SYNOPSIS

Protocol Number: BV-2007/04

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

Title:	Multicentre, Randomised, Double–Blind, Placebo-Controlled Study of the Efficacy and Safety of Broncho-Vaxom® in Adults Suffering from Chronic Rhinosinusitis
Short Title:	Broncho-Vaxom® in Adults Suffering From Chronic Rhinosinusitis
Indication:	Chronic rhinosinusitis
Phase:	3 in Switzerland (4 in Austria and Germany)
Study Code:	BV-2007/04
Study Director:	Prof JS Lacroix MD, PhD HUG Rue Gabrielle-Perret-Gentil 4 1211 Geneva 14 Switzerland
Study Centre(s):	A total of 22 active centres in Europe (Austria, Germany, and Switzerland)
Objectives:	Primary Objective: To confirm previous studies and evaluate the efficacy and safety of Broncho-Vaxom® one capsule (7 mg) per day for 30 days followed by 3 courses of 10 days in Months 3, 4 and 5 compared with placebo on the evolution of the disease in adults suffering from chronic rhinosinusitis.
Design:	Randomised, placebo-controlled, double-blind, parallel group, multicentre study.
Treatment:	Broncho-Vaxom® capsules containing 7 mg of lyophilised extract per capsule (Verum batch number 21044) and matching placebo capsules (placebo batch number 21265) were identically conditioned (batch number 21338) and 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. Total duration of treatment was 60 days. Study duration was 6 months for all patients.
Inclusion Criteria:	1. Adult outpatients of either sex, aged ≥18 to ≤75 years 2. The patient must have experienced a facial pain especially unilaterally; and at least one of the two following symptoms (>50% of days in the last 3 months) • More than 12 consecutive weeks of symptomatic nasal obstruction and/or • More than 12 weeks of symptomatic nasal discharge

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	3. An otorhynolaryngological evaluation and diagnosis of chronic inflammatory rhinosinusitis (hyperplastic mucosa, nasal polyps), endoscopic signs and/or computerised tomography scan 4. Written informed consent
Exclusion Criteria:	1. Patients with sinus surgery within the last 3 months 2. Patients with acute illness within the last two weeks requiring antibiotics 3. Patients with acute intestinal infection 4. Patients with asthma 5. Patients with immunosuppression (due to medications including oral steroids, or due to autoimmune diseases, human immunodeficiency virus infection, cystic fibrosis, immunodeficiency, malignancies, uncontrolled diabetes mellitus and chronic renal failure) 6. Patients with sinister signs requiring immediate intervention (e.g., swelling of eyes or eyelids/eye redness, displaced globe, double vision, reduced vision, orbital symptoms, severe unilateral frontal headache, frontal swelling, signs of meningitis or focal neurological signs) 7. Patients with serious concomitant disease which may have interfered with or modified the outcome (severe or moderate decompensation) 8. Patients with acute bacterial rhinosinusitis defined as an increase of symptoms after 5 days or persistent symptoms after 10 days with <12-weeks duration 9. Female patients who were pregnant, lactating or of child-bearing potential and not protected from pregnancy by a sufficiently reliable method (oral contraceptives, intrauterine device or a Pearl index <1) 10. Patients under immunosuppressive or immunostimulating therapy (registered pharmaceuticals) within one month prior to study start 11. Patients who were under systemic corticosteroid therapy within one month prior to study start taking a regular dose of oral corticosteroids greater than or equal to the equivalent of 10 mg prednisolone per day for longer than two weeks 12. Patients who were unable to comply with the requirements of the protocol, especially if they were thought to be unable to complete the questionnaires or diary 13. Patients with a known allergy, previous intolerance or known hypersensitivity to the study medication 14. Patients who had participated in another clinical study and/or treatment with an experimental drug within 3 months prior to study start and during the present study
Primary and Secondary Endpoints:	<u>Primary Endpoint</u>: • Total 20-item Sino-Nasal Outcome Test (SNOT-20) score

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	Secondary Endpoints: • Survival: Time until only one symptom is mild or no symptoms are reported • Consumption of rescue medication • Global assessment of efficacy • 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) during which the patient's eligibility for the study was assessed. This included completion of the SNOT-20. 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 deterioration 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 • A physical examination and recording of vital signs • Collection and check of patient diary • Completion of SNOT-20 test • Compliance check of study medication • Accounting for rescue 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. At the final visit (Visit 7) only, a global assessment of efficacy was performed by the investigator and the patient. Patients were asked to return for unscheduled visits in case of occurrence of increase of symptomatology or recurrence of an acute rhinosinusitis, or if they experienced an SAE.
Sample Size:	200 patients planned (100 patients per treatment group) 206 patients treated (104 patients received Broncho-Vaxom® and 102 patients received placebo)
Statistical Methods:	For the primary efficacy variable, the following 3 null hypotheses were tested by means of analyses of covariance (ANCOVAs) with the factors centre, treatment group and total SNOT-20 at baseline as covariates:

1. H_{01}: The AUC of the total SNOT-20 from baseline to Visit 6 is equal for the placebo and Broncho-Vaxom® treatment groups.
2. H_{02}: The changes from baseline to Visit 4 regarding the total SNOT-20 score are equal for the placebo and Broncho-Vaxom® treatment groups.
3. H_{03}: The changes from baseline to Visit 6 regarding the SNOT-20 are equal for the placebo and Broncho-Vaxom® treatment groups.

A multiple test procedure with a priori ordered hypotheses was carried out. The confirmatory test procedure was stopped if at one step the corresponding null hypotheses could not be rejected. The change from baseline at each post baseline visit and the AUC were compared between the two treatment groups using an ANCOVA model. The ANCOVA model included the treatment group (the effect of interest), the corresponding baseline score (the covariate) and the factor of centre. A mixed model repeated measures (MMRM) analysis on the change from baseline SNOT-20 score was performed as a sensitivity analysis. A mixed effects linear model for repeated measures was fit to the observed change from baseline score at each visit (Visits 2 to 6). These analyses were repeated for the per-protocol set as a sensitivity analysis.

Secondary efficacy variables:

The mean SNOT-20 sub-scores (nasal, sleep, general, ear, practical and emotional), changes from baseline in mean SNOT-20 sub-scores and consumption of rescue medication (antibiotics, corticosteroids and analgesics) were summarised. (Formal analysis of some secondary endpoints was not included in the protocol and original statistical analysis plan. They were added in the revised statistical analysis plan.)

Secondary endpoints were analysed for the full analysis set (FAS) only.

An ANCOVA model was used to analyse the mean change from baseline for SNOT-20 sub-scores.

The survival time, defined as the time from first evaluation of SNOT-20 score to the date of evaluation of SNOT-20 score where only one symptom was mild or no symptoms were reported (the earliest event was evaluated), was analysed using a Logrank test and stratified by centre.

A binary logistic regression model was used to analyse use of rescue medication.

An ordinal logistic regression method was used to analyse the investigator and patient's global assessment of efficacy, by treatment group. (This was a change from the analysis planned in the protocol which used a Mann-Whitney rank sum test. Ordinal logistic regression was considered a more appropriate method. The global efficacy assessment was included in the primary efficacy hierarchical hypotheses defined in the protocol. This was removed for the analysis as it is a secondary variable.)

Safety variables:

Treatment-emergent adverse events (TEAEs) were summarized using

	Medical Dictionary for Regulatory Activities (Version 14.0). Descriptive statistics were performed for laboratory parameters and change from baseline for each visit was 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.
Conclusion:	The primary efficacy endpoint was improvement in disease-specific quality of life as measured by change in SNOT-20 total score. Mean AUC for SNOT-20 total score from Visit 1 to Visit 6 was 213.7 in the Broncho-Vaxom® group and 241.1 in the placebo group. During the study (i.e., from Visit 1 to Visit 7), mean SNOT-20 total scores decreased from 1.77 to 1.13 in the Broncho-Vaxom® group and from 1.97 to 1.35 in the placebo group. The Baseline (Visit 1) SNOT-20 total scores were low in both treatment groups indicating that patients in this study experienced a 'very mild' or 'mild to slight' problem. The changes from Baseline in SNOT-20 total score at Visit 7 were similar for both treatment groups (-0.63 in the Broncho-Vaxom® group and -0.61 in the placebo group). There was no statistically significant difference in the AUC for SNOT-20 total score between the treatment groups. There were also no statistically significant differences in changes from Baseline in SNOT-20 total score at any visits following treatment with Broncho-Vaxom® compared with placebo. With the exception of SNOT-20 nasal score at Visit 6, there were also no statistically significant differences between the Broncho-Vaxom® and placebo groups in any of the secondary endpoints evaluated. For SNOT-20 nasal score, a greater change from Baseline was observed at all visits in the Broncho-Vaxom® group compared with the placebo group, and the difference was statistically significant at Visit 6 (p=0.027). Broncho-Vaxom® was generally well tolerated. The majority of TEAEs were mild or moderate in severity. The incidence of TEAEs and severe TEAEs was similar in both treatment groups. More patients experienced TEAEs that were considered treatment related in the Broncho-Vaxom® group (29.8%) compared with the placebo group (17.6%). Generally, the most frequently reported TEAEs (all causality and treatment-related) were related to the disease under study. More patients discontinued the study due to TEAEs in the placebo group compared with the Broncho-Vaxom® group. No deaths were reported during the study. The incidence of SAEs was similar in both treatment groups; 4 patients in the Broncho-Vaxom® group and 5 patients in the placebo group experienced at least one SAE. 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 CRFs 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 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. In addition, study design issues were identified that lead to a study population with mainly mild chronic rhinosinusitis. Given the lack of severity of chronic rhinosinusitis in the study population, the study lacks sufficient power to demonstrate a difference. This was confirmed by a retrospective power analysis. All the quality issues were assessed to be mainly due to a poor quality monitoring of the trial and poor data management by the original CROs . Based on all these above issues, the trial has to be considered as flawed and no conclusion can be made on the efficacy of OM-85 BV in chronic rhinosinusitis.