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 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 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. - The required number of AOMs in the last year was reduced from 4 to 3 (starting from 01.10.2012). - 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. - 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. - Suitable patients are identified and approached in advance through screening of the patient file - The14-day telephone interviews are eliminated. Instead, parents complete an online diary at weekly intervals. - The investigator completes documentation in an electronic CRF, rather than a paper version. - 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: