



## 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
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##### **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 pertaining 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
<b>Arm title</b>	Otovoven

Arm description:

Participants received Otovoven at first signs of URI until symptoms resolved

Arm type	Experimental
Investigational medicinal product name	Otovoven®
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)

<b>Arm title</b>	Placebo
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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)

<b>Number of subjects in period 1</b>	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			
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			
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 Otovoven 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 ( $\pm$ 0.66)	0.43 ( $\pm$ 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	$\leq$ 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 ( $\pm$ 0.69)	0.52 ( $\pm$ 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 ( $\pm$ 1.77)	1.96 ( $\pm$ 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 ( $\pm$ 0.57)	0.39 ( $\pm$ 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 ( $\pm$ 0.43)	0.12 ( $\pm$ 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 ( $\pm$ 6.58)	4.9 ( $\pm$ 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 ( $\pm$ 0.95)	1.81 ( $\pm$ 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 ( $\pm$ 0.62)	2.36 ( $\pm$ 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
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End point description:

End point type	Secondary
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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 ( $\pm$ 0.82)	0.57 ( $\pm$ 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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19
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### Reporting groups

Reporting group title	Otovowen
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Reporting group description: -

Reporting group title	Placebo
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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 tonsillitis			
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 %

<b>Non-serious adverse events</b>	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 occurrences (all)	1 / 152 (0.66%) 1	3 / 150 (2.00%) 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	
influenza 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	
accidental device ingestion			

subjects affected / exposed occurrences (all)	1 / 152 (0.66%) 1	0 / 150 (0.00%) 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 occurrences (all)	1 / 152 (0.66%) 1	0 / 150 (0.00%) 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 occurrences (all)	1 / 152 (0.66%) 1	0 / 150 (0.00%) 0	
Congenital, familial and genetic disorders			
Kidney duplex subjects affected / exposed occurrences (all)	0 / 152 (0.00%) 0	1 / 150 (0.67%) 1	
phimosis subjects affected / exposed occurrences (all)	1 / 152 (0.66%) 1	0 / 150 (0.00%) 0	
Nervous system disorders			
speech disorder developmental subjects affected / exposed occurrences (all)	0 / 152 (0.00%) 0	1 / 150 (0.67%) 1	
Blood and lymphatic system disorders			
Lymphadenitis subjects affected / exposed occurrences (all)	0 / 152 (0.00%) 0	2 / 150 (1.33%) 2	
leucocytosis subjects affected / exposed occurrences (all)	1 / 152 (0.66%) 1	0 / 150 (0.00%) 0	
Ear and labyrinth disorders			
ear pain subjects affected / exposed occurrences (all)	5 / 152 (3.29%) 5	4 / 150 (2.67%) 5	
Tympanic membrane perforation subjects affected / exposed occurrences (all)	0 / 152 (0.00%) 0	1 / 150 (0.67%) 1	
Tympanic membrane hyperaemia subjects affected / exposed occurrences (all)	0 / 152 (0.00%) 0	1 / 150 (0.67%) 1	
Middle ear effusion subjects affected / exposed occurrences (all)	19 / 152 (12.50%) 21	13 / 150 (8.67%) 14	
cerumen impaction subjects affected / exposed occurrences (all)	1 / 152 (0.66%) 1	0 / 150 (0.00%) 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 discomfort			
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	
photosensitivity 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	<ul style="list-style-type: none"><li>- The upper age limit in the inclusion criteria was raised from 35 to 59 months.</li><li>- The required number of AOMs in the last year was reduced from 4 to 3 (starting from 01.10.2012).</li><li>- 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.</li><li>- 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.</li><li>- Suitable patients are identified and approached in advance through screening of the patient file</li><li>- The 14-day telephone interviews are eliminated. Instead, parents complete an online diary at weekly intervals.</li><li>- The investigator completes documentation in an electronic CRF, rather than a paper version.</li><li>- A power of attorney for study consent is created by a parent/custodian.</li></ul>

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: