SYNOPSIS

EBV09/01

Name of Company:	OM Pharma S. A.
Name of Finished Product:	Broncho-Vaxom® drops
Name of Active Ingredient(s):	Bacterial lysates of *Haemophilus influenzae, Diplococcus pneumoniae, Klebsiella pneumoniae* and *ozaenae, Staphylococcus aureus, Streptococcus pyogenes* and *viridans, Neisseria catarrhalis*.

Title:	Double-blind, placebo-controlled, randomised clinical study of Broncho-Vaxom® drops in children suffering from recurrent Respiratory Tract Infections
Short Title:	Not Applicable
Indication:	Recurrent Respiratory Tract Infections
Phase:	III
Study Code:	EBV09/01
Co-ordinating Investigator:	Prof. Nicola Principi Università di Milano - 20122 Milano - Italy
Study Centres:	29 European sites of which 28 were active, located in 6 countries: • Hungary: 10 sites, • Czech Republic: 6 sites, • Italy: 4 sites, • Romania: 4 sites, • Belgium: 4 sites (1 inactive site), • Portugal: 1 site.
Objectives:	Primary Objective: • To show that Broncho-Vaxom® drops decrease significantly the rate of Respiratory Tract Infections (RTIs) when compared to placebo. Secondary Objectives: To assess the: • Proportion of patients with recurrent RTIs (*i.e.* presenting 3 or more RTIs) up to the end of treatment period, • Proportion of patients with at least one additional RTI up to the end of the study period (during the follow up period), • Proportion of patients suffering from Gastro-Intestinal Infections (GIIs) during the treatment period,

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	• Rate of GIIs up to the end of the treatment period, • Severity of RTI symptoms, using a symptom score sheet, • Duration of RTIs, • Type and duration of concomitant treatments using a medication score: systemic antibiotics, systemic corticoids, antipyretics, mucolytics, cough suppressants, ß2-sympathomimetics, antihistaminics and gargle fluids, • Proportion of patients suffering from infection due to Respiratory Syncytial Virus (RSV), influenza and ß-haemolytic streptococcus detected with quick detection kits from throat and nasal swabs, • Occurrence of Adverse Events (AEs) and Serious Adverse Events (SAEs).
Design:	Multicentre, randomised, double-blind, parallel, placebo-controlled study
Treatment:	Broncho-Vaxom® arm (145 subjects): 10 drops of solution (320 µL) containing 3.5 mg of bacterial extract. Placebo arm (138 subjects): 10 drops of matched solution (320 µL). Treatment period: 10 drops/day for 30 days, then 1 month without treatment, followed by 10 drops/day for 10 days per month during 3 months. Follow-up period without treatment: 2 months Mode of administration: oral route, to be taken in the morning on an empty stomach.
Inclusion Criteria:	• Out-patient of either gender. • Patient aged between 12 months and 6 years (included in his/her 7th year). • Patient known to his/her physician as suffering from recurrent RTIs (documented RTIs, minimum 4 episodes during the year preceeding the study period). • Patient suffering from an RTI at the enrolment visit, according to one of the definitions given below (except rhinosinusitis which did not respect the inclusion criterion #5). • The beginning of this infection should not exceed 7 days prior to inclusion and had to occur after a steady period (without infection) of at least one week. • Patient whose parent(s) or legal representative had given their written informed consent.

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Exclusion Criteria:	• Patient with tonsillectomy and/or adenoidectomy if performed after the first RTI during the year preceding the study period.
	• Patient with allergic asthma.
	• Patient with mucoviscidosis.
	• Patient with known significant systemic disease, *i.e.* hepatic and/or renal disease.
	• Patient with malignant disease.
	• Patient with auto-immune disease and other systemic diseases related to immune system disorders.
	• Patient with diseases of the gastro-intestinal tract which would have impaired absorption of the study medication.
	• Patient with a known allergy or previous intolerance to the study medication.
	• Patient treated with the following medications:
	  • Oral vaccination with live vaccine within 4 weeks before study start,
	  • Previous and/or concomitant immunosuppressive or immunostimulating therapy within 3 months before study start,
	  • Concomitant treatment with systemic corticosteroids for more than 10 consecutive days,
	  • Concomitant treatment with any other investigational drug within 1 month before study start.
	• Patient whose parent(s) or legal representative were unable to comply with the rules of this clinical study, especially if they did not accept IPCs.
	• Participation in another clinical trial within 1 month prior to study start.
	• Patient with history of non-compliance with study medications.

Primary and Secondary Endpoints:	<u>Primary Endpoint</u>: • Mean rate of RTIs up to the end of the treatment period. <u>Secondary Endpoints</u>: • Proportion of patients with recurrent RTIs (*i.e.* presenting 3 or more RTIs) up to the end of treatment period (Visit 6), • Proportion of patients with at least one additional RTI up to the end of the study period (during the follow up period) (Visit 7),

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	• Proportion of patients suffering from GIIs (at least 3 out of the 4 following symptoms: diarrhoea, vomiting, fever and abdominal pain) during the treatment period, • Rate of GIIs up to the end of the treatment period (Visit 6), • Severity of RTI symptoms using a symptom score sheet, • Duration of RTIs, • Type and duration of concomitant treatments using a medication score, • Proportion of patients suffering from viral infection due to RSV, influenza A and B, or from bacterial infection due to ß-haemolytic streptococcus A detected with quick detection kits from throat and nasal swabs.

Procedures:	Seven-month study divided in 2 periods:
	• A five-month period between Visit 1 and Visit 6, subdivided in:
	  • A daily treatment period during Month 1, between Visit 1 and Visit 2,
	  • A period without treatment during Month 2, between Visit 2 and Visit 3,
	  • A daily treatment period during the first 10 days of Month 3, between Visit 3 and Visit 4,
	  • A daily treatment period during the first 10 days of Month 4, between Visit 4 and Visit 5,
	  • A daily treatment period during the first 10 days of Month 5, between Visit 5 and Visit 6,
	• A two-month follow-up period without treatment during Month 6 and Month 7, between Visit 6 and Visit 7.
	Intermediary Phone Calls (IPCs) were performed between each visit in order the site 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.

Sample Size:	278 subjects planned (125 patients per treatment arm, plus 10% drop rate), number based on a standardised difference between the treatment arms equal to 0.412. 283 subjects randomised of which 278 were included in the Full Analysis Set (FAS) and 256 in the Per Protocol Set (PPS).

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Statistical Methods:	The following five a priori ordered null hypotheses were tested, ***i.e.*** H_{01} for primary endpoint and H_{02}, H_{03}, H_{04} and H_{05} for secondary endpoints: • H_{01}: The mean rates of RTIs up to the end of the treatment period (Visit 6) are equal in the Broncho-Vaxom® and placebo group. • H_{02}: The proportion of patients with recurrent RTIs (***i.e.*** presenting 3 or more RTIs) up to the end of the treatment period (Visit 6) is equal in the Broncho-Vaxom® and placebo group. • H_{03}: The mean severity of the RTI (up to Visit 6) symptoms is equal in the Broncho-Vaxom® and placebo group. • H_{04}: The mean duration of the RTIs (up to Visit 6) is equal in the Broncho-Vaxom® and placebo group. • H_{05}: The proportion of patients with at least one additional RTI up to the end of the study period (Visit 7) is equal in the Broncho-Vaxom® and placebo group. A multiple test procedure with a priori ordered hypotheses was carried out. The procedure was stopped if at one step the corresponding null hypothesis could not be rejected. Descriptive analyses as well as negative binomial regression to take into account earlier withdrawal were performed for the primary endpoint statistical analysis. Descriptive analyses, Analysis Of Covariance, Cochran-Mantel-Haenszel test and Kaplan-Meier analysis were performed for the secondary endpoints statistical analysis.
Conclusion:	From September 13th, 2010, to March 23rd, 2011, a total of 283 subjects were screened and randomised (145 subjects in the Broncho-Vaxom® drops and 138 in the matched placebo treatment). A total of 276 subjects (97.5%) completed the study as per protocol, 7 subjects (3 in the Broncho-Vaxom® group and 4 in the placebo group) dropped out during the course of the study, mainly due to withdrawal of consent. All randomised subjects received at least one dose of study medication. Five subjects did not perform post-baseline evaluation and were excluded from the FAS and 22 additional subjects were excluded from the per protocol analysis, due to major protocol violations. <u>Populations of analysis:</u> • Safety Set (SS) = 283 subjects (145 subjects in the Broncho-Vaxom® drops and 138 in placebo group). • FAS = 278 subjects (143 in the Broncho-Vaxom® group and 135 in the placebo group). • PPS = 256 subjects (135 in the Broncho-Vaxom® group and 121 in the placebo group).

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	Baseline demographics and other relevant baseline characteristics: Baseline demographics were well balanced between the two treatment groups for gender and age with a majority of male subjects in both treatments arms. The mean age of the study population was 3.6 ± 1.5 years old (ranging from 1 to 7). At study entry, a total of 203 (73.0%) subjects (108 subjects in Broncho-Vaxom® group vs. 95 subjects in placebo group) presented one RTI, and only 27.0% had more than one concurrent RTI, with rhinopharyngitis being the most commonly reported type of RTI (in 86.3% of all subjects, *i.e.* 88.8% of the subjects in Broncho-Vaxom® group vs. 83.7% of the subjects in the placebo group), followed by tonsillopharyngitis in 15.8% of subjects, otitis media in 9.4% of subjects, laryngitis in 9.0% of subjects, bronchitis/bronchiolitis in 8.6% of subjects, and bronchopneumonia / pneumonia in 3.2% of subjects. In the previous subject‟s medical history, infections and infestations were the most relevant and frequently reported conditions (31.1% of subjects), with 88.7% of the subjects having received prior antibacterial treatments for systemic use (91.0% in the Broncho-Vaxom® group vs. 86.2% in the placebo group). Compliance and treatment exposure: Overall, compliance to treatment was good for 98.9% of the subjects and comparable in both treatment groups (98.6% in the Broncho-Vaxom® group and 99.3% in the placebo group). The mean total dose taken was 21.9 ± 3.1 g. Duration of study treatment was 148.7 ± 19.1 days (mean ± SD), close to the theoretical time of 150 days, (ranging from 3 to 159 days), with no difference between the two treatment groups (149.5 ± 15.8 days in the Broncho-Vaxom® group compared with 147.9 ± 22.2 days in the placebo group). Efficacy results: Primary efficacy endpoint (mean rate of RTIs up to the end of study treatment (Visit 6/premature withdrawal)). No difference between the two treatment groups was observed. The mean total number of RTIs at the end of study treatment was 3.17 ± 1.4, in the Broncho-Vaxom® group vs. 3.07 ± 1.4 in the placebo group. When adjusted to the accurate length of treatment, as calculated by the rate of RTIs per year, similar findings were observed (with total number of RTIs per year of 7.7 ± 3.4 in the Broncho-Vaxom® group vs. 7.5 ± 3.5 in the placebo group). In the multivariate analysis including the treatment arm and the countries as covariates, a trend for a lower rate of RTIs was observed for the placebo group, although the difference was not statistically significant (p-value=0.44).

Regarding the country covariate, the mean total number of RTIs was statistically lower in Czech Republic (2.9 ± 1.0, OR=0.8) and in Romania (1.5 ± 0.8, OR=0.4), as compared to Hungary, with a mean number of RTIs of 3.5 ± 1.3, similar in the other countries (Belgium, Italy and Portugal).

No difference on the primary efficacy endpoint was observed between the two treatment groups in the sensitivity analysis on the PPS.

Secondary efficacy endpoints (as exploratory results) have shown :

- a slightly lower proportion of subjects with 3 or more RTIs in the placebo group than in the Broncho-Vaxom® group at the end of the treatment period (62.2% vs. 69.9%, respectively, p=0.071).
- a similar score in the severity of the RTI symptoms between the two treatment groups at the end of the treatment period in the adjusted model (0.86 for the Broncho-Vaxom® group vs. 0.94 for the placebo group, respectively, p=0.69).
- a similar duration of the RTI (29.1 ± 18.7 days in the Broncho-Vaxom® group compared with 29.8 ± 17.7 days in the placebo group, p=0.56) at the end of the treatment period.
- a slightly higher proportion of subjects who suffered from one additional RTI during the study period in the Broncho-Vaxom® group compared to the placebo group (90.2% vs. 88.1%, respectively, p=0.25). However the median time to the additional RTI was identical between the two treatment groups (42 days; 95% CI, 33-51 days in the Broncho-Vaxom® group vs. 44 days; 95% CI, 35-53 days in the placebo group).
- a lower proportion of patients who experienced at least one GII during the treatment period in the Broncho-Vaxom® group compared to placebo group (16.8% vs. 23.7%, respectively). This same trend for a lower rate of GIIs was observed over the follow up period in favour of Broncho-Vaxom® (23.1% vs. 28.1% for the placebo group).
- a lower proportion of patients who received antibacterial treatment (i.e., the combination of penicillins, incl. beta-lactamase inhibitors or macrolides in the Broncho-Vaxom® group, as compared to the placebo group: 41.3% vs. 49.6% and 18.2% vs. 27.4%, respectively).

Safety results:

Overall, the safety profile of Broncho-Vaxom® drops was good. The incidence of related AEs was low; a total of 16 subjects (11.0%, 22 events) in the Broncho-Vaxom® group experienced at least one AE that was considered by the investigator related to treatment, compared with 15 subjects (10.9%, 21 events) in the placebo group. Most commonly reported related AEs consisted in infections and infestations (7 subjects, 4.8% in the Broncho-Vaxom® group and 6 subjects; 4.3% in the placebo group).

Related gastrointestinal disorders concerned only 2 subjects (1.4%) in the Broncho-Vaxom® group vs. 1 subject (0.7%) in the placebo group. One subject in the Broncho-Vaxom® group had two AEs that led to treatment discontinuation, the two events were not related to study drug and 2 subjects (one in the Broncho-Vaxom® group and the other in the placebo group) experienced AEs leading to dose reduction.

Neither death nor related SAEs were reported during the study.

Conclusions:

In this study evaluating the potential benefit of a new formulation of Broncho-Vaxom® (drops) in young children (≤6 years old) suffering from recurrent RTIs, no statistical difference was found between Broncho-Vaxom® and the matched placebo treatment in the primary objective of the study (reduction of RTI rate over the 5 months of the study treatment period).

These results are in contrast to the positive results observed in the previous 5 trials in children with more severe and more frequent RTIs. The absence of efficacy in this specific study might be explained by the selected study population, which was likely to be too mild as it consisted of otherwise healthy young children with recurrent mild rhinopharyngitis (common cold) or runny nose. Furthermore, with the recruitment completing by the end of March, when the incidence of RTIs decreases, a seasonal effect cannot be ruled out.

Broncho-Vaxom® drops demonstrated a good tolerability and safety profile as evidenced by a low incidence of treatment related AEs, in particular, gastrointestinal disorders in this population of young children.