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# Double-Blind Study of OM-85 in Patients with Chronic Bronchitis or Mild Chronic Obstructive Pulmonary Disease

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**Key Words**
Chronic bronchitis · Chronic obstructive pulmonary disease · OM-85 · Broncho-Vaxom

**Abstract**
***Background:*** Interventions against acute exacerbations (AEs) of chronic obstructive pulmonary disease (COPD) are increasingly called for to reduce morbidity, mortality and costs. OM-85, a detoxified immunoactive bacterial extract, has been shown to prevent recurrent exacerbations of bronchitis and COPD. ***Objectives:*** It was the aim of this study to demonstrate the protective effect of OM-85 against recurrent bronchitic exacerbations in patients with chronic bronchitis or mild COPD. The primary end point was the mean rate of AEs occurring within the study period. ***Methods:*** This double-blind multi-centre study enrolled adult outpatients >40 years old of both sexes with a history of chronic bronchitis or mild COPD at the time of an AE. The treatment consisted of one capsule of OM-85 or placebo per day for 30 days, followed by three 10-day courses for months 3, 4 and 5, with a 6-month study duration and monthly control visits. ***Results:*** One hundred and forty-two patients were treated with OM-85 and 131 received placebo. By the end of the treatment period, the mean number of AEs in the OM-85 group was 0.61 per patient versus 0.86 per patient in the placebo group (–29%; $p = 0.03$). The difference between treatments was most notable in patients with a history of current or past smoking (–40%; $p < 0.01$). No serious adverse events were attributed to the medication and no significant laboratory changes were reported. ***Conclusions:*** OM-85 significantly reduced the frequency of AEs in patients with a history of chronic bronchitis and mild COPD and was well tolerated. This study confirms the findings of previous trials conducted in elderly patients with chronic bronchitis or COPD.



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## Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of mortality and morbidity, with cigarette smoking being the main risk factor, and is characterized by permanent or minimally reversible airflow obstruction caused by chronic bronchitis, emphysema or both [1].

Functionally, COPD involves reduced maximum expiratory flow and slow forced emptying of the lungs; neither of theses features changes significantly over a period of a few months [2], but both invariably become more severe in the long term. In contrast to asthma, the abnormalities limiting airflow in COPD are, for the most part, irreversible and caused by structural changes in the lung parenchyma and the airways. Although many pharmacological attempts to improve the long-term course of the disease have been studied and are under way [3], today, the only proven way to slow down this escalation is to stop smoking. The goals of treatment for chronic bronchitis and COPD are to reduce symptoms, to prevent recurrent exacerbations and to preserve optimal lung function [1]. There have been reports suggesting that frequent exacerbations of COPD are linked to an accelerated loss of lung function [4]. Therefore, the prevention of exacerbations has become an important argument in the medical treatment of COPD.

Clinically, acute exacerbations (AEs) of COPD are commonly defined by increases in dyspnoea, cough and sputum production with increased purulence in sputum [5]. Besides viruses and pollutants, chronic colonizing bacteria, as well as bacterial superinfections, play a central role in the course of most exacerbations. The bacteria involved are relatively non-virulent and often form part of the normal upper respiratory tract flora. Impaired lung defence mechanisms, as they may occur due to damages caused by cigarette smoke or other reasons, are usually a precondition for bacterial colonization of the lower respiratory mucosa. Most of the typical bacteria produce factors which facilitate their persistence and contiguous spread across the bronchial tree. The subsequent host inflammatory responses to these infections may contribute to the progressive deterioration in respiratory function [6].

*Management of Respiratory Infections*

The therapeutic approach to infections in COPD seeks to assure optimal lung function (bronchodilation), to maintain adequate bronchial drainage and to treat the underlying bacterial infection with antibiotics.

Today, methods for specific prevention of acute airway infections are still limited to a few vaccines *(Influenza*, *Pneumococcus*, *Haemophilus)* and usually only recommended for selected patient populations, including immunocompromized and elderly persons [7].

The non-specific prevention of recurrent airway infections by immunostimulating agents has gained growing scientific interest over the past 20 years and is increasingly applied in different clinical situations.

*Rationale for an Immunotherapeutic Approach*

Adults with recurrent respiratory infections frequently have some variant of IgG deficiency, often associated with a functional impairment of specific antibody response [8]. The lung contains large numbers of lymphocytes. These can be found in different compartments, i.e. in (1) the bronchus-associated lymphoid tissue, which develops as a result of microbial stimulation, (2) the intraepithelial and lamina propria lymphocytes of the bronchi, with their typical subset composition, (3) the interstitial lymphocyte pool, (4) the lymphocytes in the bronchoalveolar space, which can be sampled by bronchoalveolar lavage, and (5) the pulmonary intravascular lymphocyte pool, which is organ specific and shows a unique migration pattern. In animals, the lung is part of the integrated mucosal immune system, as shown by protective oral immunization against the lung-pathogenic bacteria [9]. The mucosa-associated lymphoid tissues have multiple functions: in adulthood, they are principally sites of lymphocyte development, antigen processing, effector T cell development and antibody production.

Advances in the basic knowledge of these humoral and cell-mediated immune mechanisms have paved the way for different therapeutic options aimed at modulating various components of the immune response [10, 11].

Immunostimulants constitute a heterogeneous group of drugs which includes agents such as vaccines, interferons, chemical compounds and agents derived from bacteria. A detoxified example of this latter class is OM-85, an extract from 8 bacteria frequently responsible for respiratory tract infections *(Haemophilus influenzae, Klebsiella pneumoniae* and *ozaenae, Staphylococcus aureus, Streptococcus pneumoniae, pyogenes* and *viridans, Moraxella catarrhalis),* which has been shown to significantly improve COPD conditions in mostly elderly patients [12, 13].

The aim of the present study was to demonstrate the preventive effect of OM-85 in exacerbations of chronic bronchitis and mild COPD in a younger population of adult patients.

## Patients and Methods

*Selection of the Study Population*

Outpatients of either gender, aged 40–75 years, with a recent history of chronic bronchitis or mild COPD were enrolled in 44 centres (39 in Switzerland and 5 in Germany) at the time of an acute bronchitic exacerbation with at least 3 of the following 4 symptoms, including increased cough, increased or coloured sputum, or increased dyspnoea. Their spirometry performed within the last 12 months before inclusion had to show a forced expiratory volume in 1 s ($FEV_1$) $\geq$50% predicted. Based on their past medical history, these patients fulfilled the diagnostic criteria of chronic bronchitis or COPD, i.e. the Global Initiative for Chronic Obstructive Lung Disease stages I or II. All patients gave their written informed consent.

Patients meeting any of the following criteria at study entry were excluded: allergic asthma, mucoviscidosis, bronchiectasis, $\alpha_1$-antitrypsin deficiency, severe cardiovascular disease (e.g., left ventricular failure, stroke), significant hepatic or renal insufficiency (i.e. alanine aminotransferase and aspartate aminotransferase $>$ 2 times the upper limit of normal and serum creatinine $>$150 μmol/l, respectively), cancer, auto-immune disease and other systemic diseases related to immune system disorders, a known allergy or previous intolerance to the study medication, female patients who were pregnant, breast-feeding or of child-bearing potential without reliable contraceptive methods, unreliable patients (non-compliance, alcoholism), or major surgical procedure or participation in another clinical trial within 3 months of study start.

The following medications/therapies were not allowed at the specified time points: treatment with antibiotics within 1 week before the trial start, previous concomitant immunosuppressive or immunostimulant therapy during the last 3 months before study entry, concomitant treatment with systemic corticosteroids (exceeding 2 weeks), or concomitant treatment with an unregistered drug during the whole trial.

In this study, a new AE was defined as the presence of at least 3 of the following symptoms: (1) increased sputum, (2) coloured sputum, (3) increased dyspnoea and (4) increased cough, occurring after a steady period of at least 1 week without antibiotics.

At the planned visits, the investigator recorded the number of exacerbations since the last scheduled visit, as they were reported by the patients, whether these occurrences had caused a supplementary intercurrent visit or not.

*Efficacy Assessment*

To evaluate the efficacy of OM-85 in COPD and chronic bronchitis, the following parameters were assessed at inclusion and at every monthly or intercurrent visit: symptoms (amount and colour of sputum, severity of dyspnoea, frequency of cough, fever), diagnosis of AE, type and duration of concomitant medications and absenteeism. The safety and tolerability of OM-85 were evaluated by recording adverse events during the study and safety laboratory parameters at trial inclusion and end.

*Administered Treatments*

The treatment with OM-85 (Broncho-Vaxom®, OM Pharma, Meyrin/Geneva, Switzerland) or placebo was randomly assigned to the eligible patients who were asked to take 1 capsule per day (in the morning on an empty stomach) for 30 days, starting with the initial visit, followed by 3 courses of 10 days each at the beginning of months 3, 4 and 5, followed by 1 month without treatment. The randomization occurred in blocks of 4 per centre. The test medications had identical appearances.

Occasional treatments with antibiotics, oral corticosteroids limited to at most the equivalent of 10 mg prednisolone per day, inhaled corticosteroids or anticholinergics and other necessary drugs were allowed as far as they were not forbidden as stated above in the Selection of the Study Population. All concomitant medications had to be recorded on the case report form.

*Ethics*

The protocol was approved by all Ethics Committees and the trial was conducted and reported in compliance with current Good Clinical Practice guidelines. In accordance with the Declaration of Helsinki, patients were allowed to discontinue the study at any time. In case of withdrawal, details were to be recorded on the case report form. Withdrawn patients were not replaced.

*Statistics*

In order to prove a 15–20% statistically significant decrease in the number of AEs in the OM-85 group with respect to placebo, the sample size was calculated as being 125 analysable subjects in each group, under the assumption that the AE rate is about 60% in the placebo group, with $\alpha = 0.05$ and $\beta = 0.2$.

Episodes of AEs were controlled and defined as such as part of the blind review process. The mean rate of AEs (per patient, per month) computed at each visit up to month 6 was the primary parameter used for comparing the efficacy of OM-85 to that of placebo. All other tests and calculations performed on other variables were secondary end points. The hypothesis H0 'the two treatment groups show similar levels of infection rates' was tested by analysis of variance (ANOVA) for repeated measures.

Frequencies were compared by $\chi^2$ and/or Fisher's exact test and comparison over the study period was performed by the Mantel-Haenszel test. The evolution of scores between baseline and study end was analysed by ANOVA for repeated measures.

In the survival analysis, the significance of the difference between the survival data was performed with a log-rank test.

## Results

*Patients*

Two hundred and seventy-six patients (mean age 58 years, range 22–78) were enrolled and randomized, of whom 3 were never exposed to the test drugs. The remaining 273 patients received the test treatments, combined with standard care, and were allotted to the 'intent to treat sample' (ITT). Forty patients were removed (table 1), resulting in a 'per protocol' sample of 233 patients. There was no difference between treatment groups with regard to the demographic variables, with the exception of a higher percentage of female patients in the placebo group (table 2). The possible influence of this unbalanced distribution is explored below.

**Table 1.** Disposition of patients

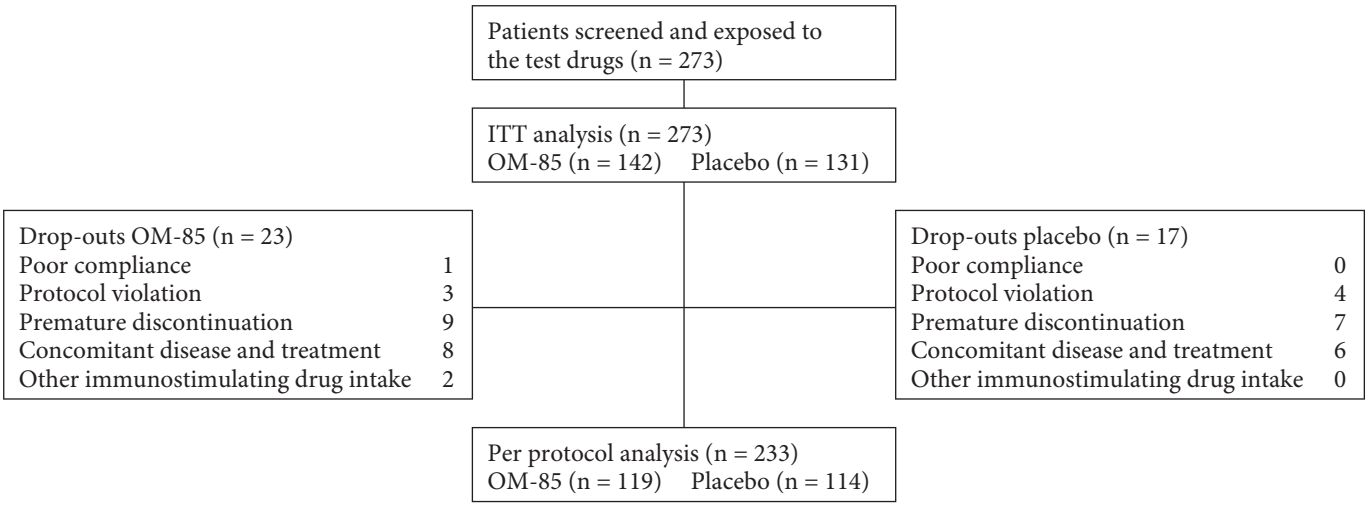


**Table 2.** Demographic and other characteristics of the ITT population

| Parameters | OM-85 (n = 142) | Placebo (n = 131) |
|---|---|---|
| Age, years | | |
| Mean | 57.3 | 57.9 |
| 95% CI | 55.7–58.9 | 56.2–59.6 |
| Male, % | 54.9 | 43.5 |
| Height, cm | | |
| Mean | 168.0 | 167.7 |
| 95% CI | 166.5–169.5 | 166.6–169.4 |
| Weight, kg | | |
| Mean | 74.5 | 74.7 |
| 95% CI | 71.9–77.1 | 72.1–77.3 |
| Body mass index | | |
| Mean | 26.3 | 26.5 |
| 95% CI | 25.4–27.2 | 25.7–27.3 |
| $FEV_1$, % | | |
| Mean | 85.0 | 82.6 |
| 95% CI | 81.7–88.3 | 79.9–86.1 |
| Forced vital capacity, % | | |
| Mean | 91.0 | 89.7 |
| 95% CI | 88.2–93.8 | 86.7–93.3 |
| Exacerbations in previous year | 2.96 ± 1.69 | 3.32 ± 1.64 |
| Allergy, % | 16.9 | 16.8 |
| Flu vaccination, % | 52.2 | 51.9 |
| Smokers, % | 33.1 | 28.2 |
| Non-smokers, % | 38.7 | 41.2 |
| Ex-smokers, % | 28.2 | 30.5 |

*Efficacy Parameters*

At the end of the observation period (6 months), the OM-85-treated patients had a markedly lower mean cumulated rate of AEs compared with the placebo-treated patients (–0.22 mean exacerbations/patient, or –23.7%; p = 0.08) as shown in table 3. By the end of the active treatment (5 months), the mean rate of AEs was significantly lower in the OM-85 group (–0.25, or –29.1%; p =

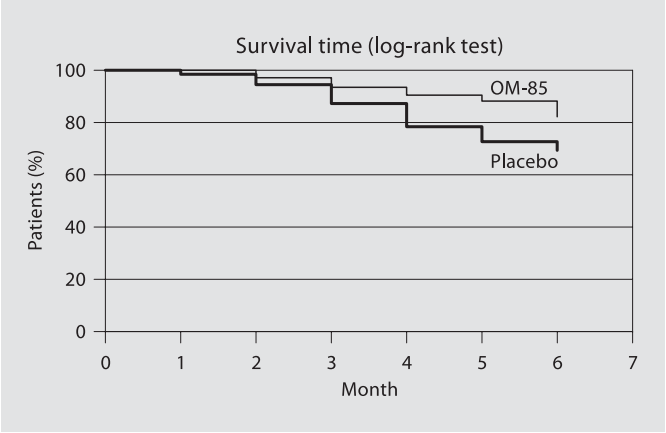


**Fig. 1.** Percentage of patients remaining free from further exacerbations (ITT population).

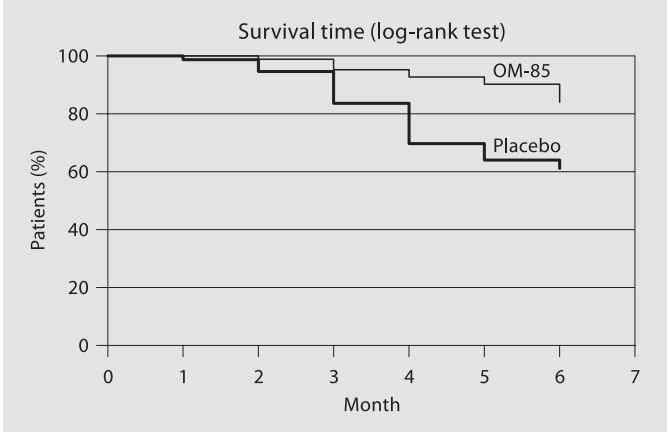


**Fig. 2.** Percentage of current and ex-smokers remaining free from further exacerbations (ITT population).

**Table 3.** Cumulated rate of AEs

| Month | OM-85 | | | Placebo | | | Difference | t test |
|---|---|---|---|---|---|---|---|---|
| | n | mean | 95% CI | n | mean | 95% CI | mean | p value |
| 1 | 142 | 0.09 | 0.04–0.14 | 131 | 0.15 | 0.12–0.18 | 0.06 | 0.15 |
| 2 | 138 | 0.27 | 0.18–0.36 | 126 | 0.35 | 0.30–0.40 | 0.08 | 0.28 |
| 3 | 135 | 0.38 | 0.27–0.49 | 124 | 0.55 | 0.54–0.56 | 0.17 | 0.07 |
| 4 | 133 | 0.53 | 0.39–0.67 | 123 | 0.73 | 0.72–0.74 | 0.20 | 0.06 |
| 5 | 131 | 0.61 | 0.46–0.76 | 123 | 0.86 | 0.85–0.87 | 0.25 | 0.03 |
| 6 | 129 | 0.71 | 0.54–0.88 | 121 | 0.93 | 0.92–0.94 | 0.22 | 0.08 |

0.03) (table 3). A univariate repeated measure analysis of the number of AEs confirmed the significant difference in favour of OM-85 ($p = 0.03$). The number of AEs is made up of AEs observed at the planned visits after inclusion plus the number of AEs which led to an intermediary consultation. At the planned visits, there were 48 AEs reported in the OM-85 group versus 68 in the placebo group, and additionally, 48 and 53 AEs leading to intermediary visits, thus totalling 96 AEs in the OM-85 group versus 121 in the placebo group. This is an overall difference of 20.7% during the 6 months of the study. The reduction in the number of AEs mainly stems from a reduction in the number of patients having presented more than 2 AEs after inclusion during the 6 months of the study: the probability of remaining free of AEs was significantly ($p = 0.014$) higher in the OM-85-treated group, i.e. fewer patients suffered from recurrent AEs, than in the placebo group (fig. 1).

At the time of the scheduled visits, the mean symptom scores of the patients were similar in both groups. Only increased dyspnoea was found somewhat more frequently in the placebo group at 5 months. This assessment may underestimate the true difference in symptoms, because it does not include symptoms caused by the exacerbations occurring between the scheduled visits. There were no significant differences in absenteeism or in the AE-related prescribed therapies of antibiotics or corticosteroids. The prescriptions were related to symptoms present at the corresponding visit only in about 50% of the cases.

*Factors Influencing the Outcome*

There was a slightly higher percentage of women in the placebo group, but gender 'per se' did not affect the outcome, although there was a larger proportion of nonsmokers among the female population and they had a

better preserved lung function (data not shown). On the other hand, the difference between treatments was significantly ($p = 0.001$) more pronounced among patients suffering from 2 or more AEs after inclusion and with a history of current or past smoking (fig. 2), with significantly fewer OM-85-treated patients suffering from recurrent AEs. At the end of the study, the mean cumulated number of AEs per patient was $0.62 \pm 0.83$ in the OM-85 group, compared with $1.04 \pm 1.08$ AEs in the placebo group (–40.3%; $p < 0.01$).

When stratified by smoking status (>10 cigarettes per day), the largest treatment effect was observed among ex-smokers. Ex-smokers differed from non-smokers mainly in the larger proportion of males and lower $FEV_1$ values (data not shown). The mean cumulated number of AEs at the end of the study period in ex-smokers was $0.65 \pm 0.79$ with OM-85 versus $1.40 \pm 1.26$ with placebo (–53.6%; $p < 0.01$). This difference mainly stems from a reduction in the number of ex-smokers with recurrent AEs: 50% of the placebo patients reported 2 or more AEs in the study period, compared with only 15% among the OM-85-treated patients. The group of active smokers represented a fairly distinct sub-population, on average almost 3 years younger than the ex- and non-smokers, with lower $FEV_1$ values than non-smokers, but without a significant difference in the mean cumulated rate of AEs during the study (data not shown).

*Safety*

Actively questioned, 195 patients (OM-85: 104, placebo: 91) complained about 513 adverse events (OM-85: 264, placebo: 249, n.s.) of which a fairly important number were in fact respiratory system manifestations overlapping with the studied disease (e.g., AEs, tonsillitis, symptoms of influenza, sinusitis), representing 30.6 and 27.9% of the adverse events reported with OM-85 and placebo, respectively. No deaths occurred during the trial. Treatment was discontinued in 9 placebo-treated patients and in 5 OM-85-treated patients. Serious adverse events leading to hospitalization were AEs (3 cases in the OM-85 group, 1 in the placebo group), previously known and planned surgery (2 cases in the OM-85 group, 1 in the placebo group), trauma (1 case in the OM-85 group), intestinal cramps (1 case in the placebo group) and appendicitis (1 case in the placebo group). In none of the serious adverse events a causal relationship with the trial preparation was suspected. All patients recovered.

There were no significant changes in the biochemical variables measured in blood in both treated groups.

## Discussion

The current study revealed the cumulated mean rate of AEs to be significantly smaller (–0.25 exacerbations per patient, or –29%) in the OM-85-treated group during active therapy (i.e. months 1–5). Over the entire study duration (5 months of treatment and 1 month follow-up), the OM-85-treated patients had 0.22 fewer AEs per patient (–24%), less than the placebo-treated patients (ITT analysis). Similar findings were recorded in the per protocol analysis. These results are in line with previously published studies of OM-85 in the same pathologies but in elderly patients, demonstrating a protective effect of OM-85 against recurrent respiratory infections in chronic bronchitis and COPD [12, 13].

Our trial was performed in younger patients (mean age 57 years) with only mild COPD who usually have a lower rate of AEs than the more advanced cases. The fact that a protective effect of OM-85 was demonstrated in current or ex-smokers with a lower $FEV_1$ indicates a possibly larger treatment effect in a more severe patient population. On the other hand, active smoking seems to reduce the protective effect of OM-85 in the prevention of exacerbations. Several secondary end points (symptoms, absenteeism, antibiotics and other medications) showed a trend in favour of the active therapy but did not reach the threshold of significance.

The analysis of the safety data confirms the very favourable safety profile of OM-85. There were no serious adverse events causally linked to the medication in either treatment group and no significant differences in adverse events between OM-85 and placebo.

In the current trial, the percentage of women was somewhat higher in the placebo group. The prevalence of chronic bronchitis in the general population aged >50 years in Switzerland is 16.7% in men and 8.9% in women [14]. The consequences of this asymmetry between the treatment groups on the overall treatment effect can only be subject to speculation. Given that the women in our study population had a better preserved lung function, they may represent a group wherein the protective effect of OM-85 is less evident. In addition, there is some question as to the reason why these women were considered to have chronic bronchitis or mild COPD. There might be a link to a different symptom perception in women compared with men, which may have introduced an additional bias against the treatment in this study.

The efficacy of OM-85 has been investigated in numerous clinical studies conducted in children, adults, the elderly or patients with immune disorders and suffering

from COPD, chronic rhinosinusitis or other respiratory tract infections [12, 13, 15–18]. Regarding the outcomes of two key studies in adults with chronic bronchitis and COPD, they showed that OM-85 had a beneficial effect on AEs and the incidence of complications [12, 13]. However, these two studies differ in important aspects from the current trial: significantly older patients, narrow monitoring of symptoms and exacerbations by nurses or mere inclusion of institutionalized patients, as compared with outpatients mostly in private practice in the current study. Moreover, in the study by Collet et al. [13], the patient collective was formed by smokers and ex-smokers with relevant pulmonary obstruction. Our trial should thus be regarded as completing the picture given by earlier studies, making it extendable to younger patients with mild COPD or chronic bronchitis, treated under ambulatory conditions in private practice. Furthermore, as already shown in different cost-effectiveness studies [19, 20], the efficacy of OM-85 translates into a significantly reduced need for medical services and treatments, with important savings in direct and indirect costs for both out- and inpatient care. The reduction in bronchitic exacerbations demonstrated in our study led to a reduction in the number of consultations of 2.2 per 10 patients and 6 months, with the corresponding diagnostic work-up and treatment costs. These aspects, as well as a possible influence on the number of hospitalizations, were not addressed in the present study.

The degree of protection from AEs demonstrated in this trial compares favourably with the effects of other pharmacological treatments for COPD in more advanced disease stages. It remains to be investigated to which extent these findings can be repeated in such advanced COPD patients, in selected patients with frequent exacerbations and whether this protective effect may be additive to the other treatments.

In conclusion, OM-85 significantly reduced the rate of AEs in patients with chronic bronchitis or mild COPD, particularly in those with a history of current or past smoking and in those suffering from frequent recurrent exacerbations (at least 2 after the one present at inclusion in this 6-month study). It also presented a good safety profile comparable with that of placebo.

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