



Randomised, double-blind, placebo-controlled trial of EPs 7630 in adults with COPD



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Received 4 June 2012; accepted 11 February 2013

Available online 7 March 2013

KEYWORDS

COPD;
Efficacy;
EPs 7630;
Exacerbations;
Herbal drug
preparation;
Pelargonium sidoides

Summary

Background: Preventing and managing exacerbations is one major component in COPD treatment. We investigated whether EPs 7630, a herbal drug preparation from the roots of *Pelargonium sidoides*, could prolong time to acute exacerbation in patients with COPD stage II/III.

Methods: In this randomised, double-blind, placebo-controlled clinical trial, patients were randomly allocated to oral 24-week add-on therapy with 3 × 30 drops/day EPs 7630 (*n* = 99) or placebo (*n* = 101) to a standardised baseline-treatment. Primary endpoint was time to first exacerbation of COPD. Secondary endpoints were number of exacerbations, consumption of antibiotics, quality of life, patient satisfaction, inability to work, and tolerability.

Abbreviations: AE, adverse event; AIDS, acquired immune deficiency syndrome; COPD, chronic obstructive pulmonary disease; EPs 7630, a herbal drug preparation from the roots of *Pelargonium sidoides*; FAS, full analysis set; FEV₁, forced expiratory volume during one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; H₀, null-hypothesis; IMPSS, Integrative Medicine Patient Satisfaction Scale; ITT, intention-to-treat; LOCF, last observation carried forward; MCID, minimal clinically important difference; PP, per protocol; RTI, respiratory tract infections; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire.

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Results: Median time to exacerbation was significantly prolonged with EPs 7630 compared to placebo (57 versus 43 days, Kaplan–Maier-estimate; $p = 0.005$, one-sided centre-stratified log-rank test). The superiority of EPs 7630 was also confirmed in secondary endpoints, e.g., fewer exacerbations, less patients with antibiotic use, improved quality of life, higher patient satisfaction, and less days of inability to work. The incidence of minor gastrointestinal adverse events was higher in the EPs 7630 group.

Conclusions: The results demonstrate a statistically significant and clinically relevant superiority of add-on therapy with EPs 7630 over placebo and a good long-term tolerability in the treatment of moderate to severe COPD. EPs 7630 prolonged time to exacerbations and reduced exacerbation frequency and antibiotic use.

Trial Registration No.: ISRCTN01681733.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation that is not fully reversible, usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.¹ A phenotype of COPD is chronic bronchitis, which is defined as the presence of chronic productive cough for at least 3 months/year in two consecutive years.² A systematic review showed that COPD may affect 9–10% of adults ≥ 40 years.³ One of the most common risk factors is cigarette smoking, but there is consistent evidence from epidemiologic studies⁴ that non-smokers may develop chronic airflow obstruction due to occupational dusts and chemicals,⁵ passive smoking⁶ and indoor and outdoor air pollution.⁷ Acute COPD exacerbations contribute to the morbidity and mortality associated with the disease and account for the greatest burden on the health care system due to frequent clinic visits, hospitalisations and lost productivity.⁸ Effective COPD management includes assessment and monitoring of the disease, reducing risk factors, managing stable disease and – as a major aim – prevention and management of exacerbations.^{1,9} Therapeutic alternatives or add-on therapies to the standardised guideline treatment which could reduce exacerbations are highly desired. A promising therapeutic option may be EPs 7630^e, a herbal drug preparation from *Pelargonium sidoides* roots, for which anti-infective activities and notable immunomodulatory capabilities have been demonstrated in vitro, e.g. moderate direct antibacterial activity,¹⁰ strong indirect antibacterial activity like inhibition of interaction between group A-streptococci and host epithelia,¹¹ improved phagocytosis, improved oxidative burst and intracellular killing by human peripheral blood phagocytes,¹² release of tumour necrosis factor and nitric oxide,¹³ stimulation of interferone- β ,¹⁰ increase of natural killer cell activity,¹⁴ and inhibition of sickness behaviour in mice.¹⁵ Systematic meta-analysis of clinical trials with EPs 7630 in acute bronchitis showed superior efficacy compared to placebo with a significantly more effective and faster reduction of bronchitis-specific symptoms such as coughing, sputum production and dyspnoea, as well as a good tolerability.¹⁶ Encouraging results for the efficacy and safety of *Pelargonium sidoides* have also been reported in acute rhinosinusitis^{17,18} and common cold.¹⁹

The aim of this multicentre, placebo-controlled, double-blind clinical study was to investigate whether EPs 7630 prolongs time to first exacerbation and reduces exacerbation frequency compared to placebo as an add-on therapy in patients with moderate to severe COPD.

Methods

Study subjects

Patients eligible to participate in the study were male or female adults (≥ 18 years) with a history of chronic bronchitis (characterised by cough and sputum production on most days for ≥ 3 months/year for at least 2 consecutive years), stable disease, ≥ 3 exacerbations in the prior 12 months and a forced expiratory volume during one second (FEV₁; post-bronchodilator spirometric measurement) $< 80\%$ and $\geq 30\%$ of predicted normal value (COPD-II/III). The spirometry for grading and reversibility testing of the COPD patients was always performed at least 6 h after the last ipratropiumbromide/fenoterol inhalation. Only patients with an improvement of FEV₁ ≤ 0.3 l after 2 puffs of ipratropiumbromide/fenoterol, who had given written informed consent, were included in the study. Major exclusion criteria were: relevant cardiac diseases, pneumonia, active pulmonary tuberculosis, cystic fibrosis, bronchiectasis, lung cancer, asthma, infiltrates or other abnormalities of the lungs, COPD-IV, acute exacerbation within the last 4 weeks, known concomitant bacterial infection or respiratory tract infections (RTI), AIDS; concomitant medication with beta-blockers, ACE-inhibitors, regular inhalative glucocorticoids (except COPD-III) or oral glucocorticosteroids (except during an exacerbation), anticholinergics (except ipratropiumbromide in Berodual[®]N), or β -2-agonists other than salmeterol or fenoterol in Berodual[®]N, analgesics except paracetamol, mucolytics and antitussives other than dextrometorphan/bromhexine/ammonium chloride (Zedex[®]), immunomodulators (e.g., bacterial vaccines), or coumarin-derivatives; known alcohol or drug abuse; tendency to bleed, gastrointestinal disorders, severe heart, renal or liver diseases and/or immunosuppression; known

^e EPs[®] 7630 is the active ingredient of the product Umckaloabo[®] (ISO Arzneimittel, Ettlingen, Germany).

hypersensitivity to *Pelargonium sidoides*; pregnancy/lactation; simultaneous participation in another clinical trial.

Study design

This randomised, double-blind, placebo-controlled clinical trial with two parallel treatment groups was conducted in Ukraine in 18 centres situated in the regions of Kiev and Lugansk between March 2006 and June 2008. The study was performed according to Good Clinical Practice, the Declaration of Helsinki and legal regulations. Ethics committee and regulatory authority approvals were obtained before study commencement.

Interventions

The study comprised patient screening prior to enrolment and a 24-week double-blind treatment period including seven regular visits (day 0, weeks 4, 8, 12, 16, 20 and 24 with a window of ± 5 days) and intermediary visits in case of an exacerbation. After obtaining written informed consent, baseline assessments (demographic data, physical examinations, laboratory tests, chest X-ray, bronchitis symptom score of cough, sputum and sternal pain, and spirometry tests to determine FEV₁ and FVC before and after ipratropiumbromide/fenoterol) were performed. Ipratropiumbromide/fenoterol had to be used as a substitute for salbutamol in bronchoreversibility tests, because the latter was not available in the Ukraine at the time of study conduct. Eligible patients were then assigned randomly to EPs 7630 or placebo in a double-blind manner. Randomisation was carried out in balanced blocks using the validated random number generator RCODE in the biometrical department of Schwabe Pharmaceuticals by a person not involved in the clinical conduct of the study. Study medication was numbered according to a randomisation list and patients received the medication labelled with their medication number in the order of inclusion into the study by a pharmacist. The assigned study medication was dispensed prospectively at enrolment to enable self-initiation of therapy by the patient. The investigators received sealed emergency envelopes for individual patients, all of which were returned unopened after completion of the trial.

According to GOLD,¹ inhalative baseline-treatment for COPD-II included salmeterol (Serevent[®]) regularly and ipratropiumbromide/fenoterol (Berodual[®]N) as needed and for COPD-III salmeterol and budesonide (Budesonid[®]) regularly and Berodual[®]N as needed. In case of exacerbations additional oral prednisolone (Prednisolon[®]) and augmentin (Augmentan[®]) or ofloxacin (Ofloxacin[®]) were prescribed by the investigator.

As add-on therapy, patients were randomly given either active trial medication containing EPs 7630, a herbal drug preparation from the roots of *Pelargonium sidoides* (1:8–10), extraction solvent: ethanol 11% (w/w), or matched placebo. Dosing of the study medication was 3 × 30 drops/d EPs 7630 or placebo for 24 weeks. Compliance was documented by measuring the returned trial medication using a measuring template. The patients were asked to document chronic bronchitis symptoms, health status, and consumption of

allowed concomitant and study medication in a diary on a daily basis during the whole study period. FVC and FEV₁ were measured²⁰ at each visit using a MicroDL spirometer (Micro Medical Ltd., Rochester, England). Predicted FEV₁ values were calculated²¹ with reference equations. Spirometry pre- and post-bronchodilator (two puffs of ipratropiumbromide/fenoterol) was performed (at least three acceptable manoeuvres, the highest value being documented).

Sample size calculation

Due to the lack of empirical data in the indication under investigation, there was some uncertainty concerning the treatment effect and the overall time course to be expected for the primary outcome variable "time to first acute exacerbation". Consequently, the assumptions to be made for sample size calculation were debatable and it was doubtful whether the desired power could actually be achieved in a fixed sample size design. Therefore, the study was planned and performed with an adaptive interim analysis.²² For sample size calculation the following assumptions were stated a priori: If the rate of first exacerbation of COPD is 0.25 in the active treatment group and 0.50 in the placebo group, the power for early rejection of H₀ in the interim analysis at $\alpha_1 = 0.0115$ with the one-sided log-rank test is 90% for $n = 204$ patients. Thus a sample size of 2 × 100 patients should provide sufficient power to already achieve the study aim in the first stage of the trial if the assumptions specified above are correct.

Outcomes

The primary efficacy variable was time to first exacerbation of COPD. Since it is estimated that only 50% of all exacerbations are reported to physicians²³ and since there is no standardised and unanimously accepted definition of exacerbation of COPD,²⁴ time of first exacerbation was derived either from reported or unreported exacerbation. Reported exacerbations were defined as a COPD deterioration due to a subjective increase in one or more chronic symptoms over baseline, e.g. increased sputum production, sputum purulence and/or dyspnoea, which requires an extra visit to the investigator and may warrant a change in regular therapy, e.g. treatment with systemic steroids and/or antibiotics (date of extra-visit, documented by the investigator in the case record form; i.e. moderate exacerbation). Unreported exacerbations were derived from the patient's diary and defined as an increased use of at least twofold mean dose of ipratropiumbromide/fenoterol on at least five consecutive days caused by an increase in respiratory symptoms over baseline that required change in therapy, but which could be self-managed by the patient²³ (date of first increase, documented by the patient in the diary; i.e. mild exacerbation). This definition of exacerbations also complies with the proposed definition that an exacerbation of COPD would be an increase in respiratory symptoms over baseline that usually requires change in therapy.²⁴ An acute exacerbation (moderate or mild) was considered as subsided if the total score of the symptoms cough, sputum production, and sternal pain documented by the patient in his patient's diary decreased to baseline (defined as the mean of total score of these

symptoms documented in the patient's diary during the last five days prior to onset of the current acute exacerbation). In some patients, an exacerbation was not associated with an increase in the total score mentioned above. In this case, the episode was considered as subsided when the mean dose of ipratropiumbromide/fenoterol on five consecutive days during the exacerbation was equal or less the mean dose of the five days prior to the exacerbation.

Secondary efficacy variables were: Number and duration of exacerbations during treatment, health status (validated, disease-specific St. George's Respiratory Questionnaire (SGRQ)²⁵), patient satisfaction with treatment (Integrative Medicine Patient Satisfaction Scale (IMPSS), a 5-point verbal rating scale: 1 = "very satisfied", 2 = "satisfied", 3 = "neutral", 4 = "dissatisfied", 5 = "very dissatisfied") and duration of inability to work. Safety parameters comprised surveillance of adverse events (AEs), laboratory safety parameters, and sputum examination.

Analysis

Each patient's allocation to the different analysis populations (full analysis set (FAS) according to the intention-to-treat (ITT) principle, per protocol (PP) set, safety analysis set) was defined prior to unblinding. The following type I error rates and decision boundaries for the interim analysis were specified: Global one-sided type I error rate $\alpha = 0.025$; boundary for the one-sided p -value for accepting the null-hypothesis within the interim analysis $\alpha_0 = 0.40$; one-sided local type I error rate for rejecting the null-hypothesis within the interim analysis $\alpha_1 = 0.0115$. The trial could be continued if the p -value of the interim analysis fell between 0.0115 and 0.40. In this case, the boundary for rejection of the null-hypothesis after the second part for the product of p -values of both stages was $c_\alpha = 0.0038$.²⁶ Within the pre-specified confirmatory analysis the null-hypothesis of equal survival curves was tested with the one-sided centre-stratified log-rank test. If a patient did not suffer an exacerbation during follow-up or was previously lost to follow-up, data were treated as censored. The corresponding two-sided confidence interval was calculated. The Kaplan–Meier method²² was used to estimate the survival functions, i.e. the probability of suffering no exacerbation until a certain day during the study period. Regarding the secondary efficacy variables, descriptive statistical methods were used for the comparison of both treatment groups and the resulting p -values were interpreted accordingly. After baseline, missing values for efficacy variables were replaced applying the last observation carried forward (LOCF) method unless stated otherwise.

Results

Study population

The patients were recruited from March through June 2006. Of the 211 patients enrolled for screening, 200 were subsequently randomised and allocated to receive either EPs 7630 (99 patients) or matching placebo (101 patients). Eleven patients did not fulfil the inclusion and/or exclusion criteria, 6 out of them due to asthma. One patient in the EPs 7630

group could not be analysed for efficacy due to early drop-out (lost to follow-up at baseline). Thus, the ITT population comprised 199 patients (EPs 7630: 98; placebo: 101) (Fig. 1). All patients were included in the safety analysis. The evaluation of demographic data and other baseline characteristics revealed no noticeable differences between both treatment groups (Table 1). All patients had been treated previously with cough and cold preparations, antibacterials for systemic use (EPs 7630: 94.9%; placebo: 98.0%), drugs for obstructive airway diseases (EPs 7630: 94.9%; placebo: 95.1%), analgesics (EPs 7630: 60.2%; placebo: 57.4%) and nasal preparations (EPs 7630: 49.0%; placebo: 56.4%) being the most frequently documented pre-study medication. The most frequently documented intake of concomitant medication for COPD according to GOLD was also comparable between both groups (data not shown). The mean duration of treatment was about 168 days (planned treatment duration 168 days) and compliance was nearly 100% in both groups.

Primary efficacy variable

The median time to first exacerbation was 57 days in the EPs 7630 and 43 days in the placebo group (Kaplan–Maier estimate; mild and moderate exacerbations). The probability of remaining free of exacerbations was significantly higher for the EPs 7630 group during the whole study period, i.e. fewer patients suffered from exacerbations compared to placebo and the time to first exacerbation was prolonged ($p = 0.005$, one-sided centre-stratified log-rank test) (Fig. 2a). Confirmatory analysis revealed a statistically significant advantage of EPs 7630 and therefore the null-hypothesis of equal survival curves could be rejected within the interim analysis which is therefore identical with the final analysis presented in this publication. There was also a statistically significant advantage of EPs 7630 with respect to moderate exacerbations which was even more pronounced ($p < 0.0001$), whereas the difference for mild exacerbations was not significantly different between both groups ($p = 0.0949$) (Fig. 2b and c). Similar survival curves with a significant difference between the two treatment groups were also revealed by subgroup analysis of moderate exacerbations in COPD II patients, smokers, ex-smokers and never-smokers, males and females. These data, together with the corresponding FEV₁ value at baseline and the consumption of ipratropiumbromide/fenoterol during the study, are shown in Table 2.

Secondary efficacy variables

The mean number \pm SD of moderate and mild exacerbations (moderate only/mild only) during treatment was 1.80 ± 1.64 ($0.38 \pm 0.53/1.69 \pm 1.66$) with EPs 7630 compared to 2.20 ± 1.59 ($0.86 \pm 0.68/1.94 \pm 1.67$) with placebo ($p = 0.08$ ($p < 0.001/p = 0.298$), two-sided t -test). For EPs 7630 patients, the median duration of moderate exacerbations was about one day shorter (11 versus 12 days; $p = 0.102$, two-sided t -test). In the EPs 7630 group, 37/98 (37.8%) patients needed antibiotic treatment with augmentin or ofloxacin during exacerbations compared to 74/101 (73.3%) of placebo patients ($p < 0.0001$, two-sided χ^2 -test), with a shorter mean duration of treatment (8 versus 9.8 days, $p = 0.0466$, two-

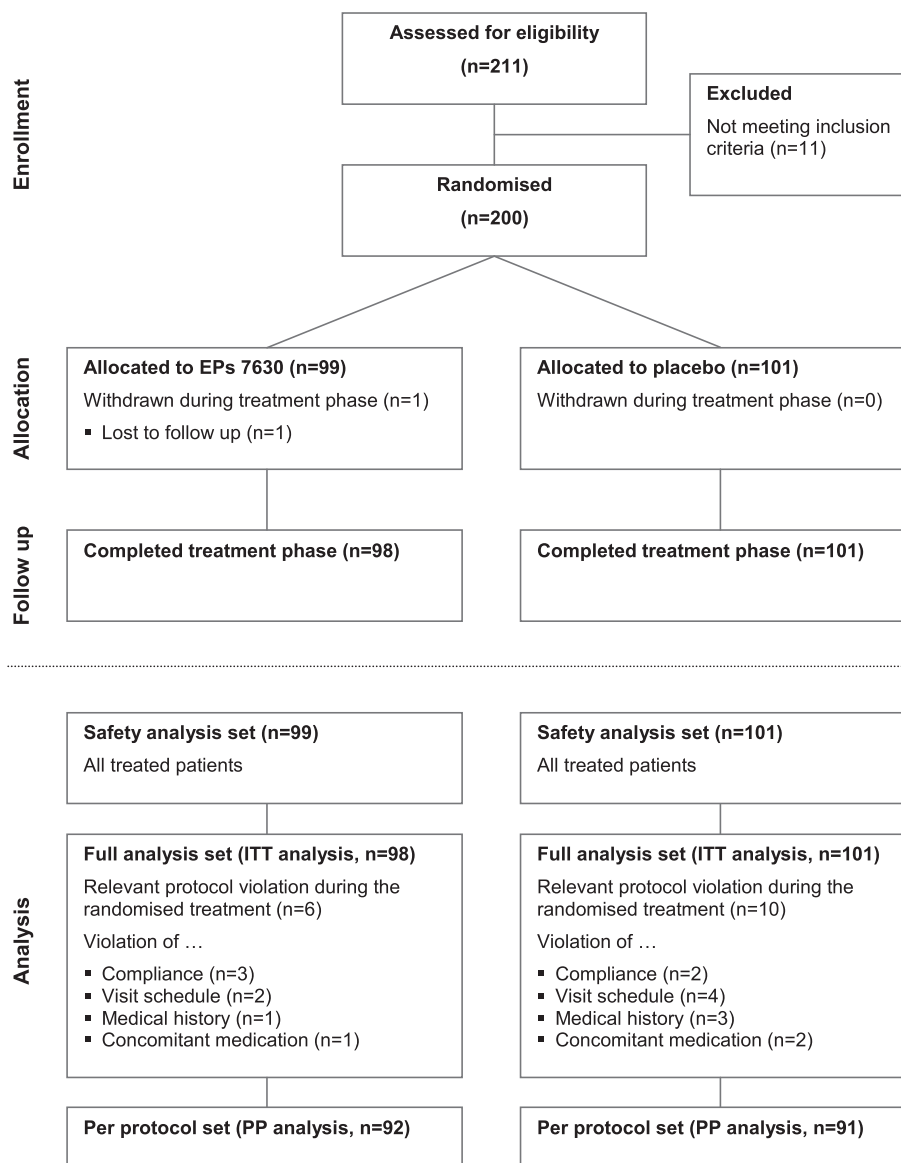


Figure 1 Flow diagram: disposition of patients and analysis sets.

sided *t*-test). The mean decrease from baseline to week 24 in the total SGRQ score was 12.7 ± 10.7 for EPs 7630 and 7.0 ± 11.5 points for placebo, respectively ($p < 0.01$, two-sided *t*-test) (Fig. 3). After 24 weeks, patient satisfaction with treatment was significantly higher with EPs 7630 compared to placebo ($p < 0.0001$, two-sided Mantel–Haenszel χ^2 -test) (Fig. 4). The mean number of days off work during an exacerbation (mild and moderate) was 1.97 ± 3.2 with EPs 7630 and 4.08 ± 6.1 with placebo ($p = 0.004$, two-sided *t*-test), and the total number within the 24-week study period was 2.96 ± 4.7 and 7.17 ± 8.1 days, respectively ($p < 0.001$, two-sided *t*-test) (Fig. 5).

Safety analysis

During the treatment period, 51/99 (51.5%) patients treated with EPs 7630 suffered from 79 adverse events (AEs) compared to 40/100 (40.0%) patients with 46 AEs in the placebo group, most of which were mild in intensity.

None of the AEs were classified as serious. A causal relationship of AEs with the study medication could not be excluded for 18 patients but was assessed as unlikely. The total number of days of exposure to study medication reached 16,563 days for EPs 7630 and 16,998 days for placebo resulting in an incidence of suspected adverse drug reactions (events/day of exposure) of 0.001 and <0.001 , respectively. All other AEs were considered as “unrelated” to study medication. According to the system organ classification, “gastrointestinal disorders” (EPs 7630: 16.2%/placebo: 6.9%) was the most frequently reported system organ class for which a causal relationship could not be excluded.

Clinical laboratory parameters showed no relevant group differences between baseline and treatment termination. The percentage of patients with sputum present was also comparable between both groups throughout the study (EPs 7630: 79.8% at baseline and 69.7% at week 24; placebo: 75.3% at baseline and 76.2% at week 24).

Table 1 Demographic, clinical and physiological data at baseline (ITT population, $n = 199$) (number (%) or mean \pm standard deviation).^a

Demographic characteristics	EPs 7630 ($n = 98$)	Placebo ($n = 101$)
Sex		
male	46 (46.9%)	42 (41.6%)
female	52 (53.1%)	59 (58.4%)
Age (years)	51.9 \pm 9.8	50.3 \pm 12.1
Height (cm)	168.6 \pm 8.7	169.4 \pm 8.2
Weight (kg)	79.5 \pm 12.9	77.7 \pm 15.1
Body mass index (kg/m ²)	28.0 \pm 4.3	27.1 \pm 4.9
Number of exacerbations during the past 12 months		
3 exacerbations	82 (83.7%)	90 (89.1%)
4 exacerbations	16 (16.3%)	11 (10.9%)
Smoker status		
Current smoker	44 (44.9%)	42 (41.6%)
Pack year calculation	17.5	14.8
Ex-smoker	13 (13.3%)	21 (20.8%)
Pack year calculation	18.0	15.6
Never-Smoker	41 (41.8%)	38 (37.6%)
Total number of patients with comorbidities	75 (76.5%)	80 (79.2%)
Main comorbidities according to system organ classes		
Cardiac disorders	10 (10.2%)	15 (14.9%)
Gastrointestinal disorders	25 (25.5%)	23 (22.8%)
Hepatobiliary disorders	27 (27.6%)	28 (27.7%)
Metabolism and nutrition disorders	14 (14.3%)	12 (11.9%)
Musculoskeletal and connective tissue disorders	18 (18.4%)	14 (13.9%)
Vascular disorders	24 (24.5%)	23 (22.8%)
Score of cough, sputum production and sternal pain	5.59 \pm 1.21	5.72 \pm 1.32
Spirometry at baseline before and after ipratropiumbromide/fenoterol		
FEV ₁ predicted (%)	before	60.92 \pm 12.04
	after	59.76 \pm 11.87
FEV ₁ (l)	before	63.81 \pm 13.01
	after	62.83 \pm 12.69
FVC (l)	before	1.95 \pm 0.56
	after	1.93 \pm 0.52
	before	2.04 \pm 0.58
	after	2.03 \pm 0.55
	before	2.57 \pm 0.80
	after	2.57 \pm 0.69
	before	2.66 \pm 0.79
	after	2.67 \pm 0.73

FEV₁ = Forced Expiratory Volume during one second; FVC = forced vital capacity.

^a Statistical testing revealed no descriptively significant difference at baseline.

Discussion

This study was designed to evaluate the effect of EPs 7630 as add-on therapy to a standardised baseline-treatment in patients with moderate to severe COPD. As it is recommended that pharmacological trials in COPD should last at least three and ideally six months in order to look at clinically meaningful outcomes in COPD,²⁷ treatment duration in this study was 24 weeks. COPD patients with frequent exacerbations in the past have a larger probability of suffering frequent COPD exacerbations in the future.²⁴ Therefore, in order to allow reliable detection of a possible effect on the time to first exacerbation and exacerbation frequency during the study period, only patients with at least 3 exacerbations during the past 12 months were allowed to enter the study. Due to the short recruitment duration of only 4 months and due to the block randomisation used in the trial, the study participants are considered to be comparable concerning any seasonal impact.

The comparably low age of COPD patients seen in this study is in line with results from other recently published Ukrainian trials.^{28,29} This supports the results of a systemic review and meta-analysis of studies carried out in 28 countries between 1990 and 2004 which show that the prevalence of COPD is already higher in patients over 40 years of age.³

The results of the presented trial show statistically significant superiority of EPs 7630 compared to placebo in the confirmatory analysis for the primary efficacy variable "time to first acute exacerbation", which was significantly prolonged in EPs 7630-treated patients ($p = 0.005$, one-sided centre-stratified log-rank test) – especially in acute exacerbations which led to an extra visit by the patient (moderate exacerbations, $p < 0.0001$). In mild exacerbations derived from the patient's diary on the basis of a twofold increase in ipratropiumbromide/fenoterol consumption on at least 5 days, this difference was not significant. This finding is in line with the fact that ascertainment using less specific healthcare utilisation data such as a change in

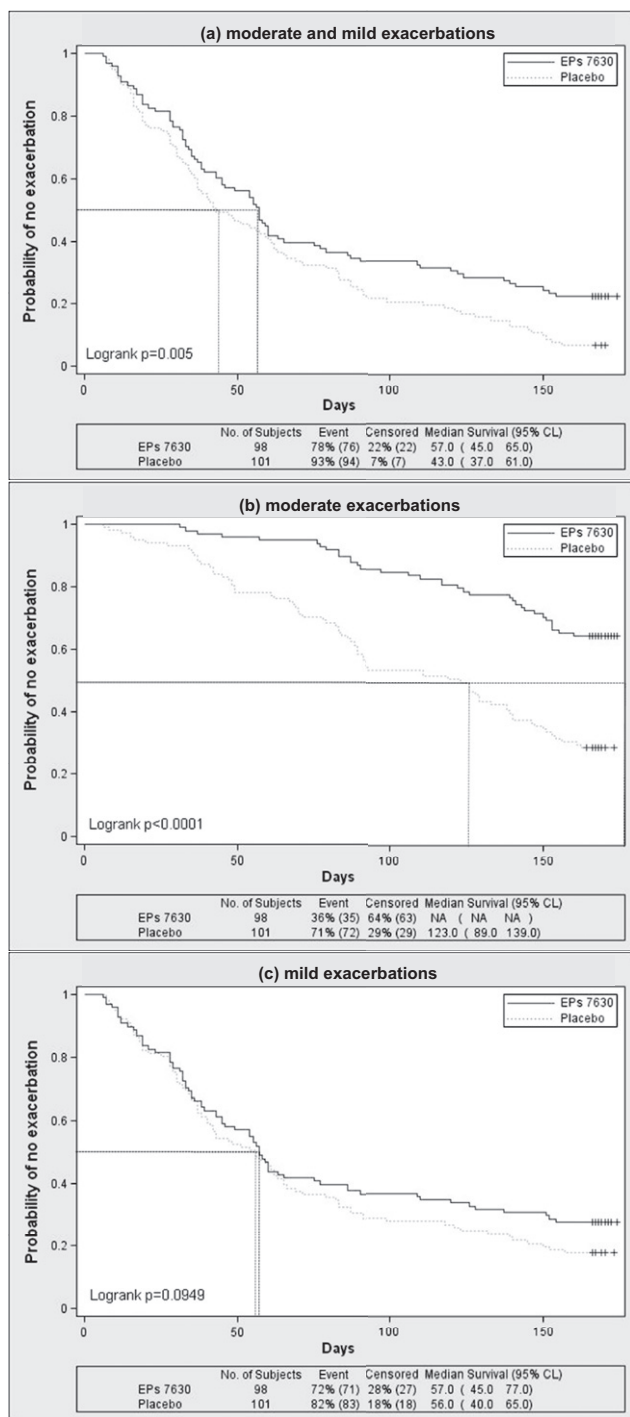


Figure 2 Survival function estimates. (a) Moderate and mild exacerbations, (b) moderate exacerbations only, (c) mild exacerbations only. *p*-values of the one-sided centre-stratified log-rank test.

regular medication is considered to be less satisfactory and that the onset of an exacerbation could be better defined from the date of first healthcare contact.³⁰

Subgroup analyses of the time to first moderate exacerbations revealed a significant superiority of EPs 7630 compared to placebo for both genders, patients in COPD stage II, and for every smoker status. For the subgroup of

smokers, the time to first moderate and mild exacerbations was significantly longer in the EPs 7630 group compared to placebo. For COPD III patients, the survival curve of EPs 7630 was above that of placebo, but the difference did not reach significance due to the small patient number in this subgroup. Although cigarette smoking is still the most commonly encountered risk factor, there is consistent evidence from published studies that non-smokers may also develop COPD due to exposure to indoor and outdoor air pollution, workplace exposure to dust, fumes or chemicals, passive smoking, history of repeated lower respiratory-tract infections during childhood, history of pulmonary tuberculosis, chronic asthma, intrauterine growth retardation, poor nourishment, and poor socioeconomic status.^{4–7,31} In this study, about one third of participants were non-smokers and the average pack-years were only 15–18. This is consistent to the results of a review published recently, which show that the proportion of non-smoking COPD patients worldwide is much higher than previously believed in both developed and developing countries, amounting to up to 35–50% in recent studies.³¹ There was a comparable but slightly higher percentage of women in both groups. As shown by the results of the performed subgroup analysis according to gender, this did not affect the study outcome of this trial, although there was a larger proportion of non-smokers among the female population. The high percentage of non-smoking women in this study is not surprising as, in Ukraine, about three-quarters of women are non-smokers while a percentage of household cooking with solid fuel of up to 75% was reported.³² Indoor pollution from biomass cooking and heating in poorly ventilated dwellings is an important risk factor for COPD, especially among women in developing countries.^{31,33}

Significant differences in favour of EPs 7630 were also shown for secondary parameters, e.g., reduction in exacerbation frequency, less consumption of antibiotics, improved quality of life, higher patient satisfaction with treatment and less days of inability to work. COPD patients develop significant disability during progressive disease, and respiratory disease-specific questionnaires, such as the SGRQ, provide sensitive measurements of disturbance in daily life and well-being. Effects on health status are therefore a useful outcome measure in COPD and a reduction in exacerbation frequency and less need for antibiotics as shown in this study would be expected to result in improved well-being.²³

This also holds true for our study in which EPs 7630-treated patients showed a consistent, statistically significant and clinically meaningful improvement in health status and fewer days off work. In the EPs 7630 group, the mean number of moderate exacerbations calculated for one year was about one exacerbation less compared to placebo. This difference corresponds to the suggested minimal clinically important difference (MCID) of exacerbation frequency in COPD.³⁴

Looking at SGRQ score results, the placebo response rate seen in our study might appear to be surprisingly high. Nevertheless, a comparable placebo response rate was seen in a 9-month, randomised, double-blind, multicenter study comparing the effect of tiotropium and placebo in 554 patients with moderate to severe COPD: for the subgroup of patients with comparable FEV₁ values as measured

Table 2 Two-sided *p*-values of the log-rank test for moderate exacerbations of different subgroups, mean FEV₁ predicted at baseline before/after reversibility test and mean daily puffs of inhalative ipratropiumbromide/fenoterol (ITB/Fen) during the study.

	EPs 7630 (<i>n</i> = 98)	Placebo (<i>n</i> = 101)	<i>p</i> -value (log-rank test, two-sided)
COPD II			<i>p</i> < 0.0001
Number of patients	79 (80.6%)	78 (77.2%)	
FEV ₁ predicted (%) at baseline			
before ITB/Fen	65.5 ± 8.1	64.8 ± 8.1	
after ITB/Fen	68.4 ± 9.4	67.9 ± 9.1	
ITB/Fen (mean daily inhaled puffs ± SD)	0.98 ± 0.76	1.02 ± 0.72	
COPD III			<i>p</i> = 0.2426
Number of patients	19 (19.4%)	23 (22.8%)	
FEV ₁ predicted (%) at baseline			
before ITB/Fen	41.9 ± 5.1	42.8 ± 4.9	
after ITB/Fen	44.8 ± 7.7	45.6 ± 6.1	
ITB/Fen (mean daily inhaled puffs ± SD)	1.98 ± 1.18	1.91 ± 1.15	
Smokers			<i>p</i> = 0.0016
Number of patients			
male	30 (65.2%)	25 (59.5%)	
female	14 (26.9%)	17 (28.8%)	
FEV ₁ predicted (%) at baseline			
before ITB/Fen	63.4 ± 12.2	60.7 ± 10.3	
after ITB/Fen	66.6 ± 12.6	63.9 ± 10.7	
ITB/Fen (mean daily inhaled puffs ± SD)	1.12 ± 0.99	1.18 ± 0.93	
Ex-Smokers			<i>p</i> = 0.0127
Number of patients			
male	8 (17.4%)	11 (26.2%)	
female	5 (9.6%)	10 (17.0%)	
FEV ₁ predicted (%) at baseline			
before ITB/Fen	55.0 ± 10.7	58.8 ± 16.6	
after ITB/Fen	57.5 ± 11.7	62.1 ± 16.6	
ITB/Fen (mean daily inhaled puffs ± SD)	2.02 ± 1.03	1.32 ± 1.00	
Never-Smokers			<i>p</i> = 0.003
Number of patients			
male	8 (17.4%)	6 (14.3%)	
female	33 (63.5%)	32 (54.2%)	
FEV ₁ predicted (%) at baseline			
before ITB/Fen	60.1 ± 11.8	59.3 ± 10.6	
after ITB/Fen	62.8 ± 13.3	62.1 ± 12.6	
ITB/Fen (mean daily inhaled puffs ± SD)	0.97 ± 0.69	1.21 ± 0.86	
Male			<i>p</i> < 0.0001
Number of patients	46 (46.5%)	42 (41.6%)	
FEV ₁ predicted (%) at baseline			
before ITB/Fen	58.5 ± 12.9	56.3 ± 13.3	
after ITB/Fen	60.6 ± 13.5	59.5 ± 13.7	
ITB/Fen (mean daily inhaled puffs ± SD)	1.33 ± 1.03	1.46 ± 1.02	
Female			<i>p</i> < 0.0001
Number of patients	52 (52.5%)	59 (58.4%)	
FEV ₁ predicted (%) at baseline			
before ITB/Fen	63.0 ± 10.9	62.2 ± 10.2	
after ITB/Fen	66.7 ± 11.9	65.2 ± 11.5	
ITB/Fen (mean daily inhaled puffs ± SD)	1.04 ± 0.83	1.05 ± 0.80	

Values of FEV₁ predicted are given as mean ± SD.

in our study (baseline FEV₁ > 50% predicted), an improvement of -7.38 ± 1.44 points under placebo was reported.³⁵

In our study, the difference in the mean decrease of the SGRQ total score from baseline to week 24 was 5.7 points

higher in the EPs 7630 group as compared to placebo and therefore above the suggested MCID of 4 points for this measure.³⁶ When considering the fact that all patients of our own trial received baseline-treatment for COPD

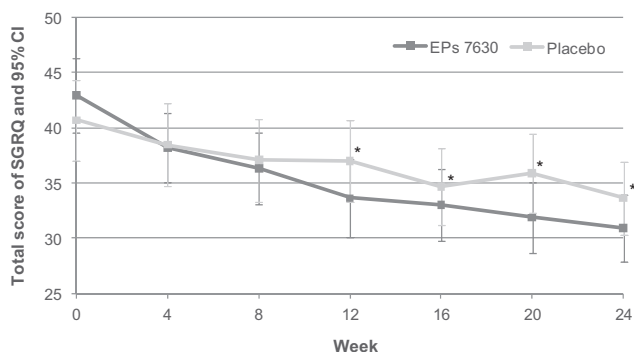


Figure 3 Health impairment according to the St. George's respiratory questionnaire (SGRQ) during treatment phase (p -value of two-sided t -test <0.01 , between-group comparison for difference to baseline).

according to GOLD and that the documented intake of concomitant medication was comparable between both groups, the advantage as shown for EPs 7630 compared to placebo appears to be even more impressive.

The efficacy and safety of EPs 7630 in patients suffering from RTI – like acute bronchitis, rhinosinusitis and common cold – with a significantly faster reduction in disease-specific symptoms like coughing, sputum production and dyspnoea have already been shown.^{16,17,37–40} Whether the overall benefit of EPs 7630 treatment in COPD – a multi-component disease, associated with inflammation, airway obstruction, mucociliary dysfunction and structural changes in the lung – is solely attributable to the antimicrobial effects and notable immune-modulatory capabilities shown for EPs 7630 and its isolated constituents in in-vitro studies^{10–15} has yet to be determined. However, the analysis showed consistently greater efficacy of EPs 7630 compared to placebo when added to basic COPD therapy.

In conclusion, the results of this study with EPs 7630 demonstrate a statistically significant and clinically relevant superiority over placebo in the add-on treatment of patients with moderate to severe COPD, which was shown in prolongation of time to first exacerbation and by reducing exacerbation frequency and antibiotic use. EPs

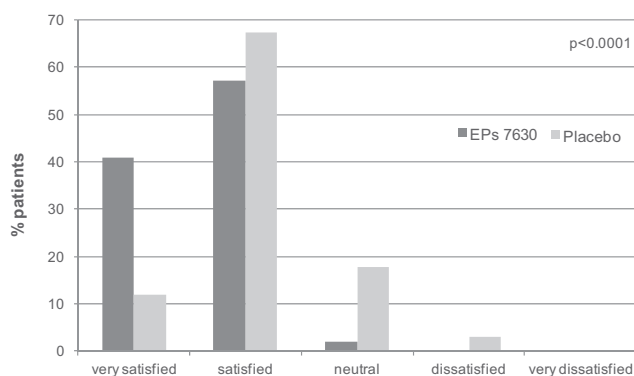


Figure 4 Patient satisfaction with treatment (IMPSS). Relative frequencies of the categories at week 24 and p -value of two-sided Mantel–Haenszel χ^2 -test.

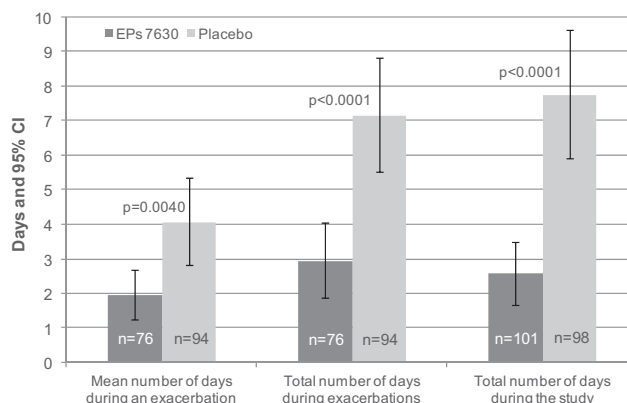


Figure 5 Mean duration (days) of inability to work during an exacerbation, total number of days with inability to work during exacerbations and during the 24-week study period.

7630 presented a good long-term safety profile. Further clinical studies are warranted to determine the therapeutic value of this new controller drug in COPD therapy.

Acknowledgements

We thank all physicians at the participating Ukrainian centres: Dr. E. V. Babakova, Kiev Clinical Hospital No. 2, Kiev; Dr. N. I. Bazaleeva, Faculty of Internal Medicine, Lugansk State Medical University, Lugansk; Dr. L. M. Bibik, Central Polyclinic of Desnianskiy region, Kiev; Dr. E. P. Chaykina, Faculty of Internal Medicine, Lugansk State Medical University, Lugansk; Dr. I. I. Dayniak, Central Polyclinic of Darnitskiy region, Kiev; Dr. O. A. Gubanova, Central Polyclinic of Desnianskiy region, Kiev; Dr. S. A. Hylko, Central Polyclinic of Darnitskiy region, Kiev; Prof. Dr. L. N. Ivanova, Lugansk State Medical University, Lugansk; Dr. L. E. Kirilchuk, Central Polyclinic of Desnianskiy region, Kiev; Dr. V. Krivoruchek, Polyclinic No. 1 of Desnianskiy region, Kiev; Dr. N. S. Kutsalo, Polyclinic No. 1 of Desnianskiy region, Kiev; Dr. J. E. Lyalyukhina, Central Polyclinic of Darnitskiy region, Kiev; Dr. E. V. Pileva, Faculty of Internal Medicine, Lugansk State Medical University, Lugansk; Dr. N. B. Sigov, City Clinical Hospital No. 9 of Lugansk, Lugansk; Dr. A. V. Sigova, Faculty of Internal Medicine, Lugansk State Medical University, Lugansk; Dr. T. V. Sysoykina, Faculty of Internal Medicine, Lugansk State Medical University, Lugansk; Dr. O. G. Timoshenko, Polyclinic No. 1 of Desnianskiy region, Kiev.

We also thank all the patients, nurses and clinical research associates who collaborated in this study and Dr. Elfi Schachner-Wünschmann for medical writing and editing services. The study and medical writing services were funded and study medication was provided by Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany.

Conflict of interest

HM was a scientific advisor to the study and made substantial contributions to conception and design of the study, interpretation of data and revision of the article.

DAP was the principal investigator of the study and made substantial contributions to acquisition of data, reviewing of the report and revision of the article. OMB was a co-investigator of the study and made substantial contributions to acquisition of data, reviewing of the report and revision of the article. FAM was the project leader of the study and made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and revision of the article. MK was the responsible biometrician of the sponsor and made substantial contributions to conception and design of the study, interpretation of data and revision of the article. MT was the responsible biometrician of the sponsor and made substantial contributions to interpretation of data and revision of the article. The corresponding author had full access to all the data and final responsibility for the decision to submit for publication. All authors gave their final approval to the version to be published.

Prof. Matthys has received honoraria from Dr. Willmar Schwabe GmbH & Co. KG; Dr. Pliskevich has no conflict of interest to disclose. Dr. Bondarchuk has no conflict of interest to disclose. Dr. Malek is an employee of Dr. Willmar Schwabe GmbH & Co. KG; Mr. Tribanek was an employee of Dr. Willmar Schwabe GmbH & Co. KG from 2006 until 2010; Prof. Kieser was an employee of Dr. Willmar Schwabe GmbH & Co. KG from 1992 until 2007.

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