SYNOPSIS

Protocol Number: BV-2005/01

Name of Company:	OM Pharma
Name of Finished Product:	Broncho-Vaxom® (Broncho-Munal®)
Name of Active Ingredient:	OM-85

Title:	Double-Blind, Placebo-Controlled, Randomised Clinical Study of Broncho-Vaxom® in Children Suffering from Recurrent Upper Respiratory Tract Infections
Short Title:	Efficacy and Safety Study of Broncho-Vaxom® in Children Suffering From Recurrent Respiratory Tract Infections
Indication:	Recurrent respiratory tract infections
Phase:	4
Study Code:	BV-2005/01
Study Co-ordinator:	Prof. Nicola Principi Università di Milano Clinica Pediatrica 1a Via della Commenda, 9 I-20122 Milano Italy
Study Director:	Prof. Urs B Schaad University Children‟s Hospital (UKBB) Römergasse 8 CH-4005 Basel Switzerland
Study Centres:	There were 399 patients recruited in 57 active centres in 8 countries (Hungary, Italy, Romania, Czech Republic, Slovakia, Austria, and Switzerland).
Objectives:	Primary Objective: • To confirm the efficacy and safety of Broncho-Vaxom® compared with placebo in children suffering from recurrent upper respiratory tract infections (URTIs)
Design:	Randomised, placebo-controlled, double-blind, parallel group, multicentre study
Treatment:	Broncho-Vaxom® capsules containing 3.5 mg of lyophilised extract per capsule (Batch number 19052) and matching placebo capsules (Batch number 20679) were provided by the Sponsor (OM Pharma). The capsules were administered orally, in the morning, on an empty stomach. The capsules could be opened and the content poured into a drink (e.g., water, fruit juice, or milk). Patients received one capsule per day of Broncho-Vaxom® (3.5 mg) or placebo 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 or placebo) for the first 10 days of Months 3, 4, and 5. Total duration

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	of treatment was 60 days. Patients were monitored until the end of Month 7 (i.e., following a further 2 months without treatment).
Inclusion Criteria:	1. Outpatients of either sex 2. Aged between 2 and 6 years old (or in their 7th year) 3. Known to his/her physician as suffering from recurrent URTIs (documented URTIs, minimum of 4 episodes during the year preceding the study period) 4. Suffering from an URTI at the enrolment visit; the beginning of this infection was not to exceed 7 days prior to inclusion and had to occur after a steady period (without infection) of at least one week 5. Written informed consent provided by the patient"s parent(s) or legal representative
Exclusion Criteria:	1. Suffering from pneumonia or bronchiolitis at the enrolment visit 2. Tonsillectomy and/or adenoidectomy if performed after the first URTI during the year preceding the study period 3. Allergic asthma 4. Mucoviscidosis 5. Significant systemic disease, i.e., hepatic and/or renal disease 6. Malignant disease 7. Auto-immune disease and other systemic diseases related to immune system disorders 8. Diseases of the gastrointestinal tract which would impair absorption of the study medication 9. A known allergy or previous intolerance to the study medication 10. Patients treated with the following medications: • Antibiotics within one week before study start • 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 corticosteroids • Concomitant treatment with any other investigational drug within one month before study start 11. Patients whose parent(s) or legal representatives were unable to comply with the rules of this clinical study, especially if they did not accept intermediary phone calls (IPCs) 12. Participation in another clinical study within 3 months prior to study start

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Primary and Secondary Endpoints:	Primary Endpoint: Mean rate of URTIs recorded in the treatment period, defined as the number of URTIs experienced by a patient during the treatment period (Visit 1 through Visit 6, or Visit 1 to last visit prior to Visit 6 if they discontinued early) Secondary Endpoints: • Proportion of patients with recurrent URTIs, defined as patients with 3 or more URTIs up to the end of the treatment period (Visit 6) • Proportion of patients with at least one additional URTI during follow-up • Severity of URTI • Duration of URTI • Type and duration of prescribed concomitant mediation e.g., antibiotics and expectorants • Immunoglobulin G 2 (IgG_2) level at baseline (Visit 1) and at the end of the treatment period (Visit 6) • Kiddy-KINDL® quality of life (QoL) questionnaire (patients aged 4 to 7 years old) • Safety: physical examination, vital signs, laboratory values, and occurrence of adverse events (AEs) and serious adverse events (SAEs)
Procedures:	Patients attended an inclusion visit (Visit 1) with their parent(s) or legal representative, during which the patient‟s eligibility for the study was assessed. This included assessment of previous and current URTIs, and, for eligible patients, completion of a QoL questionnaire (patients aged 4 to 7 years old only) and collection of a blood sample for immunoglobulin G (IgG) 2 levels. Eligible patients were randomised to either Broncho-Vaxom® or placebo and given sufficient study medication for 30 days to be taken during Month 1. Patients returned to the study centre at the end of Months 1, 2, 3, 4, 5, and 7 (Visits 2, 3, 4, 5, 6, and 7, respectively) for the following: • Recording of any concomitant medications • A physical examination and recording of vital signs • Recording of number of URTIs since last scheduled visit • Recording of the presence of signs and symptoms of URTI including assessment of the severity of symptoms • Compliance (except Visit 3) • Control of IPC report(s) • Reporting of any AEs In addition, patients aged 4 to 7 years old completed a Kiddy-KINDL QoL questionnaire at Visits 2, 6, and 7. A blood sample was collected at Visit 6

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	only for assessment of IgG_2 levels. During the treatment period, one IPC was planned between 2 visits (approximately 15 days after the visit). During the follow-up period, one IPC was planned (one month after Visit 6). Patients could return for unscheduled visits if required due to a new URTI, any worsening condition, or other medical event potentially related to the study medications. If a URTI was present at the final visit (Visit 7), the patient"s progress was followed until the disappearance of the symptoms. Otherwise the patient was discharged from the study.
Sample Size:	420 patients planned (210 patients per treatment group) 399 patients randomised and 398 treated (197 patients received Broncho-Vaxom® and 201 patients received placebo)
Statistical Methods:	For the primary efficacy variable the number and percentage of patients with one or more URTIs and the number and percentage of patients reporting 1, 2, 3, 4, or more than 5 URTIs between Visits 1 and 6 were summarised for the full analysis set (FAS) and per protocol set (PPS) by treatment group. The number of URTIs per patient was analysed using a negative binominal model including treatment and centre as main effects, and log of time in the treatment period as the offset variable to account for early dropouts. Estimates of the odds ratio with 95% confidence intervals were presented. This analysis was repeated for the PPS as sensitivity analyses. These summaries and the primary analysis were also performed for each study period (i.e., between Visits 1 and 2, between Visit 2 and 3, etc.). The primary analysis based on the FAS was repeated including, in the following order, concomitant antibiotic use, sex, and age as covariates. <u>Secondary efficacy variables:</u> The proportion of patients with recurrent URTIs and those with at least one additional URTI during follow-up were summarised. The severity and duration of each URTI were also summarised. In addition, the number and percentage of patients who used concomitant medication, the duration of use of concomitant medication, and the standardised total score from the Kiddy-KINDL QoL questionnaire were summarised. A binary logistic regression model was used to analyse the proportion of patients with recurrent URTIs (FAS and PPS), the proportion of patients with at least one additional URTI during follow-up (FAS and PPS), and type and duration of prescribed concomitant medication (FAS only). The time to the third URTI and time to the first additional URTI were analysed using a Logrank test, stratified by centre (FAS and PPS). An analysis of covariance model which included treatment group (the effect of interest) was used to compare the mean change in IgG_2 levels from Baseline (Visit 1) at Visit 6. A mixed model repeated measures model, using the 0.05 significance level,

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	was used to analyse change from baseline in standardised total score (Kiddy-KINDL QoL questionnaire) at Visit 2, 6, and 7. Safety variables: Treatment-emergent AEs were summarized using Medical Dictionary for Regulatory Activities Version 14.0. The raw scores and change from baseline in heart rate and body temperature were summarised by visit and treatment group. Abnormalities reported during the physical examination were summarised. The number and percentage of patients who reported each coded medication were summarised by treatment group for prior and concomitant medications separately. Use of specific concomitant medications of interest (antibiotics and expectorants) were analysed separately as secondary efficacy variables.
Conclusion:	The rationale for performing the present study was to support the efficacy and safety of Broncho-Vaxom® in children suffering from recurrent URTIs. The treatment schedule for this was used in previous studies and was in accordance with the indication and regulatory approvals in European countries at the time of study conduct. A total of 399 patients were randomised and 398 were treated (197 patients received Broncho-Vaxom® and 201 patients received placebo). Demographic and baseline characteristics were very similar between the treatment groups. The primary endpoint was the mean rate of URTIs (mean of the total number of URTIs per patient) up to the end of the treatment period in the Broncho-Vaxom® group compared with the placebo group. There was no statistically significant difference in the rate of acute URTIs following treatment with Broncho-Vaxom® compared with placebo (p=0.916 for Visit 1 to Visit 6), or between any two visits during the study. Of the patients who experienced a URTI during the study, 92 (23.2%) experienced one, 87 (22.0%) experienced two, and 91 (23.0%) experienced three. There was only a minority of patients who experienced more than 3 URTIs. Similar results were observed for the secondary efficacy endpoints assessed. Broncho-Vaxom® was generally well tolerated and tolerance was similar to that observed for placebo. It is important to note that quality control at OM/Vifor Pharma identified several data quality issues during the analysis phase of the study. Numerous inconsistencies were found between case report forms and datasets. In addition, a large amount of missing data was identified. These quality issues were assessed to be mainly due to insufficient monitoring of the trial and poor data management by the Contract Research Organisation (CRO) tasked with study conduct and data management. A number of activities were initiated by OM/Vifor Pharma in an attempt to conduct an analysis of the data that were accurate, complete, and reliable. Unfortunately many of the inconsistencies could no longer be clarified at the study site or at the original CRO responsible for the data collection. Also, a post-hoc analysis of the reported pre-study URTIs, an important study inclusion criterion, was conducted. Based on the protocol definition of a URTI, it appears that many patients

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	probably did not have at least four documented URTIs in the year before the study began, as quite a number were just reported by parents. This reduced the number of valid patients in the study and thus the statistical power of the study to be able to detect a difference in the treatment arms. Based on all these above mentioned factors, OM/Vifor Pharma considers the study to be flawed. Vifor Pharma is of the opinion that efficacy conclusions on OM-85 BV cannot be made based on this study.