Clinical trial results:
Double-Blind, Placebo-Controlled, Randomised Clinical Study of Broncho-Vaxom® in Children Suffering from Recurrent Upper Respiratory Tract Infections

Summary

EudraCT number	2006-002980-17
Trial protocol	HU BE CZ AT IT SK
Global end of trial date	10 October 2008

Results information

Result version number	v2 (current)
This version publication date	09 April 2017
First version publication date	08 December 2016
Version creation reason	• New data added to full data set For this study, we selected by error that the article 46 of Regulation (EC) No 1901/2006 did not apply. Therefore, to amend the error, we have generated an updated version 2 so as to proceed with the submission of the full data-set, according to the regulation.
Summary attachment (see zip file)	BV-2005/01 (BV-2005_01 Vifor Pharma.pdf)

Trial information

Trial identification

Sponsor protocol code	BV-2005/01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	OM Pharma
Sponsor organisation address	22, rue du Bois-du-Lan, Meyrin 2/Geneva, Switzerland, 1217
Public contact	Udo-Michael Göhring , Vifor Pharma, udo-michael.goehring@viforpharma.com
Scientific contact	Udo-Michael Göhring , Vifor Pharma, udo-michael.goehring@viforpharma.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 October 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 October 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to confirm the efficacy and safety of Broncho-Vaxom® compared with placebo in children suffering from recurrent upper respiratory tract infections (URTIs).

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki including amendments in force up to and including the time the study was conducted. The study was conducted in compliance with all International Conference on Harmonisation (ICH) E6 Guidelines for Good Clinical Practice (GCP) and all applicable regulatory requirements.

Prior to initiation of the study, the protocol, the patient information sheet and the Informed Consent Form (ICF) were reviewed and approved by Independent Ethics Committees (IEC) operating in accord with current regulations. If a local IEC did not exist, the Investigator submitted the protocol and accompanying documents to a regional committee. If a regional committee did not exist, the Sponsor (OM Pharma) assisted the Investigator in submitting the protocol to an appropriate committee. Any modifications to the protocol, following initial IEC approval, were submitted to the IEC for review and approval prior to implementation.

Before each patient was admitted to the study, a signed and dated informed consent was obtained from the patient“s parent(s) or his/her legally authorised representative
according to the regulatory and legal requirements of the participating country. This consent form was retained by the Investigator as part of the study records. A copy of the document was provided to the patient. No investigations specifically required for the study were conducted until valid consent was obtained. The content of the informed consent was in accordance with the current revision of the Declaration of Helsinki, current ICH and GCP guidelines, and OM Pharma policy.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 October 2007
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	Austria: 12
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Czech Republic: 51
Country: Number of subjects enrolled	Slovakia: 25

Country: Number of subjects enrolled	Hungary: 147
Country: Number of subjects enrolled	Italy: 78
Country: Number of subjects enrolled	Romania: 75
Worldwide total number of subjects	399
EEA total number of subjects	398

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)	1
Children (2-11 years)	398
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: -

Pre-assignment

Screening details:

Patients were randomly allocated to one of two treatment groups (Broncho-Vaxom® or placebo) according to the random permuted block scheme. For each centre a balanced set of treatments were prepared.

Period 1

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

Blinding implementation details:

The box wallets, labels, and Broncho-Vaxom and placebo capsules did not differ in appearance (concerning form, weight, colour, texture of content, etc.) to ensure patient and investigator blinding. The investigator was provided with a sealed envelope containing the code for each patient“s randomisation number. The code was only to be broken in the event of a serious adverse event (SAE).

Arms

Are arms mutually exclusive?	Yes
Arm title	Broncho-Vaxom®

Arm description:

Broncho-Vaxom® is an immunostimulant drug comprised of the lyophilised extract from 8 strains of bacteria. Broncho-Vaxom® is registered in numerous countries for the prevention of recurrent infections of the airways and acute infectious exacerbations of chronic bronchitis, and as a co-medication in the treatment of acute airway infections.

Arm type	Experimental
Investigational medicinal product name	Broncho-Vaxom
Investigational medicinal product code	
Other name	lyophilised extract
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients received one capsule per day of Broncho-Vaxom® (3.5 mg) for 30 days during the first month of treatment. Following one month without treatment, patients received one capsule per day (Broncho-Vaxom® 3.5 mg) for the first 10 days of Months 3, 4, and 5. Total duration of treatment was 60 days.

The capsules were administered orally, in the morning, on an empty stomach.

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

Patients received one capsule per day of placebo for 30 days during the first month of treatment. Following one month without treatment, patients received one capsule of placebo per day for the first 10 days of Months 3, 4, and 5. Total duration of treatment was 60 days.

The capsules were administered orally, in the morning, on an empty stomach.

Number of subjects in period 1	Broncho-Vaxom®	Placebo
Started	198	201
Completed	192	196
Not completed	6	5
Consent withdrawn by subject	1	3
Adverse event, non-fatal	1	-
Poor compliance	-	1
Unknown	-	1
Lost to follow-up	2	-
Lack of efficacy	1	-
Inclusion/exclusion criteria not fulfilled	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Broncho-Vaxom®

Reporting group description:

Broncho-Vaxom® is an immunostimulant drug comprised of the lyophilised extract from 8 strains of bacteria. Broncho-Vaxom® is registered in numerous countries for the prevention of recurrent infections of the airways and acute infectious exacerbations of chronic bronchitis, and as a co-medication in the treatment of acute airway infections.

Reporting group title	Placebo

Reporting group description: -

Reporting group values	Broncho-Vaxom®	Placebo	Total
Number of subjects	198	201	399
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	1	0	1
Children (2-11 years)	197	201	398
Age continuous Units: years			
arithmetic mean	3.6	3.5	
full range (min-max)	1 to 6	2 to 6	-
Gender categorical Units: Subjects			
Female	87	90	177
Male	111	111	222

End points

End points reporting groups

Reporting group title	Broncho-Vaxom®

Reporting group description:

Broncho-Vaxom® is an immunostimulant drug comprised of the lyophilised extract from 8 strains of bacteria. Broncho-Vaxom® is registered in numerous countries for the prevention of recurrent infections of the airways and acute infectious exacerbations of chronic bronchitis, and as a co-medication in the treatment of acute airway infections.

Reporting group title	Placebo

Reporting group description: -

Primary: Mean rate of URTIs

End point title	Mean rate of URTIs

End point description:

Defined as mean of the total number of URTIs experienced by a patient during the treatment period.

End point type	Primary

End point timeframe:

Visit 1 through Visit 6, or Visit 1 to last visit prior to Visit 6 if they discontinued early.

End point values	Broncho-Vaxom®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195[1]	201[2]		
Units: patients with a URTI	165	170		

Notes:

[1] - Full Analysis Set population

[2] - Full Analysis Set population

Statistical analyses

Statistical analysis title	Analysis of the Rate of URTIs (Visit 1 to Visit 6)
Comparison groups	Broncho-Vaxom® v Placebo
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.916
Method	Negative binomial model
Parameter estimate	Odds ratio (OR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.22

Statistical analysis title	Analysis of the Rate of URTIs (Visit 1 to Visit 2)
Comparison groups	Broncho-Vaxom® v Placebo
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	Negative binomial model
Parameter estimate	Odds ratio (OR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.4

Statistical analysis title	Analysis of the Rate of URTIs (Visit 2 to Visit 3)
Comparison groups	Broncho-Vaxom® v Placebo
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.829
Method	Negative binomial model
Parameter estimate	Odds ratio (OR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.34

Statistical analysis title	Analysis of the Rate of URTIs (Visit 3 to Visit 4)
Comparison groups	Broncho-Vaxom® v Placebo
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.651
Method	Negative binomial model
Parameter estimate	Odds ratio (OR)
Point estimate	0.94

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.24

Statistical analysis title	Analysis of the Rate of URTIs (Visit 4 to Visit 5)
Comparison groups	Broncho-Vaxom® v Placebo
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.529
Method	Negative binomial model
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.22

Statistical analysis title	Analysis of the Rate of URTIs (Visit 5 to Visit 6)
Comparison groups	Broncho-Vaxom® v Placebo
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.773
Method	Negative binomial model
Parameter estimate	Odds ratio (OR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.4

Statistical analysis title	Analysis of the Rate of URTIs (Visit 6 to Visit 7)
Comparison groups	Broncho-Vaxom® v Placebo

Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.553
Method	Negative binomial model
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.23

Secondary: Proportion of patients with recurrent URTIs

End point title	Proportion of patients with recurrent URTIs
End point description:	
Defined as patients with 3 or more URTIs up to the end of the treatment period (Visit 6).	
End point type	Secondary
End point timeframe:	
From first treatment visit (Visit 1) up to the end of the treatment period (Visit 6).	

End point values	Broncho-Vaxom®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	201		
Units: patients with 3 or more URTIs	74	82		

Statistical analyses

Statistical analysis title	Number of Patients with Recurrent URTIs
Comparison groups	Broncho-Vaxom® v Placebo
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.539
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.32

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Patients were monitored until the end of Month 7 (i.e., following a further 2 months without treatment).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups	
Reporting group title	Broncho-Vaxom
Reporting group description:	
Children suffering from recurrent URTIs receiving at least one dose of Broncho-Vaxom®.	
Reporting group title	Placebo
Reporting group description:	
Children suffering from recurrent URTIs receiving at least one dose of placebo.	

Serious adverse events	Broncho-Vaxom	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 197 (2.54%)	4 / 201 (1.99%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 197 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	0 / 197 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic thrombocytopenic purpura			

subjects affected / exposed	0 / 197 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 197 (0.51%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 197 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	1 / 197 (0.51%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 197 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 197 (0.51%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	1 / 197 (0.51%)	2 / 201 (1.00%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Broncho-Vaxom	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	135 / 197 (68.53%)	134 / 201 (66.67%)	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 197 (4.57%)	10 / 201 (4.98%)	
occurrences (all)	10	10	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	19 / 197 (9.64%)	21 / 201 (10.45%)	
occurrences (all)	44	42	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	6 / 197 (3.05%)	9 / 201 (4.48%)	
occurrences (all)	7	12	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	10 / 197 (5.08%)	20 / 201 (9.95%)	
occurrences (all)	13	31	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	24 / 197 (12.18%)	32 / 201 (15.92%)	
occurrences (all)	28	39	
Diarrhoea			

subjects affected / exposed	11 / 197 (5.58%)	13 / 201 (6.47%)	
occurrences (all)	13	17	
Enteritis			
subjects affected / exposed	10 / 197 (5.08%)	7 / 201 (3.48%)	
occurrences (all)	10	9	
Abdominal pain upper			
subjects affected / exposed	6 / 197 (3.05%)	6 / 201 (2.99%)	
occurrences (all)	6	8	
Abdominal pain			
subjects affected / exposed	4 / 197 (2.03%)	5 / 201 (2.49%)	
occurrences (all)	4	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 197 (3.05%)	7 / 201 (3.48%)	
occurrences (all)	12	10	
Epistaxis			
subjects affected / exposed	2 / 197 (1.02%)	5 / 201 (2.49%)	
occurrences (all)	2	7	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	6 / 197 (3.05%)	7 / 201 (3.48%)	
occurrences (all)	9	7	
Dermatitis			
subjects affected / exposed	5 / 197 (2.54%)	1 / 201 (0.50%)	
occurrences (all)	6	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	36 / 197 (18.27%)	35 / 201 (17.41%)	
occurrences (all)	57	51	
Varicella			
subjects affected / exposed	17 / 197 (8.63%)	17 / 201 (8.46%)	
occurrences (all)	17	17	
Ear infection			
subjects affected / exposed	16 / 197 (8.12%)	13 / 201 (6.47%)	
occurrences (all)	22	17	
Gastroenteritis			

subjects affected / exposed	11 / 197 (5.58%)	10 / 201 (4.98%)	
occurrences (all)	12	11	
Pharyngitis			
subjects affected / exposed	10 / 197 (5.08%)	8 / 201 (3.98%)	
occurrences (all)	14	9	
Tracheitis			
subjects affected / exposed	5 / 197 (2.54%)	5 / 201 (2.49%)	
occurrences (all)	7	6	
Otitis media			
subjects affected / exposed	5 / 197 (2.54%)	5 / 201 (2.49%)	
occurrences (all)	5	11	
Conjunctivitis infective			
subjects affected / exposed	3 / 197 (1.52%)	5 / 201 (2.49%)	
occurrences (all)	4	5	
Rhinitis			
subjects affected / exposed	3 / 197 (1.52%)	5 / 201 (2.49%)	
occurrences (all)	3	6	
Otitis media acute			
subjects affected / exposed	2 / 197 (1.02%)	6 / 201 (2.99%)	
occurrences (all)	2	9	
Coxsackie viral infection			
subjects affected / exposed	5 / 197 (2.54%)	1 / 201 (0.50%)	
occurrences (all)	5	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported