ORIGINAL RESEARCH

Efficacy and Tolerability of High-dose Pelargonium Extract in Patients With the Common Cold

David S. Riley, MD; Viktor G. Lizogub, MD; Andrea Zimmermann, MSc; Petra Funk, MSc; Walter Lehmacher, PhD

ABSTRACT

Context • The common cold (CC) is usually caused by a viral infection. Antibiotics are often prescribed unnecessarily for it, although no evidence exists for any benefit in the CC. Effective alternatives are needed.

Objective • The study intended to evaluate the efficacy of 7630, a proprietary extract of *Pelargonium sidoides*, the active ingredient in umckaloabo, compared with a placebo for the treatment of the CC.

Design • This was a prospective, double-blind, parallel-group, placebo-controlled, phase 3 clinical trial (RCT), with an adaptive group-sequential design with 2 parts, both of which were 2-arm trials. The first used a standard dose (SD) of 3 × 30 drops per day of the active medication and the second used a high dose (HD) of 3 × 60 drops per day of the active medication, against 3 × 30 drops per day and 3 × 60 drops per day of a placebo, respectively.

Setting • The study took place in 8 outpatient departments affiliated with hospitals.

Participants • For the entire study, 207 adults with predefined cold symptoms that had been present for 24 to 48 h prior were included in the study, with 103 participating in the SD part and 104 participating in the HD part.

Intervention • In the HD part, as covered in this article, the intervention group received treatment with 3 × 60 drops per day of the active medication and the control group received a placebo (control group), for a maximum period of 10 d.

Outcome Measures • The primary outcome measure was the sum of differences in the cold intensity score (CIS) from day 1 to day 3 and from day 1 to day 5, defined as the sum of the symptom intensity differences (SSID). The criteria for the secondary outcome, efficacy, were (1) diverse response criteria according to the total CIS; (2) changes in individual CIS symptoms; (3) changes in further cold-relevant symptoms; (4) ability to work; (5) activity level; (6) general well-being; (7) health-related quality of life—the EuroQol questionnaire with 5 dimensions (EQ-5D), including the visual analogue scale EQ-VAS; (8) time until onset of treatment effect; (9) treatment outcome; and (10) satisfaction with treatment.

Results • From baseline to day 5, the mean CIS decreased by 11.2 ± 4.8 points for the 7630 group and 6.3 ± 4.7 points for the control group. The mean SSID was 16.0 ± 7.6 points for the control group ($P < .0001$). After 10 d, 90.4% of the group receiving the active medication and 21.2% of the control group were clinically cured ($P < .0001$). In the treatment group, participants' inability to work was significantly lower, with a mean duration of 6.4 ± 1.6 d vs 8.3 ± 2.1 d for the control group ($P < .0001$), and treatment outcome—complete recovery or major improvement—was significantly better at day 5 for the active treatment group compared with the control group ($P < .0001$). Mild-to-moderate adverse events—all nonserious—occurred in 15.4% of those receiving active treatment vs in 5.8% for the control group.

Conclusions • The active medication is an effective, well tolerated, and safe treatment for the CC. It significantly reduces the severity of symptoms and shortens the duration of the disease. (*Altern Ther Health Med.* 2018;24(2):16-26.)

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The common cold (CC) is considered to be the most frequent human illness. In the United States alone, at least 1 billion colds per year have been reported, with an average frequency of 2 to 6 colds per person.[1] The disease accounts for up to 100 million physician visits annually[2] and leads to significant work absenteeism.[3] Thus, the CC is associated with a significant burden for societies and has a huge economic impact.[4]

The CC is usually caused by a viral infection. The number of different viruses responsible exceeds 200, but coronaviruses, parainfluenza viruses, respiratory syncytial viruses, adenoviruses, enteroviruses, and especially human rhinoviruses are considered to be the most prevalent.[5,6] They cause various symptoms, in which cough, nasal congestion, sneezing, rhinorrhea, headache, chills, sore throat, and fever are mostly present.[7]

Relevant information concerning the pathophysiology of these symptoms mainly comes from studies of rhinovirus infection.[8] The current understanding is that rhinoviruses attach to specific receptors on epithelial cells and trigger an inflammatory response accompanied by vasodilation, hypersecretion, and other symptoms. In contrast, direct cytopathic effects on epithelial cells are low.[6,9]

Patients seeking accelerated recovery often consult their physicians and receive prescriptions for antibiotics, although no evidence exists for any benefit in the CC.[10-12] In fact, antibiotics can cause significant adverse effects in adults,[11] and their use is associated with the constant rise in antibiotic-resistant bacteria.[13] Thus, as outlined in a recent review by Calbo et al,[14] the practice of prescribing antibiotics should be lessened by special training for physicians to reduce inappropriate antibiotic use and limit the spread of antibiotic resistance.

In many cases, the reduction of the severity and duration of symptoms can also be achieved by medication sold over the counter with products for which the efficacy and safety is supported by pharmacological and clinical studies. In this context, herbal medicinal products containing an extract of *Pelargonium sidoides*—herbal drug preparation from the roots of *P sidoides*—can reduce the severity of symptoms.[15]

In vitro evaluations have demonstrated the antiviral effects,[16] moderate direct and indirect antibacterial activity, as well as immunomodulatory capabilities of this extract. The immunomodulatory activities are mediated mainly by the release of tumor-necrosis factor α and nitric oxides, the stimulation of interferon-β, and an increase in the activity of natural killer cells.[18-22] Additional biological activities in vitro are improved phagocytosis, oxidative burst and intracellular killing of human peripheral blood phagocytes, and an inhibition of the interaction of group A streptococci and host epithelia.[17,23,24]

As discussed in a recent Cochrane review[25] and proven in several clinical trials, treatment of acute respiratory tract (RT) infections with this medication showed efficacy and tolerability compared to placebo. Six randomized, placebo-controlled clinical trials[26-31] and 3 observational studies[32-34] demonstrated effective treatment in patients suffering primarily from acute bronchitis. *P sidoides* is approved in Germany for the treatment of acute bronchitis in all age groups.[35]

Other trials include the following:

1. Two RCTs demonstrated the successful use of this medication in the treatment of patients with acute rhinosinusitis[36] and tonsillopharyngitis.[37]
2. This drug has also been demonstrated to offer a benefit to asthmatic children with upper respiratory infection on the frequency of asthma attacks, cough, and nasal congestion.[38]
3. An RCT showed significant differences with less exacerbations and antibiotic use in the active-treatment group compared with the control group when this medication was used as an add-on treatment in patients with moderate-to-severe chronic obstructive pulmonary disease.[39]

This 4-arm RCT with 2 parts was conducted to evaluate the efficacy and tolerability of 7630 in adult patients suffering from a CC. The first part was a 2-arm trial RCT that used a standard dose (SD) of 3 × 30 drops of the active medication versus placebo (30 drops 3 times per day). This results of this SD RCT results were published in 2007.[40]

Subsequently, Bachert et al[36] reported findings from a trial investigating the efficacy and safety of treatment with an increased dose of this medication (3 × 60 drops) in patients with acute rhinosinusitis. The researchers found the high dose (HD) of 7630 well tolerated and superior in efficacy to placebo.

The second part of the 2-part trial in patients suffering from the CC was a 2-arm RCT that used an HD of 7630 (60 drops 3 times per day), compared with placebo. In the current article, the research team reports the results of this RCT for acute RT infections.

METHODS

Participants

The multicenter, prospective, phase 3 RCT took place in 8 outpatient departments in Ukraine. Participants were patients consulting one of the study's investigators, who worked at one of the participating outpatient departments, during the recruitment phase of the current study.

For inclusion, a patient had to meet following criteria: (1) be a male or female patient aged 18 to 55 years; (2) have given written informed consent; (3) show either 2 major cold symptoms—nasal discharge, sore throat—and at least 1 minor cold symptom—nasal congestion, sneezing, scratchy throat, hoarseness, cough, headache, muscle aches, and fever—or show 1 major and at least 3 minor cold symptoms; and (4) have had the cold symptoms for 24 to 48 hours.

To exclude streptococcal tonsillopharyngitis, a rapid test for group A β-hemolytic streptococcus was performed for each patient. The patients had to have a negative test to be enrolled into the trial. Further major exclusion criteria were

(1) the presence of any acute ear, nose, and throat (ENT) or RT disease other than the CC; (2) recurrent tonsillitis, sinusitis, or otitis with at least 3 episodes or recurrent bronchitis with at least 6 episodes during the 12 months prior to trial enrollment; (3) a chronic ENT or RT disease (eg, allergic rhinitis, bronchitis, bronchial asthma, obstructive pulmonary disease, or cystic fibrosis); (4) treatment with antibiotics, glucocorticosteroids, or antihistamines during the 4 weeks prior to trial enrollment or treatment with cold medications that might impair the trial results; (5) cough or pain relief medications and/or any other treatment for the CC during the 7 days prior to trial enrollment; (6) a known or suspected hypersensitivity to the investigational product; (7) previous or existing, severe cardiovascular disease or unstable diabetes mellitus; (8) severe renal or hepatic dysfunction—serum creatinine, serum aspartate aminotransferase, serum alanine aminotransferase, or alkaline phosphatase more than 3 times the upper limit of normal—at any time during the 12 months prior to trial enrollment; (9) evidence of any malignant disease during the 5 years prior to trial enrollment; (10) pregnancy or breast-feeding; and (11) participation in another clinical trial in the same time period or within 3 months prior to trial inclusion. For more details, please refer to the publication of the SD study that was part of the RCT.[40]

The trial was performed according to good clinical practice[41] and the Declaration of Helsinki.[42] The approvals of the Independent Ethics Committee and the State Pharmacological Center of the Ministry of Health of Ukraine were obtained.

Procedures

The primary objective was to evaluate the efficacy and safety of the active medication (7630) in both a standard and an HD compared with a placebo in the treatments of patients suffering from the CC. The active ingredient in umckaloabo is an extract of *P sidoides* (ISO Arzneimittel, Ettlingen, Germany).

The full trial was planned and performed with a group-sequential design that allowed for early stopping or sample-size recalculation, with a maximum of 3 interim analyses. Patients were randomly assigned equally to one of the SD treatment groups—trial part 1—or to one of the HD treatment groups—trial part 2.

Eligible patients were randomly allocated—sequentially in ascending order at each trial site—to the stratified treatment groups according to computer-generated randomization lists. The lists were prepared with a balanced (one-one) block randomization by using a validated electronic data processing, random number generator (R-Code, version 4.9, M. Wrobel, Karlsruhe, Germany). Each investigator received a set of blocks with correspondingly numbered trial medications for each stratum, without knowing the block length itself, as well as sealed emergency envelopes for individual patients, all of which were returned unopened after completion of the trial.

Demographic data, vital signs, smoking habits, consumption of alcohol and caffeine, symptoms of the CC (CIS) and further relevant symptoms, medical history and history of present illness, a physical examination of the sinuses, and a rhinoscopy were obtained at baseline on day 1. Following enrollment, the patient received the study's medication and the diary. Study participants were asked to complete the assessments in the diary (see Secondary Outcomes).

Follow-up visits were scheduled on days 3, 5, and 10, at which the investigators assessed the clinical status of the patients, reviewed the patients' diaries, documented the consumption and return of investigational medication and any change in concomitant medication, and asked about occurrence of adverse events (AEs). At the end of the study, each patient's diary was returned to the investigator.

Interventions

The active trial medication was supplied to participants in 3 bottles of 50 mL each, containing either (1) 7630, a liquid, herbal-drug preparation from the roots of *P sidoides* (1:8-10), with the extraction solvent being ethanol 11% (w/w), or (2) a placebo (control group). The placebo was matched with respect to the qualitative and quantitative composition regarding the concentration of the solvents water, ethanol, and glycerol. The active ingredient was replaced with a suitable amount of a food additive specifically matching the color of the product and conferring a medicinal overall impression (including a bitter taste) to the product.

For the HD trial, patients were instructed to take 60 drops 3 times daily, at least 30 minutes before or after meals, from day 1 and continuing until day 10. Any other medication that had been taken within the 6 months prior to the start of or concurrently during the trial had to be documented. In the case of a fever >39°C, paracetamol tablets were allowed.

Outcomes

Primary Outcome. The primary outcome measure was the sum of differences in the cold intensity score (CIS) from day 1 to day 3 and from day 1 to day 5, defined as the sum of the symptom intensity differences (SSID). The SSID was calculated on the basis of the total CIS on treatment days 1, 3, and 5, according to the following equation:

$$\text{sum of } \Delta\text{CIS day k} = \text{sum of (CIS day k} - \text{CIS day 1)}$$
$$\text{for k} = 1, 3, 5$$

This means the following:

$$\text{SSID} = (\text{CIS day 3} - \text{CIS day 1}) + (\text{CIS day 5} - \text{CIS day 1})$$

The SSID accounts for the changes in the CIS between baseline (day 1) and days 3 and 5.

The CIS questionnaire consists of questions about the intensity of 10 symptoms considered to be associated with the CC and is based on a questionnaire developed by Jackson et al,[43]

which has been validated in several subsequent studies.[44,45] The cold symptoms are designated as either major—nasal drainage, sore throat—or minor—nasal congestion, sneezing, scratchy throat, hoarseness, cough, headache, muscle aches, and fever.

At each contact with the participant, the presence of a fever was assessed, with the oral temperature assigned to the following stages: ≤37°C—not present, 0 points; >37°C to 38°C—mild, 1 point; >38°C to 39°C—moderate, 2 points; >39°C to 40°C—severe, 3 points; and >40°C—very severe, 4 points. The other 9 symptoms were rated by means of a 5-point verbal rating scale (VRS), from 0 = not present to 4 = very severe. The total CIS could therefore reach a maximum of 40 points.

Secondary Outcomes. The criteria for the secondary outcome, efficacy, were (1) diverse response criteria according to the total CIS; (2) changes in individual CIS symptoms; (3) changes in further cold-relevant symptoms; (4) ability to work; (5) activity level; (6) general well-being; (7) health-related quality of life—the EuroQol questionnaire with 5 dimensions (EQ-5D), including the visual analogue scale EQ-VAS; (8) time until onset of treatment effect; (9) treatment outcome; and (10) satisfaction with treatment.

Changes in diverse response criteria according to the total CIS. The diverse response criteria were as follows: (1) the clinical cure was defined as a complete resolution of all cold symptoms—total CIS equals 0 points—or a complete resolution of all but a maximum of 1 cold symptom—CIS less than or equal to 1 symptom, and (2) the clinical response was defined as either a reduction in total CIS below 7 points or a reduction in total CIS by at least 7 points at day 5.

Changes in individual CIS symptoms. This measure was assessed by calculating the CIS per symptom for each group at different time points, identifying the mean and 95% confidence interval (CI). The measurement enabled the research team to compare the groups with regard to the decrease in each cold symptom, whether major or minor.

Changes in further cold-relevant symptoms. The criteria included limb pain, weakness all over, exhaustion, fatigue, and chills, which were assessed according to a 5-point VRS, with 0 = not present and 4 = very severe. *Remission* was defined as a symptom of mild, moderate, severe, or very severe intensity assessed on day 1 and not present on day 5, and *improvement* was defined as any decrease in symptom intensity from day 1 to day 5, not including remission.

Ability to work. This measure was calculated according to the number of days the participant took off work.

Activity level. The measure assessed a participant's ability to follow his or her usual activities. Every morning and evening, the participant answered the question, "How is your activity level this morning/evening because of your common cold?" by ticking one the following possible answers in the diary: 100%, 75%, 50%, 25%, or 0% of usual level, where 100% = not limited at all and 0% = stayed in bed. The answers were used to calculate the duration of limitation of daily activities (ie, sum of days with an activity level of less than 100%).

General well-being. This measure was assessed according to the psychological general well-being index developed by Dupuy,[46] which is a validated health-related quality of life questionnaire producing a self-perceived evaluation of psychological well-being expressed by a summary score. Patients had to answer the question, "How have you been feeling in general today?" in the diary by ticking one of the following answers: 1 = in excellent spirits, 2 = in very good spirits, 3 = in good spirits mostly, 4 = I have been up and down in spirits a lot, 5 = in low spirits mostly, or 6 = in very low spirits.

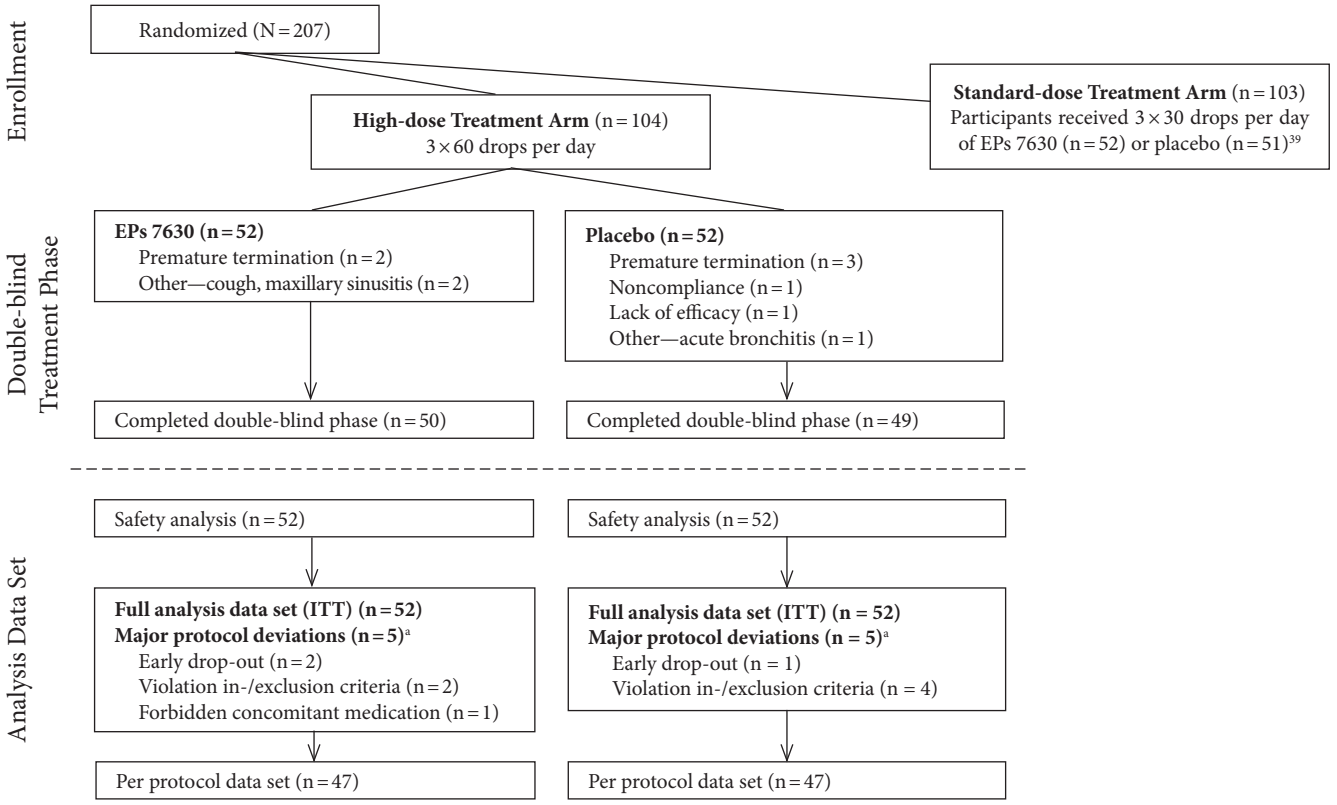
Health-related quality of life. This was assessed by means of the EQ-5D questionnaire in the diary.[47,48] EQ-5D is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D is a descriptive system comprises 5 dimensions—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension comprises 3 levels: no problems, some problems, and extreme problems. The patient was asked to indicate his/her health state by ticking the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. Moreover, the patient's self-rated health was assessed by EQ-VAS: "100 = the best health you can imagine" and "0 = the worst health you can imagine." The EQ-VAS is part of the EQ-5D questionnaire and can be used as a quantitative measure of health outcome reflecting the patient's own judgement.

Time until onset of treatment effect. This measure was assessed at day 10 or in the case of discontinuation by the patients, who indicated 1 of 6 prespecified time intervals in their diaries—within 1 to 2 days, within 3 to 4 days, within 5 to 6 days, within 7 to 8 days, within 9 to 10 days, or not at all.

Treatment outcome. This measure was assessed by the investigator at day 5 by means of the integrative medicine outcomes scale (IMOS), consisting of a 5-point rating scale—1 = complete recovery, 2 = major improvement, 3 = slight to moderate improvement, 4 = no change, or 5 = deterioration. The IMOS, which was presented by the data collection group of the European Committee for Homeopathy in 1991,[49] is widely used in conventional research as well as in complementary and alternative medicine research and describes the general health status of the patient. Its assessment appears to be positively correlated with the clinical outcome of the patients.[26,30]

Satisfaction with treatment. This measure was rated by the patients in their diaries at the end of the treatment phase (day 10) by means of the integrative medicine patient satisfaction scale (IMPSS), a 5-point scale comprising the ratings 1 = very satisfied, 2 = satisfied, 3 = neutral, 4 = dissatisfied, and 5 = very dissatisfied. The IMPSS as also presented by the data collection group of the European Committee for Homeopathy[49] describes the patient's satisfaction with treatment and is also widely used in conventional research and complementary and alternative medicine research. The assessment of this measure appears to be positively correlated with the clinical outcome of the patients.[26,30]

Figure 1. Flow Chart of Trial Procedures Including Reasons for Withdrawals



[a]More than 1 protocol deviation per patient was possible.

Abbreviations: 3 × 30, 30 drops 3 times per day; 3 × 60, 60 drops 3 times per day; ITT, intention to treat.

Adverse events. The frequency, nature, and severity of AEs and vital parameters were documented by the investigator, and at treatment days 5 and 10, the subjective tolerability was judged by the patient using a 4-point rating scale: 1 = very good, 2 = good, 3 = moderate, or 4 = bad.

Statistical Analysis

Separate plans for statistical analyses were provided for all interim analyses as well as for the final analysis. Statistical results reported in the current article were generated from all available data, with an intention-to-treat (ITT) analysis by using the last observation carried forward, unless stated otherwise.

Calculations concerning the primary outcome measure followed the recommendations of the European Medicines Agency given in the document entitled *Points to Consider on Adjustment for Baseline Covariates.*[50] Accordingly, the confirmatory analysis was based on a 2-factor analysis of covariance, with the 2 factors being the treatment group and center, and the baseline value the covariate. An overall type 1 error rate of $\alpha = .05$ (2-sided) was controlled by application of the decision boundaries of O'Brien and Fleming.[51]

Secondary outcome variables were evaluated using descriptive statistical methods, with all reported *P* values being 2 sided. Depending on the criterion, different statistical tests were used for comparison of the treatment groups. Differences between the active medication and placebo were tested by applying the χ^2 test with respect to changes in (1) individual symptoms of the CIS, (2) changes in diverse response criteria according to the total CIS, (3) changes in further cold-relevant symptoms, and (4) general well-being. Further differences between the groups regarding the duration of inability to work, the duration of activity limitation, and the changes in the health state (EQ-5D) were tested by calculating the Mann-Whitney and Wilcoxon 2-sample test statistic, whereas the group differences with respect to time until onset of treatment effect, treatment outcome—the IMOS—and satisfaction with treatment—the IMPSS—were tested applying the Mantel-Haenszel χ^2 test. All reported *P* values are 2 sided.

RESULTS

Baseline, Compliance, and Withdrawals

The statistically significant superiority of the active medication compared with placebo had already been demonstrated for both the SD and the HD parts of the trial after the second interim analysis, based on 182 patients; therefore, the trial was stopped at that stage. Twenty-five subjects were overenrolled. The final analysis was performed based on all 207 participants included. In the results described in the current article, we present the results of the HD part of the study, comprising 104 patients (Figure 1).

Table 1. Demographic Data of Participants (n = 104) at Baseline (ITT)

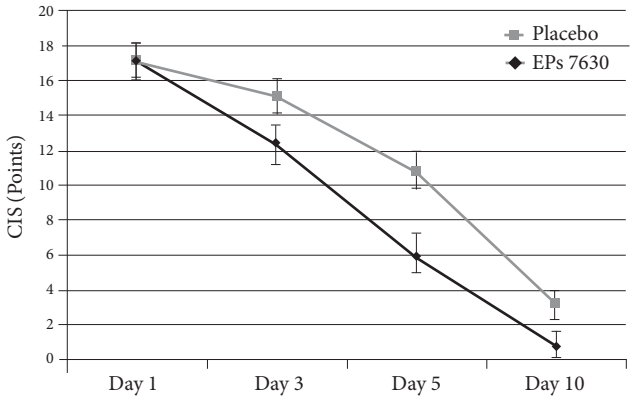
Demographic Characteristics	EPs 7630 (n = 52) n (%)	Placebo (n = 52) n (%)
Gender		
Male	14 (27%)	12 (23%)
Female	38 (73%)	40 (77%)
Age, y, mean ± SD	36.8 ± 9.9	33.8 ± 10.8
Height, cm, mean ± SD	168.7 ± 9.0	169.0 ± 7.8
Weight, kg, mean ± SD	70.6 ± 11.4	68.4 ± 13.0
BMI, kg/m^2, mean ± SD	24.8 ± 3.7	23.9 ± 3.8
Recurrence of the common cold during the past 12 mo	8 (15.4%)	8 (15.4%)
Previous common-cold medication		
Mucolytics	3 (5.8%)	4 (7.7%)
Ascorbic acid	2 (3.8%)	2 (3.8%)
Other analgetics/antipyretics	4 (7.7%)	2 (3.8%)
Smoker status		
Current smoker	6 (11.5%)	5 (9.6%)
Nonsmoker	44 (84.6%)	42 (80.8%)
Passive smoker	1 (1.9%)	2 (3.8%)
Ex-smoker	1 (1.9%)	3 (5.8%)
Alcohol consumption	22 (42.3%)	20 (38.5%)
Caffeine consumption	52 (100%)	51 (98.1%)
Negative GABHS test	52 (100%)	52 (100%)

Abbreviations: ITT, intention to treat; SD, standard deviation; BMI, body mass index; GABHS, group A β-hemolytic streptococcus.

All participants received treatment and provided efficacy data. Therefore, 104 patients—active treatment (n = 52) and control group (n = 52)—were included in the ITT analysis and the safety data set. The mean duration of treatment was 9.8 ± 0.9 and 9.8 ± 1.0 days in the 7630 and control groups, respectively. Two patients in the active treatment group and 3 patients in the control group terminated the trial prematurely. See Figure 1.

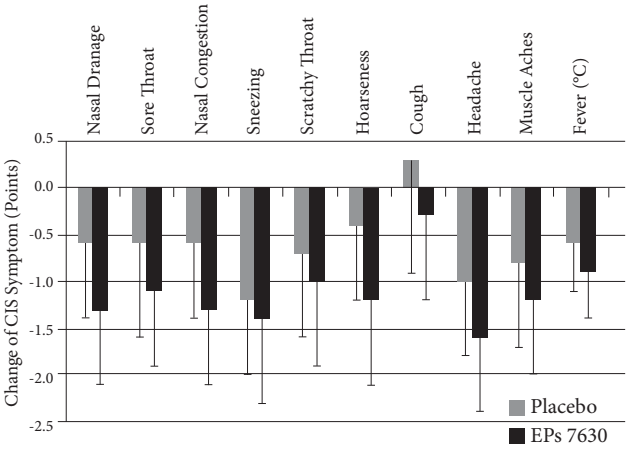
More than 95% of participants took the study's medication—7630 or the active medication—during the study's entire period, and patients' compliance was rated as very good. Demographic and baseline data are summarized in Table 1. All of the study's participants were Caucasians and approximately three-quarters of the patients were female. A comparison of the treatment groups with respect to gender, age, weight, height, and body mass index (BMI) showed no significant differences between the treatment groups. The number of patients with recurrent disease and use of CC medication previously as well as smoker status and alcohol or caffeine consumption were comparable between the groups. The group A β-hemolytic streptococcus test was negative in all participants.

Figure 2. Course of the CIS of Patients in the 2 Treatment Groups (n = 104; ITT, mean, and 95% CI)



Abbreviations: CIS, cold intensity score; ITT, intention to treat; CI, confidence interval.

Figure 3. Changes in Individual Symptoms of the CIS From Day 1 to Day 5 (n = 104; ITT, mean, and SD)



Abbreviations: CIS, cold intensity score; ITT, intention to treat; SD, standard deviation.

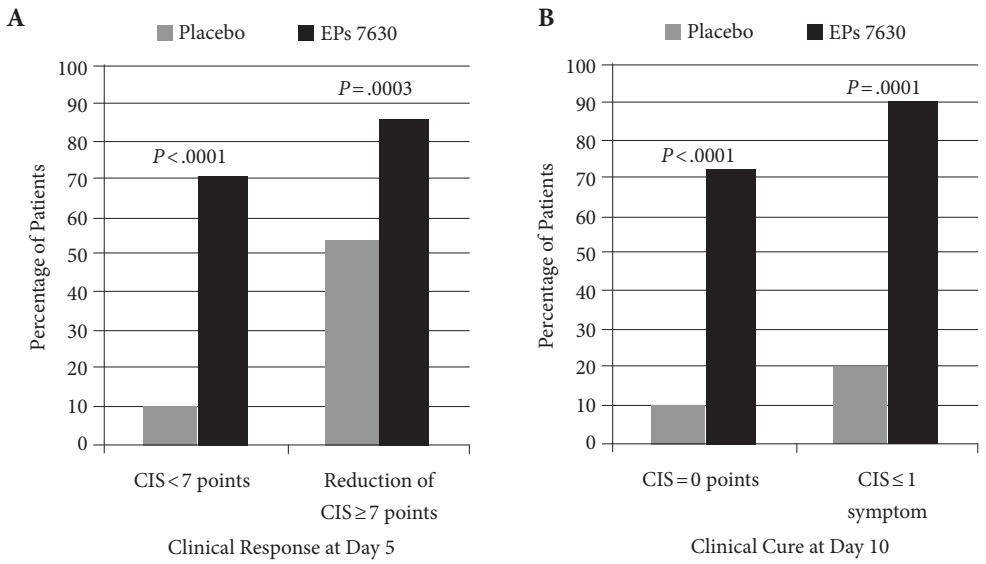
Primary Efficacy Evaluation

At baseline, the mean total CIS was comparable in the 2 treatment groups—active treatment group, 17.2 ± 3.8 points and controls, 17.1 ± 3.7 points (Figure 2). Until day 5, the mean total CIS decreased by 11.2 ± 4.8 points for the active treatment group and 6.3 ± 4.7 points for the controls. Subsequently, the decrease in CIS continued to occur, reaching 0.9 ± 2.8 for the active treatment group and 3.2 ± 2.8 for the controls on day 10. Accordingly, the mean SSID from baseline through day 3 to day 5—the primary efficacy criterion—was 16.0 ± 7.4 points for the active treatment group and 8.3 ± 7.6 points for controls, a statistically significant difference ($P < .0001$).

Secondary Efficacy Evaluation

The mean decreases in all major and minor individual symptoms of the CIS were noticeably higher for the active treatment group than for the control group (Figure 3).

Figure 4. Treatment Response on Days 5 and 10 According to 4 Response Criteria Based on the CIS (n = 104; ITT)



Note: Figure 4A shows the response at day 5 and Figure 4B shows the response at day 10.

Abbreviations: CIS, cold intensity score; ITT, intention to treat.

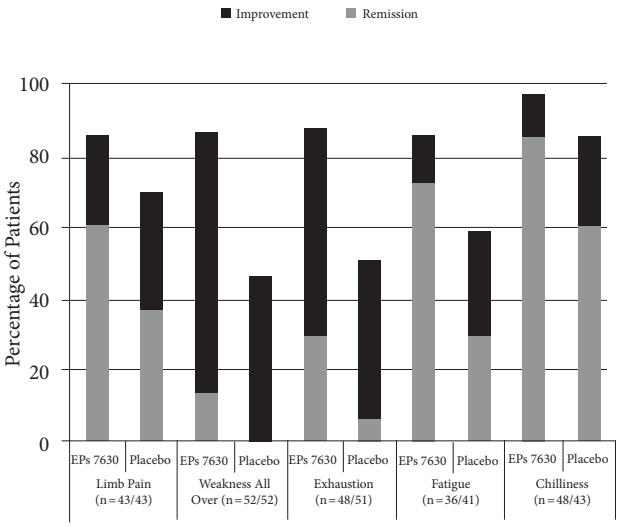
The response rates were also higher for the active treatment group than for controls. Statistically significant differences between groups for 2 response criteria had already occurred on day 5 (Figure 4A): (1) CIS <7 points—71.2% for the active treatment group versus 9.6% for the control group ($P < .0001$) and (2) reduction in CIS ≥7 points—86.5% for the active treatment group versus 53.8% for the control group ($P = .0003$). On day 10, significantly more patients were cured in the active treatment group than in the control group (Figure 4B): (1) CIS = 0 points, 73.1% versus 9.6%, respectively ($P < .0001$) and (2) CIS ≤1 symptom, 90.4% versus 21.2%, respectively ($P < .0001$).

For the further cold-relevant symptoms, significantly higher combined remission and improvement rates were found in the active treatment group compared with controls for 4 symptoms (Figure 5): (1) weakness all over—86.6% versus 46.2%, respectively ($P < .0001$); (2) exhaustion—87.5% versus 51.0%, respectively ($P = .0002$) (3) fatigue—86.1% versus 58.6%, respectively ($P = .0023$); and (4) chills—97.9% versus 86.1% of patients, respectively ($P = .0170$).

From day 1 to day 10, abnormal rhinologic findings decreased in intensity and finally disappeared completely in the active treatment group. In contrast, several patients receiving the placebo still showed at least 1 of the following rhinoscopic parameters on day 10: reddened nasal mucosa (n = 18), nasal secretion (n = 14), nasal discharge left (n = 14), and nasal discharge right (n = 13).

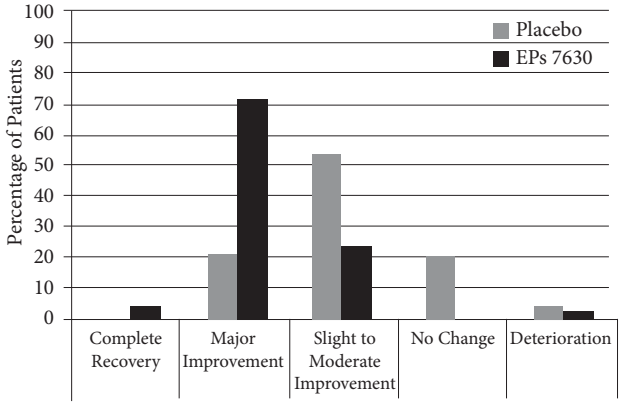
Further significant differences between the active treatment and control groups were found in terms of participants' general well-being, impaired activity, and inability to work. The number of patients with a remark on

Figure 5. Percentage of Participants Showing Improvement or Remission of Certain Cold-relevant Symptoms From Day 1 to Day 5



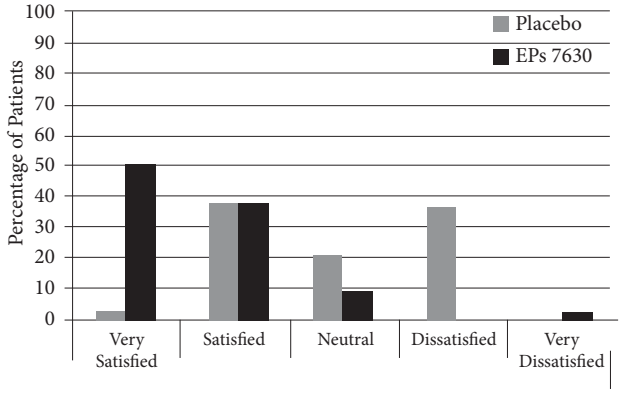
Note: Calculations were based on the number of participants with symptoms on day 1 for each group. Remission was found if the symptoms were rated as mild, moderate, severe, or very severe on day 1 and were not present on day 5. Improvement was found if any decrease in symptom intensity occurred between day 1 and day 5, excepting remissions.

Figure 6. Treatment Outcomes on the IMOS as Assessed by the Investigator at Day 5 (n = 104; ITT)



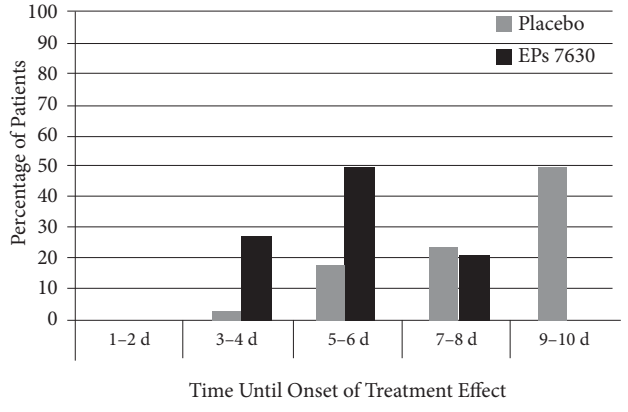
Abbreviations: IMOS, integrative medicine outcomes scale; ITT, intention to treat.

Figure 7. Satisfaction With Treatment as Shown on the IMPSS at the End of Treatment (n = 104; ITT)



Abbreviations: IMPSS, integrative medicine patient satisfaction scale; ITT, intention to treat.

Figure 8. Time Until Onset of Treatment Effect as Documented by Participants (n = 104; ITT)



Abbreviation: ITT, intention to treat.

general well-being on day 1 and with results showing improvement in general well-being from day 1 to day 5 was 96.2% in the active treatment group and 61.5% in the control group ($P < .0001$). Accordingly, the duration of activity limitation (ie, the number of days with less than 100% of participants' usual activity level) was 6.9 ± 1.5 and 8.8 ± 1.4 days in the active treatment group and the control group, respectively ($P < .0001$). And the number of days of work absenteeism was also lower in the active treatment group than in the control group: 6.4 ± 1.6 days versus 8.3 ± 2.1 days, respectively ($P < .0001$).

At baseline, analyses of participants' ratings of health-related quality of life on the EQ-5D revealed no substantial differences on the 5 dimensions of the EuroQol questionnaire—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression—between the groups. However, on day 5, the number and rate of patients with remission or improvement were higher in the active treatment group than in the control group, across all dimensions. Improvement of further items marked in the patient's diaries (eg, sleepiness/alertness and sleep quality/morning feeling) was also more pronounced in the active treatment group compared with controls. Finally, self-assessment of health-related quality of life on the EQ-VAS indicated that patients treated with active treatment group recovered significantly more from day 1 to day 5 and further to day 10 than patients in the control group ($P < .0001$).

According to the IMOS on day 5 (Figure 6), complete recovery or major improvement was seen by the investigator significantly more often in the active treatment group than in the control group, at 75.0% and 21.2%, respectively ($P < .0001$).

Analyses of treatment satisfaction revealed significant differences between the groups (Figure 7), with 88.5% versus 42.3% of patients in the active treatment group and the control group, respectively, being either very satisfied or satisfied ($P < .0001$).

In the active treatment group, participants noticed a treatment effect considerably earlier, with 76.9% stating a response within a maximum of 5 to 6 days compared with 19.2% in the control group (Figure 8). One patient (1.9%) in the active treatment group and 4 patients (7.7%) in the control group responded "not at all" ($P < .0001$).

Safety and Tolerability

During the double-blind treatment phase, 11 AEs occurred in a total of 11 of 104 patients, 8 patients in the active treatment group (15.4%) and 3 patients in the control group (5.8%). None of these AEs was classified as serious or severe in intensity. In 3 patients—1 with moderate sinusitis in the active treatment group and 2 with moderate acute bronchitis/laryngitis in the control group—the AE was considered to be unrelated to the study's drug.

Overall, a causal relationship to the trial medication could not be excluded in 8 patients. The relationship was judged as "possible" in only 3 cases and as "unlikely" in 5 cases. In the active treatment group, these were (1) mild epistaxis in 5 patients, with 2 possibly being related and 3 unlikely to be

Table 2. Frequency of AEs After SD[39] and HD Treatment

		Nonserious AEs				
		Mild	Moderate	Severe	Total	Serious AEs
SD	EPs 7630 group (n = 52)	1	1	0	2 (3.8%)	0
	Control group (n = 51)	0	1	0	1 (2.0%)	0
HD	EPs 7630 group (n = 52)	6	2	0	8 (15.4%)	0
	Control group (n = 52)	1	2	0	3 (5.8%)	0

Abbreviations: AEs, adverse events; SD, standard dose; HD, high dose.

related to the medication; (2) mild epigastric discomfort in 1 patient, with the AE possibly being related; and (3) moderate upper abdominal pain in 1 patient, with the AE unlikely to be related (Table 2); in the control group, this was mild epigastric discomfort in 1 patient, with a relationship unlikely. All AEs subsided in all patients without complications.

On day 5, the patients in the active treatment group rated the tolerability of the study's medication as slightly better than patients in the control group. A total of 51 of 52 patients in the active treatment group (98.1%) and 46 of 52 patients in the control group (88.5%) reported a good or very good tolerability. On day 10, the rating was similar, with a slight increase in favor of the rating being very good in both groups.

DISCUSSION

The results of this 2-arm HD study—part of a 4-arm, randomized, placebo-controlled double-blind trial—support the evidence for successful treatment of the CC in adults with 7630. As already demonstrated by the results of the 2-arm SD part of the study,[40] patients in the HD part receiving active treatment showed better recovery in terms of symptom improvement than participants in the control group. From day 1 to day 5, the mean total CIS decreased nearly twice as much in the active treatment group than in the control group.

The primary outcome measure—the SSID—for the CIS from day 1 to day 5, which reflects the longitudinal nature of the trial, was significantly higher in the active treatment group compared to controls. The greatest differences in treatment effect between the groups were seen in nasal drainage, nasal congestion, and hoarseness.

Analysis of secondary outcome measures revealed similar results (ie, a more favorable outcome for patients in the active treatment group). This finding was especially true for the clinical response at day 5 and the clinical cure at day 10 as well as for the cold-relevant symptoms, weakness all over, exhaustion, fatigue, and—in all of these—the current study found significant differences between the groups.

Effective treatment of the CC might have great economic impact on the health care system, because the disease is a major cause for visits to doctors and missed days of work.[2-4] The current study's results showed that the improvement in general well-being from day 1 to day 5 was significantly more pronounced in patients in the active treatment group than in those in the control group. This result correlates with the current study's findings that a therapeutic intervention with this medication reduced the mean duration of inability to work and the duration of activity limitation significantly more than placebo treatment.

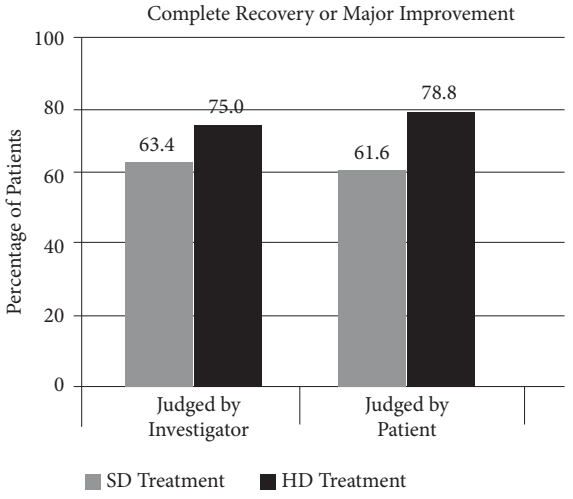
Health-related quality of life as assessed by the EQ-VAS, from day 1 to day 5, was significantly better in participants receiving the active medication compared to those receiving the placebo. Improvements in the EQ-5D dimensions—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression—indicate better mental health and lower stress, which in turn are beneficial for recovery and disease resistance.[52]

Treatment effects assessed by the investigator as well as by the participants through the IMOS support the clinical findings mentioned above. Complete recovery or major improvement at day 5 occurred significantly more often in the active treatment group than in the control group. Hence, the herbal drug in the current study has the potential to influence the course of the disease positively by reducing symptoms and shortening its duration. Moreover, satisfaction with treatment documented by the participants in their diaries by means of the IMPSS at the end of the treatment on day 10 turned out to be significantly higher in the active treatment group than in the control group.

Overall, the treatment effects of 7630 HD were more pronounced in comparison with the effects found in the SD part of the trial that was published earlier with regard to the primary and secondary outcome variables.[40] When looking at the 7630 groups, the mean SSID from baseline to day 5 was 14.6 ± 5.3 points for the SD treatment[40] compared with 16.0 ± 7.4 points for the HD treatment. This difference accounts for a 10% higher improvement with the HD treatment. Similarly, treatment outcomes on day 5 as judged by the investigators and the patients on the IMOS showed higher rates of complete recovery or major improvement for the HD treatment (Figure 9).

Due to the confirmatory nature of this phase 3 trial, more complex, multivariate analyses to investigate the potential influence of baseline variables on the course of the disease were not performed. Nevertheless, multivariate modeling could be considered as part of a meta-analysis

Figure 9. Treatment Outcome in EPs 7630 Groups on Day 5 (IMOS) after SD[39] and HD Treatments as Assessed by the Investigators and the Participants (n = 52) Both for the SD and HD (ITT)



Abbreviations: IMOS, integrative medicine outcomes scale; SD, standard dose; HD, high dose; ITT, intention to treat.

based on individual patient's data. Moreover, given the nature of the CC, conducting a trial in subsequent years would also be an interesting aspect for further investigations.

In the HD trial discussed in this article, 7 AEs in the active treatment group and 1 in the control group were considered to be potentially related to the trial medication. No serious AEs occurred, and none of the 11 AEs was classified as of severe intensity. Hence, serious risks or detrimental effects for patients are unlikely to occur during therapy with 7630. This conclusion is confirmed when looking at the subjective tolerability of the trial's medications as assessed by patients on day 5: It was rated better in the active treatment group than in the control group, with only 1 patient in the active treatment group not reporting a good or very good tolerability.

Compared with the results of the SD part of the trial,[40] the frequency of mild or moderate AEs was higher in this HD trial (Table 2). However, severe or serious AEs did not occur in any part of the trial. A dose-dependent frequency of reported AEs in patients treated with the active medication had already been reported in an earlier trial.[31] Therefore, considering both efficacy and safety, the SD may constitute the optimal dose with respect to the benefit-risk-ratio.

CONCLUSIONS

Treatment of adult patients suffering from the CC with the *P sidoides* extract 7630 was shown to be effective, safe, and well tolerated. Compared with the placebo, active treatment significantly reduced the intensity of symptoms and the duration of the CC and is a good treatment option for the CC.

ACKNOWLEDGEMENTS

We thank Dr Frank Erdnüß for medical writing and editing services. Study and medical writing services were supported by Dr Willmar Schwabe GmbH & Co KG (Karlsruhe, Germany).

AUTHOR DISCLOSURE STATEMENT

David S. Riley, Viktor G. Lizogub, and Walter Lehmacher were reimbursed for their scientific services on a contractual basis by Dr Willmar Schwabe GmbH & Co KG, (Karlsruhe, Germany); Andrea Zimmermann and Petra Funk are employees of Dr Willmar Schwabe GmbH & Co. KG.

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