

Efficacy and safety of an extract of *Pelargonium sidoides* (EPs 7630) in adults with acute bronchitis

A randomised, double-blind, placebo-controlled trial

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Summary

Background: New evidence-based treatment options are required to avoid antibiotic overuse in acute bronchitis and to replace potentially inefficacious initial antibiotic treatment.

Objective: To evaluate the efficacy and safety of an extract of *Pelargonium sidoides* (EPs 7630) compared to placebo in patients with acute bronchitis.

Design: Randomized, double-blind, placebo-controlled trial using a multi-stage adaptive design.

Setting: 36 primary care physicians (investigators) at the out-patient care setting.

Patients: 468 adults with acute bronchitis present 48 hours, Bronchitis Severity Score (BSS) 5 points, and informed consent.

Intervention: EPs 7630 or placebo (30 drops three times daily) for 7 days.

Measurement: The primary outcome criterion was the change of BSS on day 7.

Results: The decrease of BSS from baseline to day 7 was 5.9 ± 2.9 points under EPs 7630 ($n = 233$), and 3.2 ± 4.1 points under placebo ($n = 235$). The 95% CI for the difference of effects between the two treatment groups (EPs 7630 minus placebo) was calculated as $[-3.359; -2.060]$ showing a significant superiority of EPs 7630 compared to placebo on day 7 ($p < 0.0001$). Working inability decreased to 16% in the EPs 7630 group compared to 43% in the placebo group ($p < 0.0001$). In addition, the duration of illness was significantly shorter for patients treated with EPs 7630 compared to placebo ($p < 0.001$). Within the first four days, onset of treatment effect was recognized in 53.6% of patients under EPs 7630 compared to 36.2% of patients under placebo, only ($p < 0.0001$). Adverse events (AEs) occurred in 36/468 patients (EPs 7630: 20/233 patients, placebo: 16/235 patients). All events were assessed as non-serious.

Conclusion: EPs 7630 was superior in efficacy compared to placebo in the treatment of adults with acute bronchitis. Treatment with EPs 7630 clearly reduced the severity of symptoms and shortened the duration of working inability for nearly 2 days.

Key words: Acute bronchitis, randomized controlled trial, double-blind, placebo-controlled clinical trial, herbal medicine, extract of *Pelargonium sidoides*, EPs 7630

Abbreviations: AE – Adverse Event; BSS – Bronchitis Severity Score; ENT – Ear, Nose and Throat; CI – Confidence Interval

■ Introduction

Acute bronchitis is one of the most frequent infections encountered in general practice and takes a top place under the notifications of days-off work (Badura et al. 2000; Gonzales and Sande, 2000). It is predominantly caused by a viral infection with RNA-viruses, particularly the Respiratory Syncytial Virus (RSV), followed by coxsackie's-, influenza-, parainfluenza-, ECHO-viruses or adenoviruses. Therefore, treatment of acute bronchitis is symptomatically orientated. In practice, however, acute bronchitis is treated in up to 70% of cases primarily with antibiotics, although it has been proved that thereby the duration of the disease is not substantially shortened (Altiner and Abholz, 2001; Fahey and Howie, 2001; Murray et al. 2000; Bent et al. 1999). The risks of initial antibiotic treatment are gastrointestinal disorders, allergic reactions, development of resistant germs leading to a longer duration of treatment and increase of relapses. Therefore, medical associations recommend to inform patients with acute bronchitis accordingly and to prescribe primarily symptomatic treatment, only (Arzneimittelkommission der Deutschen Ärzteschaft, 2002). For physicians and patients therefore the question arises, which drugs are likely to improve or eliminate the patients' complaints without causing serious side effects. In great demand are herbal medicines whose efficacy and safety have been proven by pharmacological and clinical studies. Herbal medicines are not inherently safe (Ernst, 1998; Barrett et al. 1999), but there are medications that have been used successfully over decades for respiratory tract infections (Smith and Feldman, 1993) and are known for their excellent tolerability. The increasing interest in herbal medicines by patients and physicians in the US (Eisenberg et al. 1998) and in Europe, e.g., The Netherlands and Germany (Melchart et al. 2001), requires more clinical research into their efficacy and safety according to the state of the art.

An extract of *Pelargonium sidoides* roots, referred to as EPs 7630, is a popular plant extract used in Germany, in the Commonwealth of Independent States (CIS), in Baltic states, and in Mexico for the treatment of ENT- and respiratory tract infections. The mechanism of action of EPs 7630 is only partially understood. The clinical efficacy is supposed to be caused by antimicrobial (Kayser and Kolodziej, 1997) and immunomodulatory (Kayser et al. 2001; Koch et al. 2002) properties. Antimicrobial and immune-modulatory effects have been demonstrated for tannins (e.g. catechin, gallic acid), the principal constituents of EPs 7630, and for coumarines (e.g., umckalin). The immune-modulatory activities are mediated mainly by the release of tumour necrosis factor (TNF- α) and nitric oxides (iNO), the stimulation of interferon β (INF-

β) and the increase of natural killer cells (NK) activity (Koch et al. 2002). The present clinical trial was designed to evaluate the efficacy and safety of EPs 7630 compared to placebo in patients with acute bronchitis.

■ Methods

The trial adhered to the Declaration of Helsinki 1964, the Revisions of Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset-West 1996, and Edinburgh 2000, and the Guideline for Good Clinical Practice 1997 (CPMP/ICH/135/95) as well as the regulations of the current drug law.

Participants

After approval by the Ethics Committee in December 1999, the screening of patients who sought treatment for acute bronchitis at the study sites started in May 2000. Symptoms typical for acute bronchitis, medical and ENT history, and clinical findings including laboratory results (leukocytes, erythrocyte sedimentation test, γ -GT, GOT, GPT, Quick's test, PTT) and sputum analysis were recorded and entered into the electronic case report forms.

Patients, who met the following inclusion criteria, were suitable for the trial: age 18 years (915/918 [99.7%]), acute bronchitis (898/918 [97.8%]), duration of complaints (48 hours (683/918 [74.4%]) and Bronchitis Severity Score (BSS) 5 points (870/918 [94.8%]). The diagnosis of acute bronchitis was confirmed on clinical symptoms (Smucny et al. 2002; Snow et al. 2001) and the confidence in diagnosis was rated on a scale between 0 and 10 by the investigators.

Exclusion criteria were: indication for antibiotic treatment (e.g. suspected pneumonia) or treatment with antibiotics during the past 4 weeks before inclusion in the trial (150/918 [16.3%]), allergic asthma bronchiale (4/918 [0.4%]), tendency to bleed, severe heart, renal or liver diseases, immunosuppression (12/918 [1.3%]), drug or alcohol abuse (9/918 [1.0%]), known or supposed hypersensitivity to investigational medication (0/918), concomitant medication that might impair the study results (e.g. antibiotics) or supposed interactions of the concomitant medication with the investigational medication (16/918 [1.7%]), women during pregnancy or lactation period (31/918 [3.4%]), participation in another clinical trial during the past 3 months (0/918), irresponsible patients or patients unable to understand the nature, meaning and consequences of the trial (6/918 [0.7%]).

All 476/918 (51.9%) patients who met the criteria above and gave their written informed consent for trial participation were enrolled and randomized in sequence at each study site into the two treatment groups. Two patients (one in each group) who did not take any

investigational medication were excluded from the analysis. In addition, 6 patients (3 in each group) were excluded because the trial was not conducted in accordance with GCP by the investigator. Therefore, the data of 468 patients were analysed on an intention-to-treat basis, thereof 233/468 patients received EPs 7630 and 235/468 patients received placebo.

Statistical Design

The trial was planned according to a group sequential adaptive design with four interim analyses (Lehmacher and Wassmer, 1999; Wassmer, 1999; Wassmer et al. 2001). For all interim analyses as well as the final analysis, separate analyses plans were made based on blind data reviews according to ICH Guidelines E9 and E10. The experimentwise type I error rate was set at $\alpha = 0.025$ (one-sided). The critical values of the group sequential test design were calculated for the standardized cumulative test statistic for the design with boundary shape parameter $\Delta = 0.5$, i.e. Pocock's design (Pocock, 1977). For one-sided $\alpha = 0.025$, the resulting adjusted significance levels at each interim analysis k were given by $\alpha_k = 0.007907$ with corresponding critical values $Z_k = 2.413$ each ($k = 1, 2, 3, 4$).

Intervention

The investigational medication was administered in bottles of 50 ml containing either EPs 7630 (100 g finished product contain: 80 g EPs 7630, a special aqueous ethanolic extract [11% (m/m)] of the roots of *Pelargonium sidoides* corresponding to 8 g plant material; additional ingredient of the finished product: 20 g glycerol 85%) or placebo. Placebo was matched to a formulation of EPs 7630 with regard to colour, smell and taste as well as viscosity. The medication was manufactured by "Dr. Willmar Schwabe Pharmaceuticals", Karlsruhe, Germany. The formulation of EPs 7630 and its botanical origin were identical to the finished product Umckaloabo® registered by ISO Pharmaceuticals, Ettlingen, Germany.

The patients were instructed to take 30 drops three times daily (4.5 ml per day) at 30 min before or after the meals starting at day 0 and continuing until day 7. Any other medication that had been taken within the past 6 months or in parallel to the investigational medication had to be documented. In case of fever ($> 39^\circ\text{C}$), paracetamol tablets 500 mg were allowed. Criteria for withdrawals were: no decrease of BSS compared to baseline (non-responder), complete recovery, intake of prohibited medications (e.g. antibiotics), occurrence of adverse events or suspected lack of compliance.

Objective

The primary objective was to evaluate the efficacy and safety of EPs 7630 compared to placebo in patients with acute bronchitis.

Outcome criteria

The primary outcome criterion for assessing the efficacy of EPs 7630 compared to placebo was the change of BSS on day 7. BSS scores the most important features of acute bronchitis, namely cough, sputum, rales/rhonchi, chest pain during coughing, and dyspnoea (Williamson, 1984; Macfarlane et al. 2002). Each symptom was assessed by the investigator using a verbal 5-point rating scale ranging from 0 to 4 (0: absent; 1: mild; 2: moderate; 3: severe; 4: very severe).

Secondary outcome criteria were: Prospective defined response criteria based on BSS (A: BSS < 3 points; B: decrease of BSS ≥ 7 points; C: A+B), treatment outcome according to the Integrative Medicine Outcomes Scale (IMOS), onset of treatment effect, consumption of paracetamol, change of individual symptoms of BSS and further symptoms, patients' health status using the health-related quality of life questionnaires (SF-12 Health Survey, EQ-5D), questions about the complaints and satisfaction with treatment using the Integrative Medicine Patient Satisfaction Scale (IMPSS).

The safety of treatment was assessed with respect to frequency, nature and severity of adverse events (AEs), to tolerability assessed by investigators and by patients using a verbal 4-point rating scale, and to the results of laboratory tests.

Following enrolment (day 0), control examinations occurred on day 3–5 and day 7. At each contact, the investigator recorded the clinical status, controlled the patient's diary, documented the consumption of investigational medication and of paracetamol as well as any change in concomitant medications and asked for occurrence of any adverse events. Treatment outcome and tolerability were assessed separately by the patient and the investigator. On day 7 or at premature withdrawal of the patient, there was a final assessment including laboratory tests and sputum analysis. In addition, the patient was asked with regard to the time until start of treatment effect and satisfaction with treatment.

Blinding

The computer generated randomisation list was prepared with a balanced (1:1)-block randomisation using the program RANDU, IBM Corporation 1969. Throughout the trial, there was no indication that any patient or investigator was able to unblind the medication. The investigators received separate sealed emergency envelopes for each patient containing information about the treatment allocation. After completion of the trial, all envelopes were returned unopened by the investigators.

Quality assurance

All data collected were entered by the investigators into notebook computers using an electronic case report form (eCRF) and transmitted via internet to the

data collection center at the contract research organisation (CRO). Monitoring was conducted according to ICH GCP Guidelines. The monitor checked daily the data entered into the eCRFs for completeness and plausibility using the implemented monitoring tools. On-site monitoring visits including source data verification occurred every 4 weeks at each study site. In order to safeguard adherence to the protocol, in particular patients' informed consent and blinding, the patients were contacted via telephone by a physician not involved into the trial and interviewed in detail. The patients gave their prior consent to the telephone interviews.

Statistical Analysis

All interim and final confirmatory statistical analyses of the primary outcome variable were based on all available data according to the intention-to-treat principle. The last observation carry forward (LOCF) procedure was applied in case of premature withdrawal from the trial.

All confirmatory comparisons of the two treatments were carried out as planned, namely as 2-factorial analysis of covariance on the primary outcome variable with the two factors treatment group and site, and with the baseline value as a covariate. Results are displayed as means ± standard deviation. For confirmatory analysis, 95% Confidence Intervals (CIs) were calculated.

Results

Baseline, compliance, and withdrawals

In total, 476 patients were enrolled by 36 investigators at the out-patient care setting. Thereof, 468 patients (233 patients in the EPs 7630 group, 235 patients in the placebo group) were included in the final analysis ac-

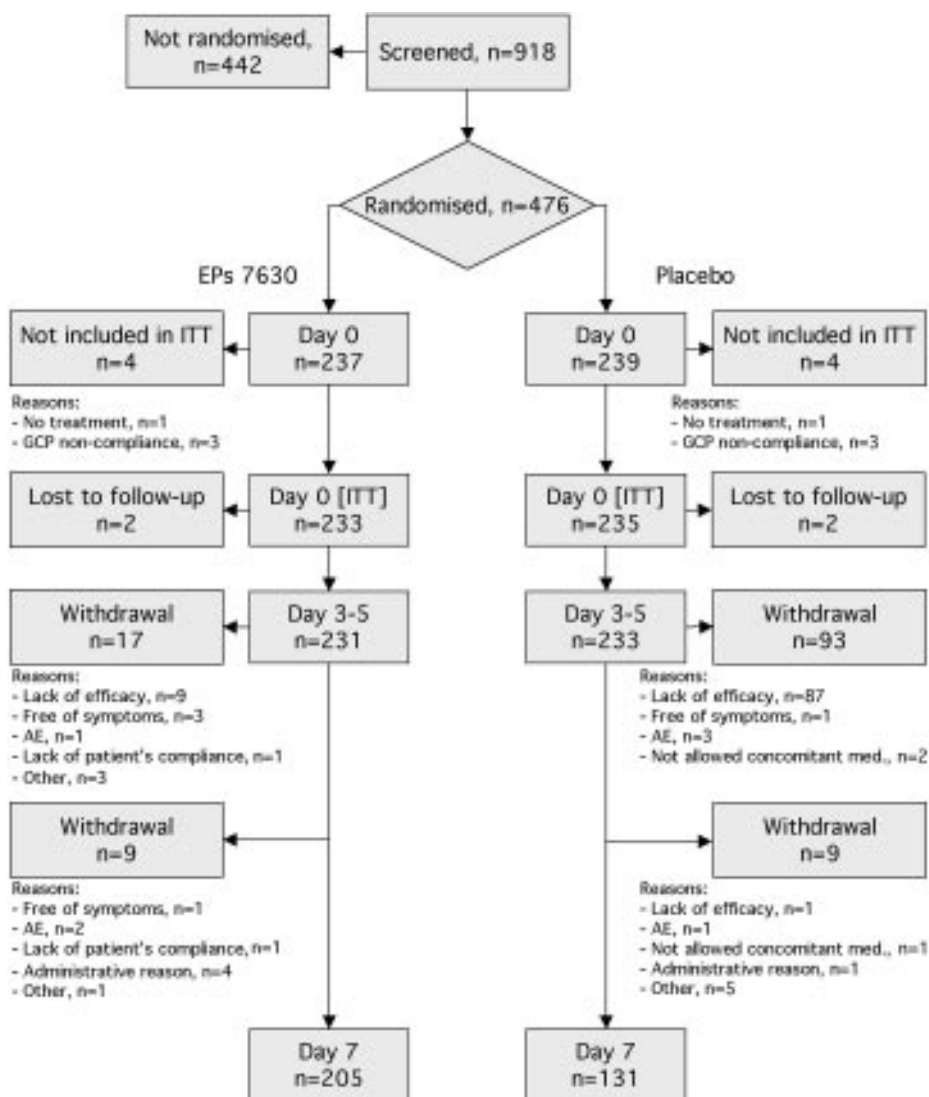


Fig. 1. Flowchart including reasons for withdrawals.

ording to the intention-to-treat principle. Details for withdrawals are presented in Fig. 1. 2/476 patients were excluded because they did not take any investigational medication and 6/476 were excluded for reasons of non-compliance with GCP. Among the 468 patients in the ITT data set, 299 patients (63.9%) were female and 169 patients (36.1%) were male. The predominance of females was slightly higher in the placebo group (EPs 7630: 139 patients [59.7%]; placebo: 160 patients [68.1%]). Demographic and baseline characteristics are listed in Table 1.

The final analysis was carried out after all patients enrolled had completed the trial, and the database was finally cleaned and locked.

Primary outcome criterion

At baseline, BSS was similar in both treatment groups (8.4 ± 2.2 points in the EPs 7630 group, 8.0 ± 2.0 points in the placebo group). The decrease of BSS over time is shown in Fig. 2. On day 7 (LOCF), BSS decreased by 5.9 ± 2.9 points under EPs 7630 and by 3.2 ± 4.1 points under placebo ($p < 0.0001$). The 95% CI for the difference of effects between the two treatment groups (EPs 7630 minus placebo) was calculated as $[-3.359; -2.060]$ showing a highly significant superiority of EPs 7630 compared to placebo on day 7. This superiority of EPs 7630 was noticeable at the first follow-up contact (day 3–5) already (BSS: 4.8 ± 2.3 points under EPs 7630, 6.2 ± 3.0 points under placebo, $p < 0.0001$).

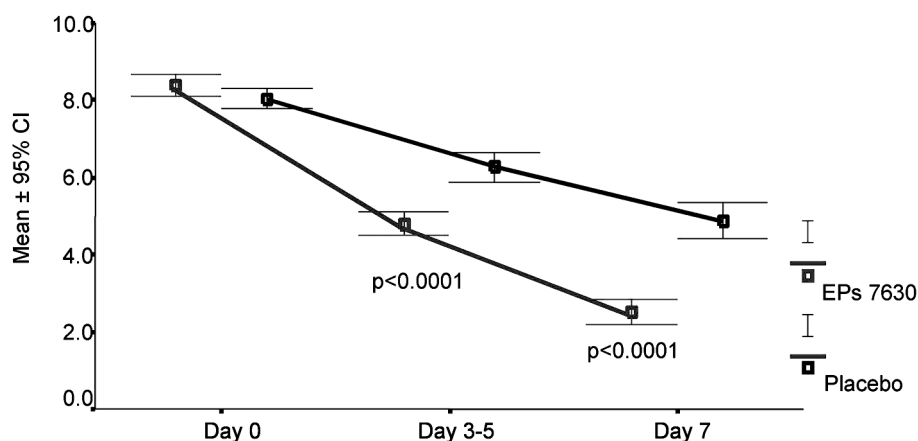


Fig. 2. Decrease of the Bronchitis Severity Score (BSS) under EPs 7630 compared to placebo (n = 468, ITT-analysis).

Table 1. Demographic information and other characteristics at baseline (values = number of patients, n = 468, ITT-analysis).

Demographic information	EPs 7630 (n = 233)	Placebo (n = 235)
Mean age ± SD [median], y	41.1 ± 14.1 [41]	39.9 ± 14.2 [39]
Mean height ± SD [median], cm	169.9 ± 9.4 [170]	169.5 ± 8.8 [168]
Mean weight ± SD [median], kg	74.8 ± 15.6 [74]	73.5 ± 14.8 [72]
Male	94	75
Female	139	160
History of respiratory infections during the past six months prior to study entry*		
Bronchitis (chronic/seldom)	8/150	15/152
Angina tonsillaris (chronic/seldom)	2/67	8/70
Rhinopharyngitis (chronic/seldom)	7/137	9/137
Otitis media (chronic/seldom)	0/20	4/12
Other (chronic/seldom)	2/4	4/3
Pre-treatment of respiratory tract infections*	42	50
Antibiotics	20	27
Acetylcysteine	13	13
Antitussives	16	20
Symptomatic treatment	16	20
Other	18	21

*multiple responses possible

In addition, it was also observed in patients with more severe bronchitis defined as BSS ≥ 8 points at baseline ($n = 279$, decrease of BSS: 6.8 ± 2.7 points under EPs 7630, 4.5 ± 4.2 points under placebo, $p < 0.0001$).

Secondary outcome criteria

Response criteria based on BSS on day 7

A BSS of less than 3 points (*response criterion A*) was observed in 150/233 patients (64.4%) under EPs 7630 compared to 89/235 patients (37.9%) under placebo (Fig. 3, $p < 0.0001$). A decrease of BSS of at least 7 points compared to baseline (*response criterion B*) was seen in 101/233 patients (43.3%) treated with EPs 7630, and 54/235 patients (23.0%) treated with placebo

($p < 0.0001$). Rapid recovery, defined as fulfilment of response criteria C ($C = A + B$), was observed in 80/233 patients (34.3%) under EPs 7630, and 48/235 patients (20.4%) under placebo ($p < 0.0001$).

Individual symptoms of BSS on day 7

The number of patients showing complete recovery or improvement with regard to individual symptoms is presented in Fig. 4. High recovery rates for EPs 7630 were observed for the symptoms rales/rhonchi, chest pain during coughing and dyspnoea. For example, on day 7, rales/rhonchi had disappeared in 165/214 patients (77.1%) under EPs 7630 and in 95/214 patients (44.4%) under placebo ($p < 0.0001$), and chest pain during coughing had disappeared in 174/208 patients (83.7%) of the EPs 7630 group and 103/214 patients

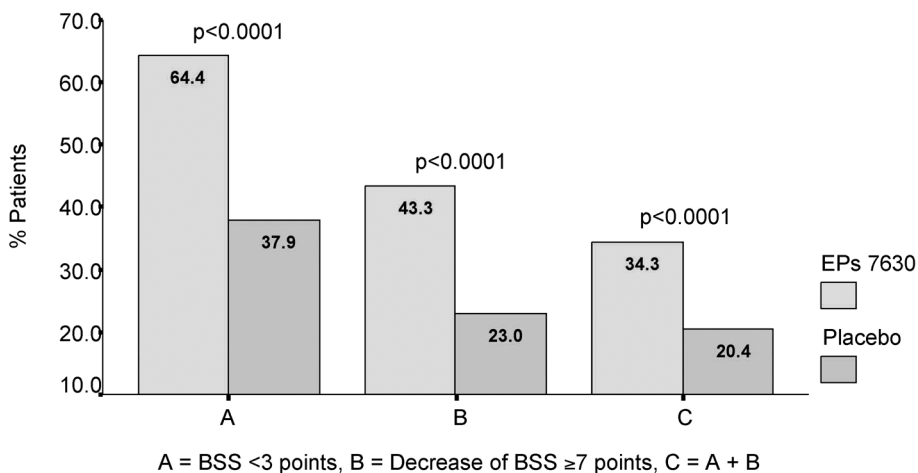


Fig. 3. Response criteria based on BSS on day 7 ($n = 468$, ITT-analysis).

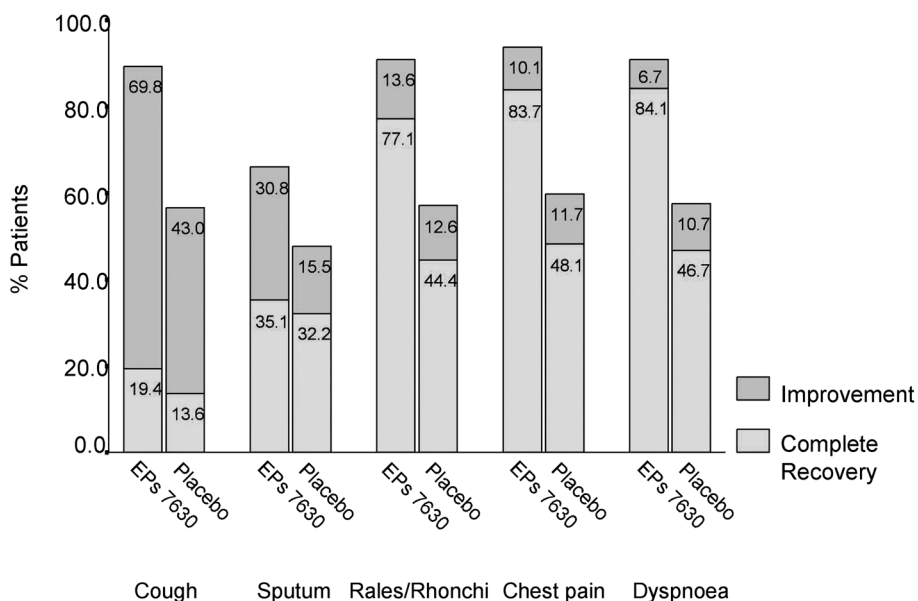


Fig. 4. Complete recovery and improvement of bronchitis-specific symptoms under EPs 7630 compared to placebo ($n = 468$, ITT-analysis).

(48.1%) of the placebo group ($p < 0.0001$). The recovery rates for cough and sputum were similar in the EPs 7630 and placebo group, but the rates for improvement of these symptoms were clearly higher in the EPs 7630 group. In the EPs 7630 group, cough disappeared or improved in 207/232 patients (89.2%) compared to 133/235 patients (56.6%) in the placebo group ($p < 0.0001$), and the symptom sputum disappeared or improved in 122/185 patients (66.0%) under EPs 7630 compared to only 83/174 patients (47.7%) under placebo ($p < 0.0002$).

Further clinical symptoms on day 7

The recovery and improvement rates of the further symptoms are displayed in Fig. 5. The highest recovery rates were found for fever. On day 7, fever had disap-

peared in 95/98 patients (96.9%) of the EPs 7630 group and in 59/101 patients (58.4%) of the placebo group ($p < 0.0001$). For the symptoms hoarseness, headache and pain in limbs, the recovery rates varied between 75% and 81.7% under EPs 7630 and between 45.0% and 54.8% under placebo ($p < 0.0001$, $p < 0.0001$, $p < 0.0001$). The weakest recovery rates were found for the symptom fatigue/exhaustion. On day 7, fatigue/exhaustion had disappeared in 142/218 patients (65.1%) under EPs 7630 and in 84/214 patients (39.3%) under placebo ($p < 0.0001$).

Days-off work and duration of illness

At baseline, 67% of the patients in both groups were unable to work (Fig. 6). On day 7, working inability decreased to 16% in the EPs 7630 group compared to

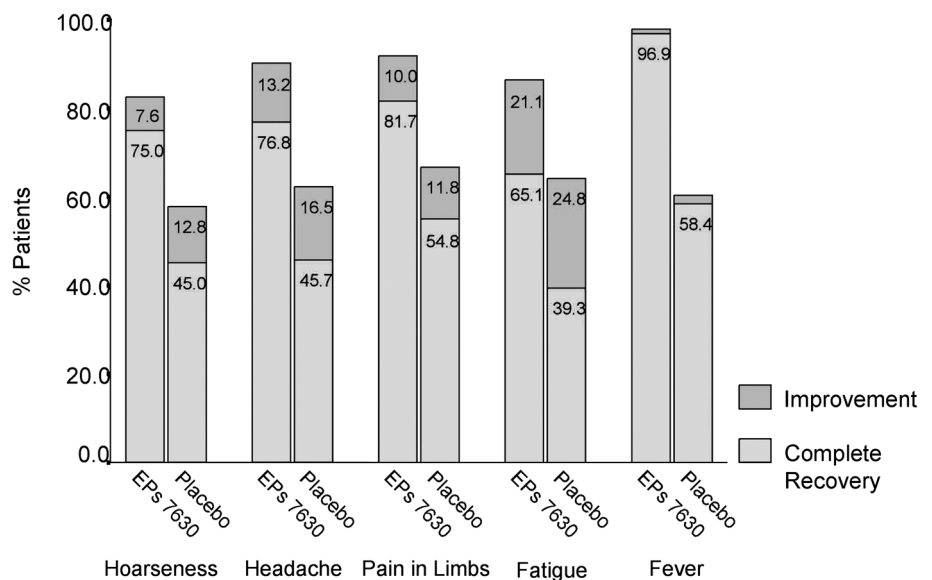


Fig. 5. Complete recovery and improvement of further symptoms under EPs 7630 compared to placebo (n = 468, ITT-analysis).

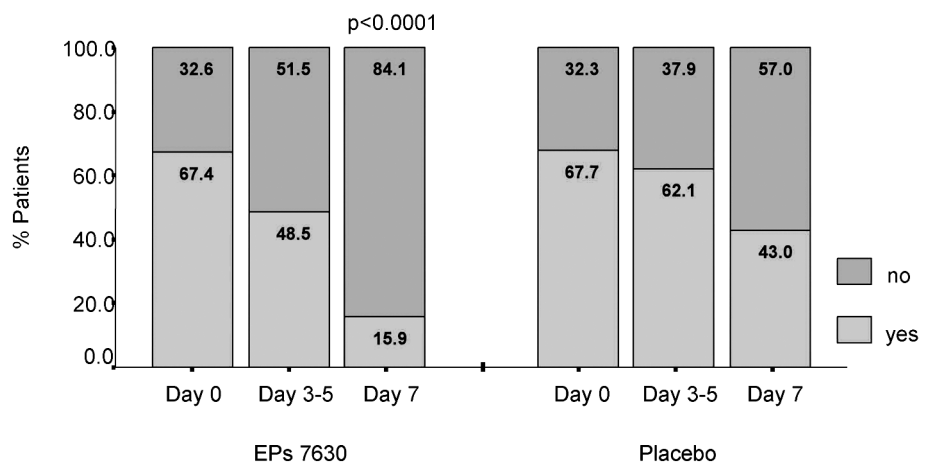


Fig. 6. Working inability of patients with acute bronchitis under EPs 7630 compared to placebo (n = 468, ITT-analysis).

Table 2. Details on adverse events (AEs).

	EPs 7630 (n = 233)		Placebo (n = 235)	
	No. of AEs	Severity Mild Moderate	No. of AEs	Severity Mild Moderate
Angina pectoris	1	1	-	-
Cardiac disorders NOS	1	-	-	-
Tachycardia NOS	1	1	-	-
Ear canal erythema	1	1	-	-
Ear hemorrhage	1	1	-	-
Ear pain	2	2	-	-
Vertigo (ear and labyrinth disorder)	3	3	1	1
Cough aggravated	1	1	-	-
Epistaxis	2	2	-	-
Pharyngitis NOS	-	-	1	1
Rhinitis NOS	1	1	1	1
Sputum purulent	1	1	-	-
Suspected pertussis	1	1	-	-
Upper respiratory tract infection NOS	-	-	1	1
Abdominal pain upper	2	2	2	2
Diarrhea NOS	1	1	4	3
Gastric function disorder NOS	1	1	-	-
Vomiting NOS	-	-	1	1
Suspected damage to hepatic parenchyma	1	1	-	-
Gastroenteritis NOS	1	1	-	-
Pharyngolaryngeal pain	1	1	1	1
Herpes simplex	1	1	-	-
Skin disorders NOS	1	1	-	-
Laceration	1	1	-	-
Muscle twitching	-	-	1	1
Brachial plexus lesion	1	1	1	1
Radicular syndrome	-	-	1	1
Vertigo (nervous system disorder)	1	1	-	-
Nervousness	-	-	1	1
Fatigue	-	-	1	1

General physical health deterioration	-	-	-	1	-	1	-	-	1	-	-	1	-	-	2
Sensation of heaviness	1	1	1	-	-	-	-	-	-	-	-	-	-	-	10
Headache NOS aggravated	1	1	1 (C)	-	-	-	-	-	-	-	-	-	1 (C)	-	11
Restlessness	-	-	-	-	-	-	-	-	-	-	-	-	-	-	11
Tooth extraction NOS	1	1	-	1	-	-	-	-	-	-	-	-	-	-	11
Peripheral coldness	1	1	1	-	-	-	-	-	-	-	-	-	-	-	10
Pyrexia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2
Total	32	22	26	10	22	5	20	9	11	11	11	11	11	10	2

* probable (A), possible (B) or improbable (C) relation to the investigational medication
 NOS: not otherwise specified

43% in the placebo group ($p < 0.0001$). In addition, the duration of illness was significantly shorter for patients treated with EPs 7630 compared to placebo ($p < 0.001$). EPs 7630-treated patients were able to return to work nearly two days earlier than placebo-treated patients (4.7 ± 3.7 days vs. 6.3 ± 4.5 days, $p < 0.0001$).

Health related quality of life and onset of treatment effect

On average, all subscales of the EQ-5D health questionnaire showed a positive tendency in favour of the EPs 7630 group at the end of the trial. For example, EQ-VAS increased by 29 units in the EPs 7630 group and by 21 units in the placebo group ($p < 0.0001$). With regard to the onset of treatment effect, patients noticed an effect earlier under EPs 7630 than under placebo. Within the first four days, onset of treatment effect was recognised in 53.6% of patients under EPs 7630 compared to 36.2% of patients under placebo, only ($p < 0.0002$).

Satisfaction with treatment

According to the entries of the patient diaries, 174/233 patients (74.7%) in the EPs 7630 group and 99/235 patients (42.1%) in the placebo group were satisfied with their treatment ($p < 0.0001$), whereas only 9/233 patients (3.9%) in the EPs 7630 group, but 63/235 patients (26.8%) in the placebo group were dissatisfied ($p < 0.0001$).

Tolerability and safety

The tolerability assessments by the investigators and the patients were similar. A very good or good tolerability was reported by 96.1% of the patients in the EPs 7630 group and by 88.1% of the patients in the placebo group.

The mean values of all laboratory parameters did not change during the trial, neither for patients under EPs 7630 nor for patients under placebo.

A total of 36/468 patients (7.7%) experienced at least one adverse event (AE) during the trial, 20/233 patients (8.6%) in the EPs 7630 group and 16/235 patients (6.8%) in the placebo group (Table 2). All adverse events were assessed as non-serious. In the EPs 7630-treated group 15 patients reported 22 mild adverse events and in the placebo group 9 mild adverse events were reported by 8 patients.

The relationship of AEs to the investigational medication was classified as “probable” in 1/235 patient (0.4%) of the placebo group, as “possible” in 2/233 patients (0.9%) of the EPs 7630 group and 2/235 patients (0.9%) of the placebo group and as “improbable” in 14/233 patients (6.0%) of the EPs 7630 group and 7/235 patients (3.0%) of the placebo group. 26 adverse events with probable, possible or improbable relation to the investigational medication were described for the patients treated with EPs 7630 and 11 for the patients treated with placebo.

The organ system most frequently affected by AEs were gastrointestinal disorders, nervous system disorders, respiratory/thoracic and mediastinal disorders, and ear and labyrinth disorders (Table 2). The number of patients with ear and labyrinth disorders was slightly higher in the EPs 7630 group (EPs 7630: 5/233 patients [2.2%]; placebo: 1/235 patients [0.4%]), whereas gastrointestinal disorders were slightly more frequently reported in the placebo group (EPs 7630: 4/233 patients [1.7%]; placebo: 7/235 patients [3.0%]).

■ Discussion

The results of the trial confirm that acute bronchitis can be treated successfully with EPs 7630. The decrease of BSS was significantly higher in patients treated with EPs 7630 (5.9 ± 2.9) compared to patients treated with placebo (3.2 ± 4.1). For all individual symptoms recovery and/or improvement rates were higher in the EPs 7630-treated patients compared to the placebo-treated patients. These symptoms are characteristic for acute bronchitis and clinically relevant. The superiority of EPs 7630 was also found in two preceding trials including 124 and 205 adults, respectively (Golovatiouk and Chuchalin, 2002; publication in preparation). The trials were performed according to a similar design. The decrease of BSS after 7 days ranged from 7.3 to 7.7 points for patients treated with EPs 7630 and from 4.6 to 5.3 points for placebo treated patients. In summary, three placebo controlled trials with a total of nearly 800 patients clearly demonstrate the efficacy of EPs 7630 in the treatment of acute bronchitis. In comparison, the effect of antibiotic treatment for patients with a clinical diagnosis of acute bronchitis appears to be only modest (Smucny et al. 2002). Moreover, antibiotics are known to be relatively harmful with regard to occurrence of adverse events but nevertheless, they are prescribed for 60% to 80% of patients with acute bronchitis who present to physicians (Smucny et al. 2002). Thus, the results of the studies with EPs 7630 are convincing arguments against the still existing widespread prescription of antibiotic treatment for acute bronchitis (Smucny et al. 2002; Hall et al. 2003).

The present trial, however, has also limitations. One is that the diagnosis of acute bronchitis has been made on clinical grounds. Since there is no gold standard to diagnose acute bronchitis, this weakness also concerns other placebo-controlled trials as well as the decision making process of physicians in general practice (Smucny et al. 2002, Snow et al. 2001; Oeffinger et al. 1997). Based on the results of the present trial, the following recommendations can be given: if acute bronchitis is diagnosed by the physician, EPs 7630 can be prescribed as initial treatment. In case that the complaints have not improved within 4 days of treatment, antibiotic treatment may be indicated. To support this strategy, another clinical trial is being carried out at the moment to assess the benefit of EPs 7630 as initial treatment in patients with acute bronchitis and the necessity to prescribe antibiotic treatment. Another limitation of the present trial is that only patients with acute onset of bronchitis (less than 48 h) have been included. However, preliminary results from a further ongoing trial suggest that EPs 7630 is also effective in patients with longer onset of symptoms prior to enrolment.

By far, the most prominent aspect for assessment of efficacy for treatment of acute bronchitis is the number of days-off work. Several metaanalyses have shown that the duration of the patients' working inability cannot be reduced by antibiotic treatment (Bent et al. 1999; Fahey et al. 1998; Smucny et al. 2002). Only the duration of cough was reduced by approximately half a day in patients treated with antibiotics compared to placebo-treated patients (0.58 days, 95% CI 0.01 to 1.16). With regard to this, EPs 7630 appears to be more effective. The number of days-off work was reduced by nearly two days in patients treated with EPs 7630 compared to patients treated with placebo.

With regard to safety, the risk of suffering from adverse events was slightly higher under EPs 7630 compared to placebo. However, the intensity of most AEs for the EPs 7630-treated patients was only mild. The amount of moderate AEs was the same in both treatment groups. Absence of serious side effects of EPs 7630 had already been observed in an outcomes study on 205 adults with acute bronchitis (publication in preparation) as well as in a large-scale outcomes study on children (Haidvogel et al. 1996). In comparison, the frequency of AEs reported for the use of antibiotics in the treatment of acute bronchitis is clearly higher. For example, in a trial comparing different antibiotics and different treatment schedules, drug-related AEs were recorded in 23–39% of patients (Henry et al. 1995). In the present trial, only 6.9% of the patients taking EPs 7630 revealed drug-related AEs, whereas only in 0.9% of the patients a probable or possible relationship to the investigational medication was assumed. In another trial comparing the treatment of cefixime with cefuroxime axetil, drug-related gastrointestinal AEs ranged from 10 to 18% of the patients (Arthur et al. 1996), which is considerably more than under EPs 7630.

In conclusion, EPs 7630 was superior in efficacy compared to placebo in the treatment of adults with acute bronchitis. Treatment with EPs 7630 clearly reduced the severity of symptoms and shortened the duration of working inability for nearly 2 days.

Responsibilities of authors and role of funding source

H. Matthys, Professor, MD, is responsible for the scientific advice and for the writing of the manuscript.

R. Eisebitt is responsible for statistical design and analysis of the trial.

B. Seith, ScD, is responsible for project management of the trial and for the writing of the manuscript.

M. Heger, MD, is principal investigator and responsible for design and conduct of the trial as well as for the editing of the manuscript.

ISO Pharmaceuticals, Ettlingen, Germany, provided funding for this trial.

Acknowledgements

W. Lehmacher, PhD, Director of the Department for Medical Statistics, Informatics and Epidemiology, University of Cologne, Germany served as external statistical expert.

G. Wassmer, PhD, Department for Medical Statistics, Informatics and Epidemiology, University of Cologne, Germany developed the multi-stage adaptive design and was together with R. Eisebitt responsible for statistical design and analysis of the trial. ClinResearch GmbH, Cologne, Germany, was the independent contract research organisation (CRO) and responsible for data management, telephone interviews, statistical analyses and reporting. Dipl. Stat. R. Hövelmann was the responsible biometrician and datamanager.

We thank the patients for their participation in this trial, and for their willingness to be interviewed.

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