SYNOPSIS

Protocol Number: BV-2007/02

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

Title:	Multicentre, Double-Blind, Placebo-Controlled, Randomised Clinical Study of Broncho-Vaxom® (Broncho-Munal®) for the Protection from Acute Exacerbations of COPD
Short Title:	Efficacy and Safety Study of Broncho-Vaxom® in Patients with Acute Exacerbations of COPD
Indication:	Acute exacerbations in patients with moderate to severe chronic obstructive pulmonary disease (COPD)
Phase:	3 (4 in Germany)
Study Code:	BV-2007/02
Study Director:	Prof Dario Olivieri, MD Rasori Hospital University of Parma Italy
Study Centre(s):	A total of 51 active centres in Europe (Austria, Belgium, Germany, and Italy)
Objectives:	Primary Objective: • To show that Broncho-Vaxom® decreases significantly the rate of exacerbations by at least 20% when compared with placebo in patients suffering from moderate to severe COPD from Stage II and III (according to the Global Initiative of Chronic Obstructive Lung Disease (GOLD))
Design:	Randomised, placebo-controlled, double-blind, parallel group, multicentre study
Treatment:	Broncho-Vaxom® capsules containing 7 mg of lyophilised extract per capsule (Batch numbers 21044 (Pack 21338)) and matching placebo capsules (Batch numbers 21265 (Pack 21338)) were provided by the Sponsor (OM Pharma). The capsules were administered orally, in the morning, on an empty stomach. Patients received 1 capsule per day of Broncho-Vaxom® or placebo for 30 days during the first month of treatment. Following 1 month without treatment, patients received 1 capsule per day (Broncho-Vaxom® 7 mg or placebo) for the first 10 days of Months 3, 4, and 5. Total duration of treatment was 60 days. Study duration was 6 months.
Inclusion Criteria:	1. Adult outpatients of either sex, aged ≥40 years 2. History of documented acute exacerbations of chronic bronchitis (AECBs) ≥2 in the previous year and COPD Stage II to III 3. A forced expiratory volume in one second (FEV_1) value of $30\% \leq FEV_1 < 80\%$ (value after bronchodilator test), predicted, and

	documented within 6 months prior to enrolment in the study 4. Smokers with a history of 20 pack years* or more; active or past smokers. (*Pack year was calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person had smoked.) 5. Written informed consent
Exclusion Criteria:	1. Patients with asthma 2. Patients with mucoviscidosis 3. Patients with bronchiectases 4. Patients with any known disseminated malignancy 5. Patients with known chronic systemic infections or inflammatory conditions (e.g., rheumatoid arthritis, systemic lupus erythematosis or active sarcoidosis) 6. Patients with previous solid organ transplantation 7. Patients with myocardial infarction or cerebrovascular accident within the 6 months prior to study enrolment 8. Patients treated with the following medications: o Corticosteroids the day of Visit 1 o Oral vaccination with live vaccine within 4 weeks before study start o Previous and/or concomitant immunosuppressive or immunostimulating therapy within 3 months before study start o Regular oral corticosteroids ≥10 mg of prednisolone for >2 weeks 9. Patient with a known allergy or previous intolerance to the study medication 10. Female patients who were pregnant, lactating or of child-bearing potential and not protected from pregnancy by a sufficiently reliable method (oral contraceptive, intra-uterine device or a Pearl index <1) 11. Patients who were unable to follow instructions and unreliable patients (including non-compliant patients, patients with known alcoholism or drug abuse or with a history of a serious psychiatric disorder) as well as patients unwilling to give informed consent or to abide by the requirements of the protocol 12. Patients with any other clinical condition which, in the opinion of the investigator, would not allow safe completion of the protocol and safe administration of the study medication 13. Patients with major surgical procedure within 3 months of enrolment in study

	14. Patients who had participated in a drug study within the 4 weeks prior to this study
Primary and Secondary Endpoints:	Primary Endpoint: • Rate of acute exacerbations recorded during the treatment period. An acute exacerbation was defined as increased and coloured sputum, increased dyspnoea and cough, fever (≥38ºC), 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 an acute exacerbation. Secondary Endpoints: • Type, severity, and duration of the acute exacerbations • Time to first acute exacerbation • Type and duration of prescribed concomitant treatment(s) • Use of healthcare resources, hospitals, and other institutions • Number and duration of hospitalisations • Duration of absenteeism from work • Spirometry (FEV_1/Forced vital capacity (FVC)) assessed at Visits 1 and 6 • St. George's Respiratory Questionnaire (SGRQ): scores for each section including symptom score (frequency and severity), activity score (activities that cause or are limited by breathlessness), impact score (social functioning, psychological disturbances resulting from airways disease), and total score • Global assessment of efficacy • 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 inclusion visit (Visit 1) during which the patient's eligibility for the study was assessed. This involved an assessment of the severity of COPD, signs/symptoms of AECB and documentation of treatment of exacerbations (if necessary). Eligible patients also completed spirometry assessments and the SGRQ. 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 worsening of any details of symptoms and/or changes in concomitant medication. At Visits 1 and 6, blood samples were collected for laboratory tests. Patients returned to the study centre at the end of Months 1, 2, 3, 4, 5, and 6 (Visits 2, 3, 4, 5, 6, and 7, respectively) for the following: • Recording of prior and concomitant medications

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	• Recording of concomitant diseases • Smoking history and status • Recording of vital signs • Collection and checking of patient diary • Signs and symptoms of AECBs • Number and severity of exacerbations since last visit • Documentation of treatment of exacerbation (if required) • Checking compliance of study medication • Reporting of any AEs In addition for Visit 3 only, study medication was delivered for Months 3, 4, and 5 with instructions for this to be taken for the first 10 days of each month. In addition, the SGRQ was completed at Visits 6 and 7. At the final visit (Visit 7), a global assessment (efficacy and safety) was performed by the investigator and the patient. Patients were asked to return for unscheduled visits if an exacerbation occurred between scheduled visits or if symptoms continued after completion of the antibiotic course.
Sample Size:	350 patients planned (175 patients per treatment group) 357 patients randomised and treated (179 patients received Broncho-Vaxom® and 178 patients received placebo)
Statistical Methods:	The primary efficacy variable was analysed using a binary logistic regression model (this was a change from the analysis planned in the protocol which used a Conchran-Mantel-Haenszel test. Logistic regression was considered a more appropriate method). Parameter estimates for the treatment effect were assessed using the Likelihood ratio test evaluated at the 0.05 significance level. The adjusted on centres odds ratio was calculated with 95% confidence intervals. The logistic regression model was repeated, firstly including the number of COPD episodes in the previous year and secondly with smoking status as a covariate. An additional analysis was performed using a negative binominal model to account for patients reporting more than one AECB and adjust for different lengths of follow-up. These analyses were repeated for the per protocol set as a sensitivity analysis. <u>Secondary efficacy variables:</u> The type, severity, and duration of acute exacerbation, duration of absenteeism from work, 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 acute exacerbation (which was added as an additional secondary efficacy variable in the revised statistical analysis plan

	(SAP)) was analysed using a Logrank test, stratified by centre. An analysis of covariance (ANCOVA) model was used to analyse the mean change from baseline in SGRQ symptom, activity and impact, and total score. Formal analysis of SGRQ data was added in the revised SAP. A binary logistic regression model adjusted on centres was used to analyse use and duration of use of concomitant antibiotics, use and duration of concomitant corticosteroid use, and healthcare resource and hospital use. An ANCOVA model, with a 0.05 significance level, including baseline covariate and centre cofactor, was used to analyse the FEV_1, FVC and ratios of FVC and FEV_1 at Visit 1 and Visit 6, and change from baseline at Visit 6. Formal analysis of spirometry data was added in the revised SAP. An ordinal logistic regression method, adjusted on centres, was used to analyse the investigator and patient's global assessment of efficacy, by treatment group. <u>Safety variables:</u> Treatment-emergent AEs (TEAEs) were summarized using Medical Dictionary for Regulatory Activities (Version 13.1). Descriptive statistics were performed for laboratory parameters and change from baseline for each visit split 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. An ordinal logistic regression method was used to summarise investigator and patient's global assessment of safety, by treatment group.
Conclusion:	The primary efficacy endpoint was improvement in the rate of acute exacerbations in the Broncho-Vaxom® group compared with the placebo group. During the study (i.e., from Visit 1 to Visit 6), 72 patients (42.6%) in the Broncho-Vaxom® group experienced acute exacerbations compared with 64 patients (37.4%) in the placebo group. The number of patients who experienced acute exacerbations was comparable across the treatment groups between all visits. There was no statistically significant difference in the rate of acute exacerbations of COPD following treatment with Broncho-Vaxom® compared with placebo. There were also no significant differences between the Broncho-Vaxom® and placebo groups in any of the secondary endpoints evaluated. Broncho-Vaxom® was generally well tolerated. The majority of TEAEs were mild or moderate in severity. The incidence of TEAEs, treatment-related TEAEs, severe TEAEs, and discontinuations due to TEAEs was similar in both treatment groups. One patient died during the study. This patient was in the placebo group and the death was not considered related to study treatment by the Investigator. The incidence of SAEs was similar in both treatment groups; 15 patients (8.4%) experienced at least one SAE in the Broncho-Vaxom® group and 14 patients (7.9%) experienced at least one SAE

	in the placebo group. The most frequently reported (experienced by more than one patient in either treatment group) SAEs were COPD, bronchitis, and urinary tract infection. The incidence of clinically significant laboratory test abnormalities was low in both treatment groups. 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. A blinded re-adjudication of all exacerbations observed during the trial was conducted by an independent expert group. Numerous cases of exacerbation were not considered to be valid events by the experts. Also, a post-hoc analysis of the reported pre-study acute exacerbations, an important study inclusion criterion, was conducted. Based on the protocol definition of an acute exacerbation, it appears that many patients probably did not have at least two documented exacerbations in the year before the study began. 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, 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.