# Clinical trial results:
# Efficacy and Safety of an Herbal-Based Medication vs. Placebo in Preventing Acute Otitis Media in Children at High Risk of Recurrence: A Placebo Controlled, Randomized, Double-blinded Parallel-Group Comparison for Superiority

## Summary

| | |
|---|---|
| EudraCT number | 2012-000341-13 |
| Trial protocol | DE |
| Global end of trial date | 01 June 2015 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 11 February 2022 |
| First version publication date | 11 February 2022 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | OTV.PRE.01 |

### Additional study identifiers

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

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Weber & Weber GmbH & Co.KG |
| Sponsor organisation address | Herrschinger Strasse 33, Inning / Ammersee, Germany, 82266 |
| Public contact | Preclinical & Clinical Trials, Weber&Weber, Weber & Weber GmbH & Co. KG, 49 81439270, zentrale@weber-weber.net |
| Scientific contact | Preclinical & Clinical Trials, Weber&Weber, Weber & Weber GmbH & Co. KG, 49 81439270, zentrale@weber-weber.net |

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 | 17 June 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 June 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 June 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To prove the superiority of Otovowen to placebo in the prevention of acute otitis media

Protection of trial subjects:

Study was conducted in accordance with ICH GCP guidelines
Study protocol, amendments, informed consent were approved by EC
The investigator / designee informed the subjects of all aspects pertainig to the subject´s participation in the study

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 24 September 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Germany: 311 |
| Worldwide total number of subjects | 311 |
| EEA total number of subjects | 311 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 311 |
| 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 study was conducted in 30 centers (pediatric practitioners) in Germany. Patient cards were screened based on inclusion / exclusion criteria for eligible patients 1-2 months prior to study start. Study medication was administered at first signs of URI, observation period per subject was 6 months.

### Pre-assignment

Screening details:

Children aged 12 to 59 months and with at least 3 episodes of acute otitis media (AOM) within 12 months prior to study inclusion as documented in their medical records.

### Period 1

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

Blinding implementation details:

Block randomization was done by computer and randomization lists were prepared. Based on the lists study drug (verum and placebo) were labeled with the appropriate randomization numbers.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Otovoven |

Arm description:

Participants received Otovowen at first signs of URI until symptoms resolved

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Otovowen® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

7 drops three times daily at first signs of URI until symptoms resolve (maximally 8 weeks of continuous application)

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Participants received placebo at first signs of URI until symptoms resolved

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

7 drops three times daily at first signs of URI until symptoms resolved (maximally 8 weeks of continuous application)

| **Number of subjects in period 1** | Otovoven | Placebo |
|---|---|---|
| Started | 156 | 155 |
| Completed | 156 | 155 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Otovoven |
| Reporting group description: | |
| Participants received Otovowen at first signs of URI until symptoms resolved | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received placebo at first signs of URI until symptoms resolved | |

| Reporting group values | Otovoven | Placebo | Total |
|---|---|---|---|
| Number of subjects | 156 | 155 | 311 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 156 | 155 | 311 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Otovowen | 0 | 0 | 0 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 75 | 67 | 142 |
| Male | 81 | 88 | 169 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Otovoven |
| Reporting group description: Participants received Otovowen at first signs of URI until symptoms resolved | |
| Reporting group title | Placebo |
| Reporting group description: Participants received placebo at first signs of URI until symptoms resolved | |

### Primary: number of AOM episodes

| | |
|---|---|
| End point title | number of AOM episodes |
| End point description: | |
| End point type | Primary |
| End point timeframe: number of AOM episodes diagnosed by a physician within 6 months after enrolment per patient | |

| End point values | Otovoven | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 156 | 155 | | |
| Units: AOM episodes | | | | |
| arithmetic mean (standard deviation) | 0.40 (± 0.66) | 0.43 (± 0.77) | | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis |
|---|---|
| Comparison groups | Placebo v Otovoven |
| Number of subjects included in analysis | 311 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Wilcoxon (Mann-Whitney) |

### Secondary: Number of unscheduled visits due to AOM

| | |
|---|---|
| End point title | Number of unscheduled visits due to AOM |
| End point description: | |
| End point type | Secondary |

End point timeframe:
within 6 months

| End point values | Otovoven | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 156 | 155 | | |
| Units: visits | | | | |
| arithmetic mean (standard deviation) | 0.42 (± 0.69) | 0.52 (± 1.02) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of unscheduled visits due to URI

| End point title | Number of unscheduled visits due to URI |
|---|---|

End point description:

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

End point timeframe:
within 6 months

| End point values | Otovoven | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 156 | 155 | | |
| Units: visits | | | | |
| arithmetic mean (standard deviation) | 2.16 (± 1.77) | 1.96 (± 1.74) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of AOMs treated with antibiotics

| End point title | Number of AOMs treated with antibiotics |
|---|---|

End point description:

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

End point timeframe:
within 6 months

| End point values | Otovoven | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 156 | 155 | | |
| Units: AOM | | | | |
| arithmetic mean (standard deviation) | 0.28 (± 0.57) | 0.39 (± 0.75) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of URI treated with antibiotics

| End point title | Number of URI treated with antibiotics |
|---|---|

End point description:

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

End point timeframe:
within 6 months

| End point values | Otovoven | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 156 | 155 | | |
| Units: URI | | | | |
| arithmetic mean (standard deviation) | 0.16 (± 0.43) | 0.12 (± 0.33) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of days with URI

| End point title | Number of days with URI |
|---|---|

End point description:

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

End point timeframe:
within 6 months

| End point values | Otovoven | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 156 | 155 | | |
| Units: Days with URI | | | | |
| arithmetic mean (standard deviation) | 41.0 (± 26.4) | 39.7 (± 29.6) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of absent days from daycare

| End point title | Number of absent days from daycare |
|---|---|

End point description:

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

End point timeframe:

within 6 months

| End point values | Otovoven | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 156 | 155 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | 10.0 (± 8.0) | 10.3 (± 9.2) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of absent days from work (parents/legal representative)

| End point title | Number of absent days from work (parents/legal representative) |
|---|---|

End point description:

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

End point timeframe:

within 6 months

| End point values | Otovoven | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 156 | 155 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | 5.0 (± 6.58) | 4.9 (± 6.64) | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Subjective evaluation of efficacy by patient/parent**

| End point title | Subjective evaluation of efficacy by patient/parent |
|---|---|

End point description:

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

End point timeframe:
within 6 months

| End point values | Otovoven | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 156 | 155 | | |
| Units: Scale 0-3 | | | | |
| arithmetic mean (standard deviation) | 1.83 (± 0.95) | 1.81 (± 0.98) | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Subjective evaluation of tolerability by patient/parent**

| End point title | Subjective evaluation of tolerability by patient/parent |
|---|---|

End point description:

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

End point timeframe:
within 6 months

| End point values | Otovoven | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 156 | 155 | | |
| Units: scale 0-3 | | | | |
| arithmetic mean (standard deviation) | 2.36 (± 0.62) | 2.36 (± 0.60) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Mean number of AOMs plus suspicious ear disease

| End point title | Mean number of AOMs plus suspicious ear disease |
|---|---|

End point description:

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

End point timeframe:
within 6 months

| End point values | Otovoven | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 156 | 155 | | |
| Units: number | | | | |
| arithmetic mean (standard deviation) | 0.56 (± 0.82) | 0.57 (± 0.88) | | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: entire study | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19 |

| Reporting groups | |
|---|---|
| Reporting group title | Otovowen |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

| Serious adverse events | Otovowen | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 152 (5.26%) | 3 / 150 (2.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| concussion | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| febrile convulsion | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| vomiting | | | |
| subjects affected / exposed | 0 / 152 (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 | |
| inguinal hernia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| bronchopneumonia | | | |
| subjects affected / exposed | 0 / 152 (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 | |
| acute tonsilitis | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastroenteritis | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| respiratory syncytial virus bronchiolitis | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastroenteritis norovirus | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 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: 5 %

| **Non-serious adverse events** | Otovowen | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 128 / 152 (84.21%) | 130 / 150 (86.67%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| skin papilloma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 152 (0.66%) | 3 / 150 (2.00%) | |
| occurrences (all) | 1 | 3 | |
| Surgical and medical procedures | | | |
| Adenoidectomy | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 1 / 150 (0.67%) | |
| occurrences (all) | 2 | 1 | |
| ear tube insertion | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 150 (0.67%) | |
| occurrences (all) | 1 | 1 | |
| circumcision | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| myringotomy | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 0 / 150 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| General disorders and administration site conditions | | | |
| gait disorder | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 150 (0.67%) | |
| occurrences (all) | 1 | 1 | |
| influenca like illness | | | |
| subjects affected / exposed | 34 / 152 (22.37%) | 44 / 150 (29.33%) | |
| occurrences (all) | 51 | 64 | |
| pain | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 150 (0.67%) | |
| occurrences (all) | 1 | 1 | |
| pyrexia | | | |
| subjects affected / exposed | 10 / 152 (6.58%) | 5 / 150 (3.33%) | |
| occurrences (all) | 11 | 6 | |
| upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 150 (0.67%) | |
| occurrences (all) | 1 | 1 | |
| local swelling | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| accidential device ingestion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Immune system disorders | | | |
| allergic reaction to antibiotics | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| hypersensitivity | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 1 / 150 (0.67%) | |
| occurrences (all) | 2 | 1 | |
| Reproductive system and breast disorders | | | |
| balanoposthitis | | | |
| subjects affected / exposed | 5 / 152 (3.29%) | 3 / 150 (2.00%) | |
| occurrences (all) | 6 | 4 | |
| testicular retraction | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| asthma | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 6 / 150 (4.00%) | |
| occurrences (all) | 2 | 10 | |
| cough | | | |
| subjects affected / exposed | 5 / 152 (3.29%) | 8 / 150 (5.33%) | |
| occurrences (all) | 8 | 11 | |
| dyspnoea | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| epistaxis | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 2 / 150 (1.33%) | |
| occurrences (all) | 0 | 2 | |
| bronchial hyperreactivity | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 5 / 150 (3.33%) | |
| occurrences (all) | 2 | 6 | |
| allergic rhinitis | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| tonsillar hypertrophy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 150 (0.67%) | |
| occurrences (all) | 1 | 1 | |
| attention seeking behaviour | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 150 (0.67%) | |
| occurrences (all) | 1 | 1 | |
| encopresis | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| phonological disorder | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| sleep disorder | | | |
| subjects affected / exposed | 3 / 152 (1.97%) | 1 / 150 (0.67%) | |
| occurrences (all) | 4 | 1 | |
| emotional disorders of childhood | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Investigations | | | |
| Cardiac murmur functional | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| skin test | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Injury, poisoning and procedural complications | | | |
| arthropod bite | | | |
| subjects affected / exposed | 3 / 152 (1.97%) | 1 / 150 (0.67%) | |
| occurrences (all) | 3 | 1 | |
| laceration | | | |
| subjects affected / exposed | 9 / 152 (5.92%) | 4 / 150 (2.67%) | |
| occurrences (all) | 9 | 5 | |
| splinter | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 152 (0.66%) | 2 / 150 (1.33%) | |
| occurrences (all) | 1 | 2 | |
| mouth injury | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 150 (0.67%) | |
| occurrences (all) | 1 | 1 | |
| face injury | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| contusion | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 2 / 150 (1.33%) | |
| occurrences (all) | 2 | 2 | |
| brain contusion | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| joint injury | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| poisoning | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| periorbital contusion | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| eye contusion | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| humerus fracture | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| ligament injury | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| nail injury | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 0 / 150 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| exposure via eye contact | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Congenital, familial and genetic disorders | | | |
| Kidney duplex | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| phimosis | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nervous system disorders | | | |
| speech disorder developmental | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| Blood and lymphatic system disorders | | | |
| Lympadenitis | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 2 / 150 (1.33%) | |
| occurrences (all) | 0 | 2 | |
| leucocytosis | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ear and labyrinth disorders | | | |
| ear pain | | | |
| subjects affected / exposed | 5 / 152 (3.29%) | 4 / 150 (2.67%) | |
| occurrences (all) | 5 | 5 | |
| Tympanic membrane perforation | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| Tympanic membrane hyperaemia | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| Middle ear effusion | | | |
| subjects affected / exposed | 19 / 152 (12.50%) | 13 / 150 (8.67%) | |
| occurrences (all) | 21 | 14 | |
| cerumen impaction | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---|---|---|
| Eye disorders | | | |
| conjunctivitis | | | |
| subjects affected / exposed | 32 / 152 (21.05%) | 25 / 150 (16.67%) | |
| occurrences (all) | 41 | 29 | |
| visual impairment | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| Eye pain | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| excessive eye blinking | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| abdominal disomfort | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| abdominal distension | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 150 (0.67%) | |
| occurrences (all) | 1 | 1 | |
| abdominal pain | | | |
| subjects affected / exposed | 9 / 152 (5.92%) | 4 / 150 (2.67%) | |
| occurrences (all) | 9 | 4 | |
| anal fissure | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 2 / 150 (1.33%) | |
| occurrences (all) | 0 | 2 | |
| aphthous stomatitis | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 2 / 150 (1.33%) | |
| occurrences (all) | 2 | 2 | |
| constipation | | | |
| subjects affected / exposed | 6 / 152 (3.95%) | 11 / 150 (7.33%) | |
| occurrences (all) | 7 | 11 | |
| diarrhea | | | |
| subjects affected / exposed | 11 / 152 (7.24%) | 6 / 150 (4.00%) | |
| occurrences (all) | 12 | 6 | |
| dyspepsia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 150 (0.67%) | |
| occurrences (all) | 1 | 1 | |
| teething | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 4 / 150 (2.67%) | |
| occurrences (all) | 0 | 4 | |
| vomiting | | | |
| subjects affected / exposed | 11 / 152 (7.24%) | 11 / 150 (7.33%) | |
| occurrences (all) | 11 | 11 | |
| anal pruritus | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| dermatitis | | | |
| subjects affected / exposed | 13 / 152 (8.55%) | 8 / 150 (5.33%) | |
| occurrences (all) | 15 | 9 | |
| allergic dermatitis | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 2 / 150 (1.33%) | |
| occurrences (all) | 1 | 2 | |
| dermatitis atopic | | | |
| subjects affected / exposed | 3 / 152 (1.97%) | 6 / 150 (4.00%) | |
| occurrences (all) | 3 | 7 | |
| dermatitis diaper | | | |
| subjects affected / exposed | 4 / 152 (2.63%) | 4 / 150 (2.67%) | |
| occurrences (all) | 4 | 4 | |
| rash | | | |
| subjects affected / exposed | 6 / 152 (3.95%) | 2 / 150 (1.33%) | |
| occurrences (all) | 6 | 2 | |
| urticaria | | | |
| subjects affected / exposed | 4 / 152 (2.63%) | 2 / 150 (1.33%) | |
| occurrences (all) | 4 | 2 | |
| photosensivity reaction | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| xeroderma | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---|---|---|
| Renal and urinary disorders | | | |
| enuresis | | | |
| subjects affected / exposed | 3 / 152 (1.97%) | 2 / 150 (1.33%) | |
| occurrences (all) | 3 | 2 | |
| urinary retention | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| dysuria | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| bone pain | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| foot deformity | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 1 / 150 (0.67%) | |
| occurrences (all) | 2 | 1 | |
| back pain | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infections and infestations | | | |
| acute tonsillitis | | | |
| subjects affected / exposed | 7 / 152 (4.61%) | 9 / 150 (6.00%) | |
| occurrences (all) | 7 | 12 | |
| bronchitis | | | |
| subjects affected / exposed | 32 / 152 (21.05%) | 39 / 150 (26.00%) | |
| occurrences (all) | 51 | 55 | |
| bronchopneumonia | | | |
| subjects affected / exposed | 3 / 152 (1.97%) | 6 / 150 (4.00%) | |
| occurrences (all) | 3 | 8 | |
| candida nappy rash | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 4 / 150 (2.67%) | |
| occurrences (all) | 3 | 4 | |
| enterobiasis | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 3 / 150 (2.00%) | |
| occurrences (all) | 0 | 3 | |

| | | | |
|---|---|---|---|
| Epstein-Barr virus infection | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| erythema infectiosum | | | |
| subjects affected / exposed | 4 / 152 (2.63%) | 3 / 150 (2.00%) | |
| occurrences (all) | 4 | 3 | |
| exanthema subitum | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 150 (0.67%) | |
| occurrences (all) | 1 | 1 | |
| gastroenteritis | | | |
| subjects affected / exposed | 31 / 152 (20.39%) | 31 / 150 (20.67%) | |
| occurrences (all) | 36 | 36 | |
| hand-foot-and-mouth disease | | | |
| subjects affected / exposed | 3 / 152 (1.97%) | 5 / 150 (3.33%) | |
| occurrences (all) | 3 | 6 | |
| impetigo | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 2 / 150 (1.33%) | |
| occurrences (all) | 1 | 2 | |
| laryngitis | | | |
| subjects affected / exposed | 3 / 152 (1.97%) | 9 / 150 (6.00%) | |
| occurrences (all) | 4 | 10 | |
| laryngotracheitis obstructive | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| lice infestation | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 2 / 150 (1.33%) | |
| occurrences (all) | 1 | 2 | |
| Molluscum contagiosum | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| mumps | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| nasopharyngitis | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 150 (0.67%) | |
| occurrences (all) | 1 | 1 | |

| | | | |
|---|---|---|---|
| oral candidiasis | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 150 (0.67%) | |
| occurrences (all) | 1 | 1 | |
| paronchya | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| parotitis | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| pharyngitis | | | |
| subjects affected / exposed | 8 / 152 (5.26%) | 9 / 150 (6.00%) | |
| occurrences (all) | 8 | 9 | |
| pharyngitis streptococcal | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 4 / 150 (2.67%) | |
| occurrences (all) | 1 | 4 | |
| pneumonia | | | |
| subjects affected / exposed | 4 / 152 (2.63%) | 1 / 150 (0.67%) | |
| occurrences (all) | 5 | 1 | |
| pyelonephritis | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| rhinitis | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 150 (0.67%) | |
| occurrences (all) | 1 | 1 | |
| scarlet fever | | | |
| subjects affected / exposed | 4 / 152 (2.63%) | 10 / 150 (6.67%) | |
| occurrences (all) | 4 | 11 | |
| sinusitis | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 3 / 150 (2.00%) | |
| occurrences (all) | 1 | 3 | |
| tonsillitis streptococcal | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 2 / 150 (1.33%) | |
| occurrences (all) | 0 | 2 | |
| urinary tract infection | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 3 / 150 (2.00%) | |
| occurrences (all) | 2 | 3 | |

| | | | |
|---|---|---|---|
| varicella | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 2 | |
| viral rash | | | |
| subjects affected / exposed | 3 / 152 (1.97%) | 2 / 150 (1.33%) | |
| occurrences (all) | 3 | 2 | |
| skin candida | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 3 / 150 (2.00%) | |
| occurrences (all) | 1 | 3 | |
| mycoplasma infection | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 1 / 150 (0.67%) | |
| occurrences (all) | 1 | 1 | |
| streptococcal infection | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 3 / 150 (2.00%) | |
| occurrences (all) | 2 | 3 | |
| bronchitis, bacterial | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| oral herpes | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 152 (0.00%) | 1 / 150 (0.67%) | |
| occurrences (all) | 0 | 1 | |
| herpangina | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| hordeolum | | | |
| subjects affected / exposed | 3 / 152 (1.97%) | 0 / 150 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| infection susceptibility increased | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| otitis externa | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---|---|---|
| pertussis | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| vulvitis | | | |
| subjects affected / exposed | 2 / 152 (1.32%) | 0 / 150 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| rhinotracheitis | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| staphylococcus skin infection | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| superinfection bacterial | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 0 / 150 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Metabolism and nutrition disorders | | | |
| iron deficiency | | | |
| subjects affected / exposed | 1 / 152 (0.66%) | 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 |
|---|---|
| 03 June 2013 | - The upper age limit in the inclusion criteria was raised from 35 to 59 months.<br>- The required number of AOMs in the last year was reduced from 4 to 3 (starting from 01.10.2012).<br>- Study duration was decreased from 12 to 6 months. All patients will be included in the period from 01.10. to 31.10.2013. The study will end for all patients after 6 months i.e. between 01 and 30 April 2014.<br>- The list of not allowed concomitant therapies has been reduced and simplified; not allowed are now only herbal and homeopathic remedies with secretolytic, anti-inflammatory and immunostimulatory effects.<br>- Suitable patients are identified and approached in advance through screening of the patient file<br>- The14-day telephone interviews are eliminated. Instead, parents complete an online diary at weekly intervals.<br>- The investigator completes documentation in an electronic CRF, rather than a paper version.<br>- A power of attorney for study consent is created by a parent/custodian. |

Notes:

## 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.

| |
|---|
| Children at inclusion were most likely not as prone to AOM as suspected or AOMs assessed during the 12 months prior to randomization were not diagnosed according to the strict criteria as specified in the study protocol for the study period |

Notes: