SYNOPSIS

Protocol Number: BV-2007/06

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

Title:	Efficacy of Broncho-Vaxom® in Elderly Patients with Chronic Bronchitis. A Double-Blind, Randomised, Placebo-Controlled Study
Short Title:	Efficacy and Safety Study of Broncho-Vaxom® in Elderly Patients with Chronic Bronchitis
Indication:	Acute lower respiratory tract infections (LRTIs) in elderly patients with chronic bronchitis
Phase:	4
Study Code:	BV-2007/06
Study Co-ordinator:	Prof Ulf Schutter Facharztzentrum am Marienhospital Hervester Str. 57 45768 Marl Germany
Study Centres:	A total of 42 active centres in Germany
Objectives:	Primary Objective: To assess new data about the preventive efficacy of Broncho-Vaxom® compared with placebo against acute LRTIs in elderly patients with chronic bronchitis.
Design:	Randomised, placebo-controlled, double-blind, parallel group, multicentre study
Treatment:	Broncho-Vaxom® capsules containing 7 mg of lyophilised extract per capsule (batch numbers 23722 (for pack 23914) and 22086 (for pack 23914)) and matching placebo capsules (batch numbers 21265 (for pack 23914) and 22085 (for pack 22086)) were provided by the Sponsor (OM Pharma). The capsules were administered orally, in the morning, on an empty stomach. Patients received one capsule per day of Broncho-Vaxom® or placebo for 30 days during the first month of treatment. Following one month without treatment, patients received one capsule per day (Broncho-Vaxom® 7 mg or placebo) for the first 10 days of Months 3, 4, and 5.
Inclusion Criteria:	1. Elderly patients (aged ≥65 years) of either sex 2. Patients with chronic bronchitis with at least 3 documented acute infections of the lower respiratory tract in the previous year resulting in a change in regular medication 3. Patients who were conscious and not bedridden invalid 4. Patients able to understand the purpose of the study 5. Written informed consent

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Exclusion Criteria:	1. Patients with allergic asthma or primary emphysema (Alpha-1 antitrypsin deficiency) 2. Patients with a forced expiratory volume in one second (FEV_1) <50% predicted 3. Patients with a history of cancer in the year before study start 4. Patients with cardiovascular heart failure with New York Heart Association Stage III or IV 5. Patients with renal insufficiency: >2 times upper limit of normal range of serum creatinine 6. Patients with hepatic insufficiency: >2 times upper limit of normal range of aspartate aminotransferase or alanine aminotransferase 7. Patients treated with the following medications: o Oral vaccination with live vaccine within 4 weeks before study start o Previous and/or concomitant immunosuppressive or immunostimulating therapy (including chemotherapy and radiotherapy) within 6 months before study start o Regular corticosteroids >20 mg of prednisolone per day for more than two weeks 8. Patients with a known allergy to bacterial agents 9. Patients who were unable to following instructions, and unreliable patients including non-complaint patients, patients with known alcoholism or drug abuse, patients with a history of a serious psychiatric disorder as well as patients unwilling to give informed consent or abide by the requirements of the protocol, i.e., unable to complete a patient diary 10. Patients who had participated in another clinical trial within the 4 weeks before study start 11. Patients who did not accept intermediary phone calls (IPCs)
Primary and Secondary Endpoints:	Primary Endpoint: • Rate of LRTIs (number recorded up to the end of the treatment period, Visit 8). The clinical signs and symptoms of LRTIs were increased sputum volume and purulence, increased dyspnoea, fever (≥38ºC), cough, and changes from usual patient treatment such as antibiotics and steroids. At least two of these symptoms had to be present plus the change in the usual treatment to fulfil the definition of a LRTI. Secondary Endpoints: • Type, severity, and duration of the LRTIs • Type and duration of prescribed concomitant treatment(s) • Number and duration of hospitalization and deaths related to respiratory disease

	• Spirometry (forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC)) at Visits 2 or 3 and Visits 4 to 8 • Global assessment of efficacy by patient and Investigator at Visit 10 • Safety: physical examination, vital signs, laboratory values and occurrence of adverse events (AEs) and serious adverse events (SAEs) • Global assessment of safety
Procedures:	Patients attended an information visit (Visit 1) and received information from the physician according to the Patient Information Sheet. Patients attended a screening visit (Visit 2) and an inclusion visit (Visit 3) during which the patient's eligibility for the study was assessed. This included completion of spirometry assessments and recording of signs and symptoms of LRTIs. Eligible patients were randomised to either Broncho-Vaxom® or placebo. They were given sufficient study medication for 30 days to be taken during Month 1 and a patient diary to record any AEs and/or changes in concomitant medication. Patients returned to the study centre at the end of Months 1, 2, 3, 4, 5, 6, and 7 (Visits 4, 5, 6, 7, 8, 9, and 10 respectively) for the following: • Past and concomitant diseases and medication(s) • Vital signs • IPC and patient diary report control • Signs and symptoms of LRTIs • Spirometry FEV_1 and FVC (except Visits 9 and 10) • Reporting of any AEs • Compliance check of study medication (except Visits 5, 9, and 10) In addition for Visit 5 only, study medication was delivered for Months 3, 4, and 5 in order to be taken for the first 10 days of each month. In addition at Visit 8 only, patients gave a blood sample for laboratory safety tests. At the final visit (Visit 10) only, a physical examination was performed by the Investigator and a global assessment was performed by the Investigator and the patient. Patients were asked to return for unscheduled visits if required due to an acute worsening or relapse, or if they experienced a serious adverse event (SAE).
Sample Size:	350 patients planned (175 patients per treatment group) 354 patients randomised and 353 treated (177 patients received Broncho-Vaxom® and 176 patients received placebo)
Statistical Methods:	The primary efficacy analysis defined in the protocol used a transformed primary efficacy variable (rate of acute exacerbations of lower respiratory tract infections, x) of $g(X) = (X + 3/8)^{1/2}$, which was planned to be analysed using t-tests. This was replaced by a negative binomial model which was better recognised and provided consistency of methodology across similar

	studies. The adjustment for dropouts was also simplified. Estimates of the rate ratio with 95% confidence intervals were assessed. The primary model was repeated including the factors of whether or not the patient had been vaccinated against influenza, whether they were a non-smoker or a current/past smoker, and their interactions with treatment. The primary analysis was repeated for the per protocol set as a sensitivity analysis. These summaries and the primary analysis were also performed for each study period. Secondary efficacy variables: The number and percentage of patients with each type of LRTI, severity of each LRTI, duration of each LRTI, time to onset of first LRTI, and number and duration of hospitalisations were summarised. No statistical analyses were performed for these endpoints. Secondary endpoints were analysed for the FAS only. The time to onset of first LRTI was analysed using a Logrank test, stratified by centre. A binary logistic regression model was used to analyse type and duration of prescribed concomitant medication, and use of healthcare resources and hospitals. A mixed model repeated measures model, using the 0.05 significance level, was used to analyse the FEV_1, FVC, and ratios of FVC and FEV_1 at Visits 2 or 3 and Visits 4 to 8, and change from baseline at Visits 4 to 8. An ordinal logistic regression method was used to analyse the Investigator and patient's global assessment of efficacy, by treatment group. Safety variables: Treatment-emergent adverse events were summarized using Medical Dictionary for Regulatory Activities (Version 14.1). Descriptive statistics were performed for laboratory parameters and change from baseline for each visit by treatment group. The raw scores and change from baseline in heart rate, systolic blood pressure, and diastolic blood pressure 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 (prior and concomitant) were summarised by treatment group for prior and concomitant medications separately. Use of specific concomitant medications of interest (antibiotics and corticosteroids) were analysed separately as secondary efficacy variables. An ordinal logistic regression method was used to summarise Investigator and patient's global assessment of safety, by treatment group.
Conclusion:	The rationale for performing the present study was to demonstrate the efficacy of Broncho-Vaxom® in elderly patients with chronic bronchitis. The treatment schedule 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 354 patients were randomised and 353 were treated (177 patients received Broncho-Vaxom® and 176 patients received placebo). Demographic and baseline characteristics were very similar between the treatment groups.

The primary efficacy endpoint was the rate of acute LRTIs up to the end of the treatment period. There was no statistically significant difference in the rate of acute LRTIs following treatment with Broncho-Vaxom® compared with placebo (p=0.879 for Visit 3 to Visit 8). The number of patients with an LRTI was low and similar for both treatment groups; 42 patients (24.6%) in the Broncho-Vaxom® group and 40 patients (23.3%) in the placebo group. Similar results were observed for the secondary efficacy endpoints assessed.

The efficacy results need to be interpreted with caution because of the lack of homogeneity between analysis sets, resulting from a high number of patients with protocol violations.

Broncho-Vaxom® was generally well tolerated. The majority of patients in both treatment groups reported at least one AE during the study (61.9% of patients in the placebo group and 61.6% of patients in the Broncho-Vaxom® group). Many of the most common AEs and treatment-related AEs were associated with the underlying disease. The proportion of patients who discontinued due to AEs was 5.1% in the Broncho-Vaxom® group and 4.5% in the placebo group. More patients in the Broncho-Vaxom® group reported SAEs (14.7% compared with 6.8% in the placebo group). Only one SAE was considered treatment-related (placebo group). The 5 deaths in this study (1.4%) comprised 3 treatment-emergent deaths (two patients in the Broncho-Vaxom® group (1.1%) and one (0.6%) in the placebo group) and two post-treatment deaths (one patient (0.6%) in the Broncho-Vaxom® group and one (0.6%) in the placebo group).

It is important to note that study management and 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 was 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. Moreover, all LRTIs observed during the trial were adjudicated, and events not fulfilling the protocol definition were excluded from the analysis. The review of LRTI history showed that a fair proportion of patients did not meet the inclusion criterion of at least 3 LRTIs in the previous year. 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 factors, OM/Vifor Pharma as well as an independent group of experts 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.