Number of episodes | | | |
| median | | | |
| inter-quartile range (Q1-Q3) | - | | |

End points

End points reporting groups

| | |
|--|-------------------------------------|
| Reporting group title | Tiotropium Bromide & Salbutamol |
| Reporting group description: Inhaled tiotropium bromide 5 ug once a day, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed, and inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath | |
| Reporting group title | Fluticasone Propionate & Salbutamol |
| Reporting group description: Inhaled fluticasone propionate 125 ug twice a day, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed, and inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath | |
| Reporting group title | Salbutamol |
| Reporting group description: Inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath | |

Primary: Proportion of episode-free days

| | |
|--|---------------------------------|
| End point title | Proportion of episode-free days |
| End point description: Episode-free days were defined as the days with no symptoms of wheeze and/or shortness of breath, no unscheduled medical visits for wheeze and/or shortness of breath, and no use of rescue or supplementary controller medications. | |
| End point type | Primary |
| End point timeframe: Up to 48 weeks | |

| End point values | Tiotropium Bromide & Salbutamol | Fluticasone Propionate & Salbutamol | Salbutamol | |
|---------------------------------------|---------------------------------|-------------------------------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 26 ^[1] | 25 ^[2] | 26 ^[3] | |
| Units: percent | | | | |
| median (inter-quartile range (Q1-Q3)) | 97 (93 to 99) | 87 (78 to 93) | 88 (79 to 95) | |

Notes:

[1] - Subjects with diary data available were included in the intention-to treat analysis.

[2] - Subjects with diary data available were included in the intention-to treat analysis.

[3] - Subjects with diary data available were included in the intention-to treat analysis.

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Primary outcome analysis -- Episode-free days |
| Statistical analysis description: The primary outcome was efficacy, assessed as intention-to treat by comparing the proportion of episode-free days between the treatment groups. Early termination of recruitment lead to re-calculation of power by replacing an assumed SD of 27% with an observed SD of 17% for episode-free days in the Salbutamol group. Calculations allowing a 20% drop-out rate yielded a sample size of 25 children per group; a total number of 80 recruited subjects was considered sufficient for data analyses. | |
| Comparison groups | Tiotropium Bromide & Salbutamol v Fluticasone Propionate & Salbutamol v Salbutamol |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[4] |
| P-value | < 0.05 ^[5] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[4] - Bonferroni correction was applied in pairwise analyses by multiplying each P value by 3.

[5] - P=0.002 between Tiotropium Bromide & Salbutamol and Fluticasone Propionate & Salbutamol groups.

P=0.003 between Tiotropium Bromide & Salbutamol and Salbutamol group.

Secondary: Unscheduled physician visits for wheeze

| | |
|-----------------|---|
| End point title | Unscheduled physician visits for wheeze |
|-----------------|---|

End point description:

Effect of intervention on the number of unscheduled physician visits for episodes of wheeze and/or shortness of breath.

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

End point timeframe:

Up to 48 weeks

| End point values | Tiotropium Bromide & Salbutamol | Fluticasone Propionate & Salbutamol | Salbutamol | |
|--|---------------------------------|-------------------------------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 27 ^[6] | 25 ^[7] | 28 ^[8] | |
| Units: Number of participants | | | | |
| Unscheduled physician visits for wheeze | 10 | 10 | 14 | |
| No unscheduled physician visits for wheeze | 17 | 15 | 14 | |

Notes:

[6] - Analysis performed as intention to treat.

[7] - Analysis performed as intention to treat.

[8] - Analysis performed as intention to treat.

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Secondary outcome analysis -- Unscheduled visits |
|----------------------------|--|

Statistical analysis description:

Bonferroni correction was applied in pairwise analyses by multiplying each P-value by 3.

| | |
|---|--|
| Comparison groups | Tiotropium Bromide & Salbutamol v Fluticasone Propionate & Salbutamol v Salbutamol |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | > 0.05 |
| Method | Chi-squared |

Secondary: Rescue Medication

| | |
|-----------------|-------------------|
| End point title | Rescue Medication |
|-----------------|-------------------|

| | |
|--|-----------|
| End point description: | |
| Effect of intervention on the need for salbutamol. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 48 weeks | |

| End point values | Tiotropium Bromide & Salbutamol | Fluticasone Propionate & Salbutamol | Salbutamol | |
|---------------------------------------|---------------------------------|-------------------------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 26 ^[9] | 25 ^[10] | 26 ^[11] | |
| Units: Percentage of days | | | | |
| median (inter-quartile range (Q1-Q3)) | 2 (0 to 7) | 13 (6 to 21) | 12 (6 to 20) | |

Notes:

[9] - Subjects with diary data available were included in the intention-to-treat analysis.

[10] - Subjects with diary data available were included in the intention-to-treat analysis.

[11] - Subjects with diary data available were included in the intention-to-treat analysis.

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Secondary outcome analysis -- Rescue medication |
| Statistical analysis description: | |
| Bonferroni correction was applied in pairwise analyses by multiplying each P-value by 3. | |
| Comparison groups | Tiotropium Bromide & Salbutamol v Fluticasone Propionate & Salbutamol v Salbutamol |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 ^[12] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[12] - P<0.001 between Tiotropium Bromide & Salbutamol and Fluticasone Propionate groups.

P<0.001 between Tiotropium Bromide & Salbutamol and Salbutamol groups.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 48 weeks

Adverse event reporting additional description:

Adverse events were charted by collecting data from daily diaries and by reviewing the medical records.

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

Dictionary used

| | |
|-----------------|------------|
| Dictionary name | ICD coding |
|-----------------|------------|

| | |
|--------------------|----|
| Dictionary version | 10 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|---------------------------------|
| Reporting group title | Tiotropium Bromide & Salbutamol |
|-----------------------|---------------------------------|

Reporting group description:

Inhaled tiotropium bromide 5 ug once a day, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed, and inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Flixotide Propionate & Salbutamol |
|-----------------------|-----------------------------------|

Reporting group description:

Inhaled fluticasone propionate 125 ug twice a day, beginning at the onset of an upper respiratory tract infection and continuing for 7 to 14 days as needed, and inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath

| | |
|-----------------------|------------|
| Reporting group title | Salbutamol |
|-----------------------|------------|

Reporting group description:

Inhaled salbutamol 0.2 mg 4 to 6 times a day as needed for wheeze and shortness of breath

| Serious adverse events | Tiotropium Bromide & Salbutamol | Flixotide Propionate & Salbutamol | Salbutamol |
|---|---|-----------------------------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 27 (14.81%) | 3 / 25 (12.00%) | 3 / 28 (10.71%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | Additional description: Anaphylactic reaction to cashew nut | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 25 (4.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Enteritis infectious | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 25 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 25 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wheezing | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 3 / 25 (12.00%) | 2 / 28 (7.14%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 25 (4.00%) | 0 / 28 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Tiotropium Bromide & Salbutamol | Flixotide Propionate & Salbutamol | Salbutamol |
|---|--------------------------------------|-----------------------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 19 / 27 (70.37%) | 22 / 25 (88.00%) | 23 / 28 (82.14%) |
| Injury, poisoning and procedural complications | | | |
| Contusion | Additional description: Minor trauma | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 3 / 25 (12.00%) | 2 / 28 (7.14%) |
| occurrences (all) | 2 | 4 | 2 |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 3 / 25 (12.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 1 | 3 | 1 |
| Exanthema | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 2 / 25 (8.00%) | 2 / 28 (7.14%) |
| occurrences (all) | 1 | 2 | 2 |
| Infections and infestations | | | |
| Otitis media | | | |
| subjects affected / exposed | 16 / 27 (59.26%) | 9 / 25 (36.00%) | 12 / 28 (42.86%) |
| occurrences (all) | 18 | 16 | 20 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 13 / 27 (48.15%) | 13 / 25 (52.00%) | 9 / 28 (32.14%) |
| occurrences (all) | 20 | 16 | 16 |

| | | | |
|-----------------------------|-----------------|-----------------|------------------|
| Wheezing | | | |
| subjects affected / exposed | 7 / 27 (25.93%) | 7 / 25 (28.00%) | 12 / 28 (42.86%) |
| occurrences (all) | 10 | 12 | 19 |
| Enteritis infectious | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 3 / 25 (12.00%) | 2 / 28 (7.14%) |
| occurrences (all) | 3 | 4 | 3 |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 25 (0.00%) | 2 / 28 (7.14%) |
| occurrences (all) | 2 | 0 | 2 |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 25 (4.00%) | 3 / 28 (10.71%) |
| occurrences (all) | 1 | 1 | 3 |
| Conjunctivitis | | | |
| subjects affected / exposed | 4 / 27 (14.81%) | 1 / 25 (4.00%) | 7 / 28 (25.00%) |
| occurrences (all) | 5 | 1 | 8 |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 25 (4.00%) | 1 / 28 (3.57%) |
| occurrences (all) | 1 | 1 | 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|--|
| Early termination leading to small numbers of subjects analyzed. |
|--|

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/35942814>