Clinical trial results:
Double-blind, placebo-controlled, randomised clinical study of Broncho-Vaxom® drops in children suffering from recurrent Respiratory Tract Infections

Summary

EudraCT number	2009-013378-42
Trial protocol	BE CZ HU IT PT
Global end of trial date	17 October 2011

Results information

Result version number	v2 (current)
This version publication date	03 March 2017
First version publication date	11 December 2016
Version creation reason	• New data added to full data set For this study, we selected by error that article 46 of Regulation (EC) No 1901/2006 did not apply and then only a summary report was submitted. 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)	EBV09/01 (EBV09_01 OM Pharma.pdf)

Trial information

Trial identification

Sponsor protocol code	EBV09/01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	OM Pharma SA
Sponsor organisation address	22 rue du Bois-du-Lan, Geneva, Switzerland, CH-1217 Meyrin 2
Public contact	Alexia Dolliner-Paire, ICTA PM, +33 380534000, bvdrops@icta.fr
Scientific contact	Alexia Dolliner-Paire, ICTA PM, +33 380534000, bvdrops@icta.fr

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	23 October 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 October 2011
Global end of trial reached?	Yes
Global end of trial date	17 October 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To show that Broncho-Vaxom® drops decrease significantly the rate of Respiratory Tract Infections (RTIs) when compared to placebo.

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki (Seoul, October 2008) including amendments in force up to and including the time the study was conducted, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), Committee for Proprietary Medicinal Products Guideline (CPMP/ICH/135/95), European Union Clinical Trial Directive (Directive 2001/20/EC) and applicable regulatory requirements.
A subject could be included into the present study only after his/her parent(s) or legal representative declared in a written form their willingness to take part in the study. In order to be able to take this decision, they were previously informed by the investigator about the content and among others aims and methods of the planned study, as well as on the benefit/risk ratio. The information had to be given both orally and in a written form. For this statement, a Patient Information Sheet (PIS) was available, which was in agreement in its text structure with each reference IEC guidelines, the Declaration of Helsinki, current ICH and GCP guidelines, and the Sponsor policy. The statement gave also indications to the parent(s) or legal representative about the insurance coverage and the resulting regulations for the delimitation of damages, about the fact that the participation in the study was entirely voluntary and would have no effect on clinical care otherwise available, and about the possibility to withdraw the consent to participate at any time without penalty or loss of further medical treatment. The parent(s) or legal representative had to be informed that they had to notify the investigator of any other medical measures during the study period and that their child could not take part simultaneously in another trial.

Background therapy: -

Evidence for comparator:

The randomisation versus placebo was justified as all subjects were allowed to take the standard treatments including antibiotics as concomitant medications during the study.

Actual start date of recruitment	13 September 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czech Republic: 41
Country: Number of subjects enrolled	Hungary: 150
Country: Number of subjects enrolled	Italy: 45

Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Romania: 39
Country: Number of subjects enrolled	Belgium: 6
Worldwide total number of subjects	283
EEA total number of subjects	283

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)	13
Children (2-11 years)	270
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:

Recruitment of subjects in the study covered a period between September 2010 and March 2011.

Pre-assignment

Screening details:

There was no screening period as the subjects were randomised at Visit 1. At this visit and before any study procedure or assessment, the eligible patient's parent(s) or legal representative had to sign the informed consent form. Subjects were then assessed with respect to their eligibility for the study and randomised to treatment.

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 boxes for the treatment had a randomisation number and the investigator was provided with sealed envelopes containing the code for each patient's randomisation number. The envelopes were checked at the end of study to ensure that the seals had not been broken. The code could only be broken under serious adverse events (SAEs) circumstances. The randomisation schedule was not available at the study centre, to the study monitors, project statisticians or the project teams of the Sponsor and CRO

Arms

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

Arm description:

Broncho-Vaxom® drops consist of a clear to slightly opalescent liquid containing 3.5 mg of OM-85 concentrate, among other constituents. This concentrate contains bacterial lysates of strains mainly involved in respiratory infections, in one daily dose, i.e. in 320 µL (10 drops): Haemophilus influenzae, Diplococcus pneumoniae, Klebsiella pneumoniae and ozaenae, Staphylococcus aureus, Streptococcus pyogenes and viridans, and Neisseria catarrhalis.

Arm type	Experimental
Investigational medicinal product name	Broncho-Vaxom®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

The drug had to be taken with a drink (fruit juice, milk, water…) or a yoghurt on an empty stomach, in the morning. The daily dose was 10 drops of solution (320 µL) containing 3.5 mg of bacterial extract, following this schedule during the study:
- The first 1-month period, each morning, so during approximately 30 days.
- The third 1-month period, each morning of the first 10 days, so during approximately 10 days.
- The fourth 1-month period, each morning of the first 10 days, so during approximately 10 days.
- The fifth and last 1-month period, each morning of the first 10 days, so during approximately 10 days.

Arm title	Placebo

Arm description:

Matched placebo liquid was used as comparator drug. It was equivalent in terms of appearance, size, weight, colour, texture, taste and smell, in order to ensure patient and investigator blinding. The constituents of placebo were: propyl 4-hydroxybenzoate, methyl 4-hydroxybenzoate, simeticone emulsion, sodium cyclamate, saccharin sodium, methocel E15, NaOH 1N and purified water.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Same as experimental product.

Number of subjects in period 1	Broncho-Vaxom®	Placebo
Started	145	138
Completed	142	134
Not completed	3	4
Consent withdrawn by subject	1	4
Adverse event, non-fatal	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Broncho-Vaxom®
Reporting group description:	
Broncho-Vaxom® drops consist of a clear to slightly opalescent liquid containing 3.5 mg of OM-85 concentrate, among other constituents. This concentrate contains bacterial lysates of strains mainly involved in respiratory infections, in one daily dose, i.e. in 320 µL (10 drops): Haemophilus influenzae, Diplococcus pneumoniae, Klebsiella pneumoniae and ozaenae, Staphylococcus aureus, Streptococcus pyogenes and viridans, and Neisseria catarrhalis.	
Reporting group title	Placebo
Reporting group description:	
Matched placebo liquid was used as comparator drug. It was equivalent in terms of appearance, size, weight, colour, texture, taste and smell, in order to ensure patient and investigator blinding. The constituents of placebo were: propyl 4-hydroxybenzoate, methyl 4-hydroxybenzoate, simeticone emulsion, sodium cyclamate, saccharin sodium, methocel E15, NaOH 1N and purified water.	

Reporting group values	Broncho-Vaxom®	Placebo	Total
Number of subjects	145	138	283
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)	5	8	13
Children (2-11 years)	140	130	270
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
Age continuous Units: years			
arithmetic mean	3.6	3.7	
standard deviation	± 1.36	± 1.58	-
Gender categorical Units: Subjects			
Female	71	65	136
Male	74	73	147

End points

End points reporting groups

Reporting group title	Broncho-Vaxom®

Reporting group description:

Broncho-Vaxom® drops consist of a clear to slightly opalescent liquid containing 3.5 mg of OM-85 concentrate, among other constituents. This concentrate contains bacterial lysates of strains mainly involved in respiratory infections, in one daily dose, i.e. in 320 µL (10 drops): Haemophilus influenzae, Diplococcus pneumoniae, Klebsiella pneumoniae and ozaenae, Staphylococcus aureus, Streptococcus pyogenes and viridans, and Neisseria catarrhalis.

Reporting group title	Placebo

Reporting group description:

Matched placebo liquid was used as comparator drug. It was equivalent in terms of appearance, size, weight, colour, texture, taste and smell, in order to ensure patient and investigator blinding. The constituents of placebo were: propyl 4-hydroxybenzoate, methyl 4-hydroxybenzoate, simeticone emulsion, sodium cyclamate, saccharin sodium, methocel E15, NaOH 1N and purified water.

Primary: Mean rate of RTIs up to the end of the treatment period (Visit 6)/Premature withdrawal

End point title	Mean rate of RTIs up to the end of the treatment period (Visit 6)/Premature withdrawal

End point description:

The total number of RTIs per subject was identified using the RTI form and was medically reviewed before database freeze, to ensure completeness of the RTIs. Coding was performed using MedDRA version 15.0. Respiratory infections which were complication of an initial infection were not counted as "new infection". In order to be counted as a "new infection", a symptom-free interval of ≥7 days between two infectious episodes had to be present.

The Full Analysis Set (FAS; N=278) population was considered for the endpoints, consisting of those subjects who were randomised to treatment, received at least one dose of randomised treatment, and attended at least
one post-baseline visit. The FAS was created in accordance with the Intent-To-Treat principles.

End point type	Primary

End point timeframe:

From the randomisation visit (Month 0 - Visit 1) to the end of the treatment period (Month 5 - Visit 6).

End point values	Broncho-Vaxom®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	135		
Units: number of RTIs				
arithmetic mean (standard deviation)	7.66 (± 3.38)	7.47 (± 3.48)		

Statistical analyses

Statistical analysis title	Comparison - negative binomial model - Univariate

Statistical analysis description:

Non-parametric analysis, using a negative binomial model (SAS® procedure: proc GENMOD, link function=LOG and dist=BIN). The response variable was RTI occurrence, treatment group and countries

were included as main effects in the model, and the log of time the subject was followed was used as an offset variable to take into account early dropouts and to adjust the regression estimates. A univariate analysis did not show a trend in favour of Broncho-Vaxom®vs placebo.

Comparison groups	Broncho-Vaxom® v Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.5708
Method	Negative binomial regression
Parameter estimate	Odds ratio (OR)
Point estimate	1.0308
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.928
upper limit	1.145
Variability estimate	Standard deviation
Dispersion value	1.39

Notes:

[1] - Univariate model includes treatment as the main effects, and time that the subject was followed is included as an offset variable taking into account early dropouts.

Statistical analysis title	Comparison -negative binomial model - Multivariate

Statistical analysis description:

Non-parametric analysis, using a negative binomial model (SAS® procedure: proc GENMOD, link function=LOG and dist=BIN). The response variable was RTI occurrence, treatment group and countries were included as main effects in the model, and the log of time the subject was followed was used as an offset variable to take into account early dropouts and to adjust the regression estimates. A multivariate analysis did not show a trend in favour of Broncho-Vaxom®vs placebo.

Comparison groups	Broncho-Vaxom® v Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.4431
Method	Negative binomial regression
Parameter estimate	Odds ratio (OR)
Point estimate	1.039
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.947
upper limit	1.14
Variability estimate	Standard deviation
Dispersion value	1.39

Notes:

[2] - Multivariate model includes treatment and country as the main effects, and time that the subject was followed is included as an offset variable taking into account early dropouts.

Secondary: Proportion of subjects with recurrent RTIs up to the end of the treatment period (Visit 6/premature discontinuation)

End point title	Proportion of subjects with recurrent RTIs up to the end of the treatment period (Visit 6/premature discontinuation)

End point description:

Subjects with recurrent RTIs were defined as subjects presenting 3 or more RTIs up to the end of treatment period/premature withdrawal (Visit 6).

End point type	Secondary

End point timeframe:

From Visit 1 to the end of treatment period (Month 5 - Visit 6).

End point values	Broncho-Vaxom®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	135		
Units: subjects	100	84		

Statistical analyses

Statistical analysis title	Comparison - Cochran-Mantel-Haenszel

Statistical analysis description:

Cochran-Mantel-Haenszel test, stratified by centres.

Comparison groups	Broncho-Vaxom® v Placebo
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.071
Method	Cochran-Mantel-Haenszel

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) were collected from the time of signature of informed consent until Visit 7, i.e. 60 days after the last dose of study medication, which was considered as the safety follow-up period, so included in the whole study duration.

Adverse event reporting additional description:

Intermediary Phone Calls (IPCs) were performed between each visit in order to assess the possible occurrence of RTIs. Unscheduled visits could be performed, among others because of occurrence of RTIs detected during IPCs, any worsening condition or other medical event.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Broncho-Vaxom®
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Broncho-Vaxom®	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 145 (0.00%)	3 / 138 (2.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Hydrocele operation			
subjects affected / exposed	0 / 145 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 145 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 145 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 145 (0.00%)	2 / 138 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 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	130 / 145 (89.66%)	117 / 138 (84.78%)	
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 145 (15.86%)	13 / 138 (9.42%)	
occurrences (all)	24	15	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	46 / 145 (31.72%)	37 / 138 (26.81%)	
occurrences (all)	62	57	
Fatigue			
subjects affected / exposed	35 / 145 (24.14%)	30 / 138 (21.74%)	
occurrences (all)	45	38	
Blood and lymphatic system disorders			

Lymphadenitis			
subjects affected / exposed	33 / 145 (22.76%)	26 / 138 (18.84%)	
occurrences (all)	47	41	
Ear and labyrinth disorders			
Ear disorder			
subjects affected / exposed	23 / 145 (15.86%)	28 / 138 (20.29%)	
occurrences (all)	36	41	
Ear pain			
subjects affected / exposed	19 / 145 (13.10%)	24 / 138 (17.39%)	
occurrences (all)	27	33	
Otorrhoea			
subjects affected / exposed	7 / 145 (4.83%)	2 / 138 (1.45%)	
occurrences (all)	9	2	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	28 / 145 (19.31%)	22 / 138 (15.94%)	
occurrences (all)	33	28	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	17 / 145 (11.72%)	18 / 138 (13.04%)	
occurrences (all)	19	22	
Vomiting			
subjects affected / exposed	17 / 145 (11.72%)	14 / 138 (10.14%)	
occurrences (all)	19	21	
Abdominal pain			
subjects affected / exposed	11 / 145 (7.59%)	9 / 138 (6.52%)	
occurrences (all)	12	12	
Respiratory, thoracic and mediastinal disorders			
Rhinitis			
subjects affected / exposed	68 / 145 (46.90%)	52 / 138 (37.68%)	
occurrences (all)	131	114	
Cough			
subjects affected / exposed	29 / 145 (20.00%)	30 / 138 (21.74%)	
occurrences (all)	44	42	
Tonsillar disorder			

subjects affected / exposed	32 / 145 (22.07%)	24 / 138 (17.39%)	
occurrences (all)	41	36	
Oropharyngeal pain			
subjects affected / exposed	14 / 145 (9.66%)	18 / 138 (13.04%)	
occurrences (all)	16	22	
Wheezing			
subjects affected / exposed	9 / 145 (6.21%)	12 / 138 (8.70%)	
occurrences (all)	10	15	
Dyspnoea			
subjects affected / exposed	10 / 145 (6.90%)	8 / 138 (5.80%)	
occurrences (all)	15	10	
Pharyngeal erythema			
subjects affected / exposed	5 / 145 (3.45%)	8 / 138 (5.80%)	
occurrences (all)	7	12	
Dysphonia			
subjects affected / exposed	7 / 145 (4.83%)	4 / 138 (2.90%)	
occurrences (all)	7	4	
Increased upper airway secretion			
subjects affected / exposed	2 / 145 (1.38%)	6 / 138 (4.35%)	
occurrences (all)	2	6	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	9 / 145 (6.21%)	3 / 138 (2.17%)	
occurrences (all)	14	4	
Urticaria			
subjects affected / exposed	6 / 145 (4.14%)	3 / 138 (2.17%)	
occurrences (all)	7	5	
Dermatitis			
subjects affected / exposed	3 / 145 (2.07%)	5 / 138 (3.62%)	
occurrences (all)	3	5	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	6 / 145 (4.14%)	6 / 138 (4.35%)	
occurrences (all)	6	8	
Infections and infestations			

Varicella subjects affected / exposed occurrences (all)	15 / 145 (10.34%) 15	13 / 138 (9.42%) 14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2011	Because of global quality issues with the previous Contract Research Organisation during the monitoring and the data management processes, the study was delegated to ICTA PM from November 2011, for all activities except pharmacovigilance, always handled by the Sponsor. This was subject to the unique substantial amendment of the study, i.e. the Amendment #1, dated 28 November 2011, where it is mentioned "Following an internal review, the Sponsor has decided to change the CRO and the biostatistician to ensure a high level of quality in compliance with the GCP standards". This amendment also cancelled the collection of the ethnic origin of the patients as no real medical reason demands it. Moreover, the collection of this data is touchy in France where ICTA PM is located, as submitted to specific data privacy procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported