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# Efficacy and Safety of a Fixed Combination Phytomedicine in the Treatment of the Common Cold (Acute Viral Respiratory Tract Infection): Results of a Randomised, Double Blind, Placebo Controlled, Multicentre Study

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## Summary

Objective *The common cold (acute viral respiratory tract infection) is one of the most frequent diseases in man, world-wide. Clinically relevant efficacy should include early improvement of all symptoms. Results of a clinical trial of a commercially available fixed combination herbal remedy (*Radix echinaceae, Radix baptisiae, Herba thujae*) are reported here. The aim of this study was to verify clinical efficacy shown in recent studies under (i) good clinical practice (GCP) quality assurance and (ii) common situations at family doctors.*

Methods *Patients attending one of 15 study centres (practitioners) as a result of an acute common cold were randomised to the double-blind placebo-controlled study. Three tablets of study medication were applied t.i.d. for 7 to 9 days. Patients daily documented the intensity of 18 cold symptoms, as well as the cold overall, using a 10-point scale and estimated their general well-being using the Welzel-Kohnen colour scales. Additionally, the severity of illness was assessed by the physician on days 4 and 8 (CGI-1). The main and confirmatory outcome measure was expressed as a total efficacy value. This was gauged from the z-standardised AUC values of the primary endpoints (rhinitis score, bronchitis score, CGI-1 and general well-being). Adverse events, overall tolerability, vital signs and laboratory parameters were documented.*

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Results *263 patients were included. For safety analysis, all patients were used. 259 patients were evaluable for primary efficacy analysis (ITT). Results were confirmed analysing only the 238 valid cases (VCs). The primary efficacy parameters showed the superiority of the herbal remedy over placebo ($p < 0.05$). Effect size was 20.6% of the standard deviation (90% CI: 0.04–41.1%; ITT) and 23.1% (1.7–44.5%; VC). In relation to the general well-being, the effect size was 33.9% of the standard deviation (12.5–55.3%; VC). Patients who suffered from at least moderate symptom intensity at baseline showed response rates (at least 50% improvement of the global score, day 5) of 55.3% in the herbal remedy group and 27.3% in the placebo group ($p = 0.017$; NNT = 3.5). In the subgroup of patients who started therapy at an early phase of their cold, the efficacy of the herbal remedy was most prominent ($p = 0.014$ for the primary efficacy parameter). The therapeutic benefit of the herbal remedy had already occurred on day 2 and reached significance ($p < 0.05$) on day 4, and continued until the end of the treatment in the total score of symptoms, bronchitis score and rhinitis score, as well as in the patients' overall rating of the cold intensity. At that time, equal levels of improvement were reached three days earlier in the verum group than in the placebo group. In 26 patients receiving the herbal remedy and 23 patients receiving placebo, adverse events were reported. Adverse drug reactions were suspected in two patients in the verum group and in four patients in the placebo group. Serious adverse events did not occur.*

Conclusions *This study shows that the herbal remedy is effective and safe. The therapeutic benefit consists of a rapid onset of improvement of cold symptoms. If patients with colds are able to start the application of the herbal remedy as soon as practical after the occurrence of the initial symptoms, the benefit would be expected to increase (e.g. self-medication).*

## Introduction and Objectives

Effective treatment of the common cold, one of the most frequent diseases in man, is desirable. Impairment of patients' daily life activities and the individuals' capacity to work results in a socio-economic wastage of resources. In Europe, the incidences can be estimated as 3–6 colds per adult per year[1], 90% of which are of viral origin[2]. Primary symptoms are reported to be rhinitis, cough, headache, pharyngitis, laryngitis, and sometimes fever. Although common colds heal spontaneously, effective treatment is needed because cold symptoms disturb the normal activities of daily life and decrease the individual's capacity for work. Clinically relevant efficacy should include the early improvement of all symptoms. Antibiotics have no benefit, except in the case of secondary bacterial infections[3,4].

The immunomodulatory effects of the herbal remedy* – including both specific and unspecific immune responses[7–9] without showing the antigenicity of the plant-derived ingredients – are reviewed elsewhere[11]. The clinical efficacy of the commercially available phytomedicine has been shown by Vorberg[5] and Reitz[6] in double-blind placebo-controlled studies. The aims of the study reported here were to verify those results using (i) good clinical practice (GCP) procedures and (ii) under general practice conditions. For this reason, study participants suffering from a common cold were not recruited by active advertisement but from patients spontaneously attending their family doctor because of their cold.

The most prominent efficacy of the herbal remedy was expected in patients starting their therapy during the initial phase of their cold when the host defence is still being built up[11]. In addition to gathering data on all study participants, a subgroup analysis

*Esberitox® N; manufactured by Schaper & Brümmer GmbH & Co KG, Germany

focused on those patients who had an indicator symptom of a minimum severity which was stable or worsening during the first three days after baseline. These patients, who were in the initial phase of their current cold, were expected to show the most noticeable clinical benefits from immunomodulation. However, when treatment decisions are being made, further developments of the host's defences cannot be readily foreseen, nor can the further development of clinical symptoms. Therefore, all patients suffering from an acute common cold at the time of attending their family doctor were considered as eligible if all other inclusion/exclusion criteria were fulfilled, and the study was primarily analysed on all patients according to the pragmatic[12] intention to treat principle.

# Methods

## Patients

Patients of both sexes aged 18–70 years who were attending their family doctor for an acute common cold were included in the study on an out-patient basis after written informed consent was obtained. Exclusion criteria were: acute influenza, the actual cold lasting longer than three days; chronic diseases of the respiratory tract; a fever resulting in a temperature greater than 38.5°C; more than one respiratory tract infection lasting longer than three weeks during the previous year; bacterial respiratory tract infection; progressive systemic diseases (such as tuberculosis, leukosis, collagenosis, multiple sclerosis, HIV infection and autoimmune diseases); organ transplantation; known inflammatory gastrointestinal disease; known impairment of resorption; intake of antibiotics during the seven days before baseline or during the study; immunosuppressing, immunostimulating or immunomodulating medication during four weeks before baseline; allergy tests or vaccination during the study; cytostatic therapy during the six months before baseline; severe internal diseases; known clinically relevant abnormalities in laboratory values; pregnancy or lactation; inability to understand the consequences of participation in the study; participation in any other study during this clinical trial or 12 weeks before baseline; and previous participation in this study.

## Treatment, Blinding and Randomisation

The treatment group medication was as follows:

- Esberitox® N tablets. Active ingredients: ethanolic-aqueous extracts of 2 mg of herba thujae occidentalis, 7.5 mg of radix echinaceae (purpureae + pallidae = 1 + 1), 10 mg radix baptisiae tinctoriae, plus other ingredients.
- Placebo tablets contained only the other ingredients.

Both types of tablets were similar in taste, smell and appearance, and blistered using opaque foil. Both were therefore indistinguishable by both patients and investigators. The dosage regimen was as follows: commencement at the time of the patients' initial visits to their physicians (baseline, day 1), three tablets t.i.d. for 7–9 days, and at least until their final visit to the investigator. Compliance was controlled by counting the unused tablets of each patient at each visit.

Randomisation (in balanced blocks of four patients), blinding and packaging using consecutive patient numbers were performed by an independent external manufacturer using the validated PC programme RanCode (idv Gauting). Patients

and investigators remained 'blinded' throughout the whole study. All other persons active in the study, including the biometrician, remained blinded at least until database lock. In case of emergencies, investigators were provided with sealed envelopes containing a code break. These all remained sealed.

Concomitant treatment was documented. Patients using antibiotics, interferons, cytokines (e.g. G-CSF, GM-CSF), interleukins or other immunotherapy, were excluded from the study. Patients using analgesics (e.g. acetylsalicylic acid), vitamins, other medications against the common cold in general, or against single cold symptoms (e.g. nasal decongestants, antipyretics, antitussives, expectorants, mouth or throat treatments), were excluded from the analysis of valid cases, but remained in the intention-to-treat (ITT) population.

## Efficacy and Safety Data

Primarily, patients documented their cold symptoms in a diary once daily in the evening (Table 1) starting at baseline (day 1). Each item was estimated on a line with a 10-point scale (0 = no symptom; 1, 2 and 3 = mild symptom; 4, 5 and 6 = moderate symptom; 7, 8 and 9 = severe symptom) and grouped during data analysis. Additionally, the diaries contained the Welzel-Kohnen colour scales, which is a validated tool for the measurement of self-estimated general well-being[13]. At day 1, day 4 (or day 3 or 5) and day 8 (or day 7 or 9) investigators estimated the severity of the patients' illnesses (clinical global impression item 1 – CGI-1)[10].

Standard safety laboratory parameters were determined at baseline and at the end of treatment.

Adverse events were documented upon free inquiry. Estimations about the relationships with the study medication were made by using a modification of the algorithm proposed by Karch and Lasagna[14]. Overall impressions of tolerability were given independently by both, the investigator and the patient using the ordinal scale of 'very well, well, moderate, bad, very bad'.

## Statistics

The main aim of the study was to demonstrate the clinical efficacy of the herbal remedy versus placebo. The primary endpoint was a total efficacy value which was calculated according to O'Brien[15] using the areas under the curve of the rhinitis score, the bronchitis score, the clinical global impression of severity of the cold and the self-estimated general well-being. In short, the sum of $z$-standardised (over both treatment groups) areas under the curve was calculated. A sample size of 240 patients was conservatively projected assuming $\delta/\sigma = 0.33$, $\alpha = 0.05$ (one-tailed) and $1-\beta = 0.8$. Further, a total score of cold was calculated as the mean of all patients' diary score items (excluding nasal congestion and the overall severity) mentioned above, in order to get an impression of the clinical relevance of differences between treatment groups.

Primarily, efficacy evaluations reported here were performed using the intention to treat (ITT) population which was defined as all treated patients with diary data and at least one CGI-1 assessment after baseline. Evaluations were repeated in the VCs, which were defined as all ITT patients who completed the study without major protocol violation. One-tailed $p$-values are reported. Safety data were evaluated in all patients who took at least one tablet of the study medication (the safety population).

For confirmatory statistical analysis, the total efficacy value according to O'Brien was

**Table 1. Battery of symptoms assessed in the patients' diaries. Individual items were condensed to local summarising scores. The rhinitis score and bronchitis score were part of the primary endpoint**

| English | Original wording | Local summarising score |
|---|---|---|
| Congested nose | Nase verstopft | |
| Runny nose | Nase läuft | |
| Sniffling | Nase „hochziehen" | **Rhinitis score** |
| Frequency of handkerchief use | Ich muß häufig die Nase putzen | |
| Frequency of sneezing | Ich muß häufig niesen | |
| Sore throat | Halsschmerzen | |
| Headache | Kopfschmerzen | |
| Joint aches | Gliederschmerzen | Pain score |
| Dizziness | Benommenheit | |
| Difficulties of swallowing | Schluckbeschwerden | |
| Cough | Husten | |
| Hoarseness | Heiserkeit | |
| Expectoration | Auswurf | |
| Chest pain | Schmerzen im Brustbereich | **Bronchitis score** |
| Shortness of breath | Atemnot | |
| Night sweats | Nachtschweiß | |
| Sweating during the day | Schwitzen am Tage | Fever score |
| Chills | Schüttelfrost | |
| **Overall severity of the cold** | Erkältung/insgesamt | |

compared across treatment groups using an analysis of covariance (covariate: symptom score at baseline). Subsequently, all triple and double combinations, as well as the single primary parameters, were tested according to Lehmacher *et al.*[16]. The *t*-test was used for the total score of cold, the overall severity of the cold and the local summarising scores. For discrete variables, the Wilcoxon U-test for independent samples was used. Categorical variables were analysed by the $2 \times 2$-test.

For responder analyses, the chi-squared test was used. Patients with at least moderate symptom intensity at baseline were assessable for responder analysis. Response was defined as 'at least 50% improvement of the global score'.

Additionally, patients were classified with regard to the initial intensity of the diary parameter of 'nasal congestion' and its development during the first three days after baseline. Among all of the diary symptoms, nasal congestion is a frequent[17] and relatively late event during a cold[17–19] and should reach a maximum after the start of the observational period in all patients who attended the study and had an early phase cold at baseline. Thus, using this algorithm, it was possible to identify those patients who had started the application of the study medication early on in their cold. In detail, the subgroup of patients was selected who fulfilled both the conditions of 'nasal congestion $\geq 4$' and 'mean of nasal congestion on days 1 through 3 not more than one point better than at baseline', i.e. moderate or severe nasal congestion stable or worsening during the first three days after baseline. It was expected that differences between the active compound and placebo medication would be most prominent in this group of patients who started 'early therapy' during their cold.

## GCP

The study started after a positive vote of the ethics committee responsible for the

principal investigator. Data validity was ensured by close monitoring performed by IMEREM, Nuremberg, who also performed data entry and data management. One study centre had to be completely excluded from the study for invalidity reasons. Statistical evaluation was done by IAS, Bielefeld. According to GCP, the validity of data and results was confirmed by an independent audit of protocol, case record forms, four investigator sites and the study report. The audit was performed by Medical Consulting, Munich.

# Results

## Conduct of Study

A total of 263 patients were included in 15 study centres.

One study centre did not recruit any patients. One centre was excluded from further study participation because data at that centre were invalid as shown by GCP monitoring. Randomisation was done per protocol.

## Participant Flow

The number of patients in each population analysis is given in Table 2. Four patients had to be excluded from the ITT population because they did not attend the investigator again and/or did not return the diary, which was essential for the primary endpoint. A further 21 patients were excluded from the VC analysis because of major protocol violations (exclusion criteria, premature termination) interfering with efficacy evaluation. Primary efficacy results are based

**Table 2. Participant flow – populations for data analysis; absolute number (percentage per column)**

| Population | Herbal remedy | Placebo | All patients |
|---|---|---|---|
| All patients (safety population) | 131 (100%) | 132 (100%) | 263 (100%) |
| Primary efficacy parameter not available | 3 (2.3%) | 1 (0.8%) | 4 (1.5%) |
| Intention-to-treat (ITT) population for primary efficacy analysis | 128 (97.7%) | 131 (99.2%) | 259 (98.5%) |
| Drop-outs and relevant protocol violators | 9 (6.9%) | 12 (9.1%) | 21 (8.0%) |
| Valid cases (VCs) for secondary efficacy analysis) | 119 (90.8%) | 119 (90.2%) | 238 (90.5%) |

**Table 3. Demographic data of study patients. Frequency or mean ± standard deviation, as well as range, are given. All patients were caucasian**

| | Herbal remedy | Placebo | All patients |
|---|---|---|---|
| Sample size | 131 | 132 | 263 |
| Sex | | | |
| male | 51 | 45 | 96 |
| female | 80 | 87 | 67 |
| Smoker | | | |
| yes | 20 | 124 | 44 |
| no | 102 | 100 | 202 |
| ex-smoker | 9 | 8 | 17 |
| Age (years) | 41.2 ± 15.0; 17–83 | 39.1 ± 13.6; 18–74 | 40.2 ± 14.3; 17–83 |
| Weight (kg) | | | |
| male | 79.7 ± 10.9; 58–112 | 78.6 ± 10.2; 60–98 | 79.2 ± 10.5; 58–112 |
| female | 65.9 ± 12.0; 49–118 | 63.8 ± 10.6; 46–93 | 64.8 ± 11.3; 46–118 |
| Height (cm) | | | |
| male | 177 ± 7; 158–193 | 177 ± 7; 160–190 | 177 ± 7; 158–193 |
| female | 166 ± 6; 152–180 | 164 ± 6; 148–175 | 165 ± 6; 148–180 |

on the ITT analysis as reported here and were confirmed using the valid cases. Patients are equally distributed in both treatment groups in all populations.

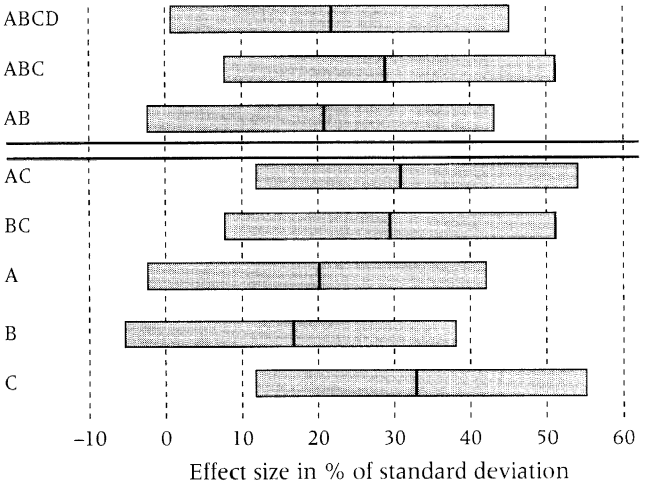
## Demographic and Other Baseline Data

Treatment groups seemed not to differ from one another in relation to the demographic data of the study patients (Table 3) and data from the general physical examination (data not shown).

## Efficacy Evaluations

With respect to the total efficacy value according to O'Brien (confirmatory primary endpoint), the herbal remedy was significantly better than the placebo, both in the ITT analysis ($p = 0.0497$) and in the VC analysis ($p = 0.0381$). The effect size was 20.6% of the standard deviation (90% CI: 0.04–41.1%; ITT) and 23.1% (1.7–44.5%; VC). Results of the confirmatory and subsequent statistical tests are shown in Table 4 ($p$-values) and Figure 1 (effect sizes). The statistically significant superiority of the herbal remedy was also found in several subsequent tests: the well-being score showed the highest sensitivity ($p = 0.0048$; VC), followed by the rhinitis score, and slightly behind it by the bronchitis score. CGI-1 did not yield a significant group difference ($p = 0.44$). In relation to the general well-being, the effect size was 33.9% of the standard deviation (12.5–55.3%; VC).

Additional analyses yielded that the time to response was reduced in the active treatment group, when compared with the




A = rhinitis score
B = bronchitis score
C = general well-being
D = clinical global impression of severity of illness

**Figure 1. Standardised effect sizes of the primary endpoint (ABCD) and subsequent subcombinations. Mean and 90% confidence intervals are shown for the VC analysis ($n = 238$ patients). If zero is not within the 90% CI, the effect size is statistically significant**

**Table 4. O'Brien-Lehmacher analysis of the primary efficacy parameters. The primary endpoint (step 1) was a total efficacy value according to O'Brien[15]. Subsequently, all triple hypotheses (step 2), double hypotheses (step 3) and single hypotheses (step 4) were tested according to Lehmacher *et al.*[16]**

| Step | Rhinitis | Bronchitis | Well-being | CGI-1 | *p*-value (VC; *n* = 238) | *p*-value (ITT; *n* = 259) |
|---|---|---|---|---|---|---|
| 1 | ● | ● | ● | ● | **0.0381** | **0.0497** |
| 2 | ● | ● | ● | – | **0.0132** | **0.0189** |
| | ● | ● | – | ● | 0.1129 | 0.1083 |
| | ● | – | ● | ● | **0.0365** | 0.0588 |
| | – | ● | ● | ● | **0.0499** | 0.0657 |
| 3 | ● | ● | – | – | 0.0568 | 0.0512 |
| | ● | – | ● | – | **0.0070** | **0.0154** |
| | ● | – | – | ● | 0.1543 | 0.1666 |
| | – | ● | ● | – | **0.0116** | **0.0182** |
| | – | ● | – | ● | 0.4120 | 0.1871 |
| | – | – | ● | ● | 0.0576 | 0.0967 |
| 4 | ● | – | – | – | 0.0581 | 0.0647 |
| | – | ● | – | – | 0.1031 | 0.0811 |
| | – | – | ● | – | **0.0048** | **0.0157** |
| | – | – | – | ● | 0.4360 | 0.4443 |

**Table 5. Standardised effect sizes of the primary endpoint (total efficacy value) and subsequent subcombinations in subgroups. Total efficacy value was calculated according to O'Brien using the *z*-standardised AUC values of rhinitis score (rhin), bronchitis score (bron), general well-being (wb; Welzel-Kohnen colour scales) and clinical global impression item 1. Subsequently all subcombinations were examined. Subgrouping was done using the diary item 'nasal congestion' as described in the text. *n* = number of cases; CI = confidence interval, *p* = *p*-value (*t*-test for the superiority of the herbal remedy)**

| | **Patients at an early phase of their cold at baseline** | | Other patients with nasal congestion at baseline | |
|---|---|---|---|---|
| *n* (placebo) | 45 | | 28 | |
| *n* (herbal remedy) | 34 | | 25 | |
| | Mean (90% – CI) | *p* | Mean (90% – CI) | *p* |
| **Total efficacy value (rhin + bron + wb + CGI-1)** | **0.49 (0.11/0.87)** | **0.017** | **–0.06 (–0.52/0.41)** | **0.580** |
| rhin + bron + wb | 0.60 (0.22/0.98) | 0.005 | –0.03 (0.49/0.43) | 0.539 |
| rhin + bron | 0.53 (0.15/0.91) | 0.011 | 0.02 (–0.45/0.48) | 0.479 |
| rhin + wb | 0.57 (0.19/0.95) | 0.007 | –0.03 (–0.49/0.44) | 0.537 |
| bron + wb | 0.61 (0.23/0.99) | 0.005 | –0.07 (–0.53/0.39) | 0.600 |
| rhin | 0.44 (0.06/0.82) | 0.029 | 0.05 (–0.41/0.51) | 0.425 |
| bron | 0.48 (0.11/0.86) | 0.018 | –0.03 (–0.49/0.44) | 0.537 |
| wb | 0.58 (0.20/0.96) | 0.007 | –0.10 (–0.56/0.37) | 0.636 |
| CGI-1 | 0.11 (–0.27/0.48) | 0.323 | –0.11 (–0.57/0.36) | 0.648 |

placebo group (Figure 2, $p_{overall} = 0.022$), in patients who suffered from at least moderate symptom intensity at baseline. Already on day 3, 18.4% of patients in the same active treatment group showed a response, in contrast to 0 patients in the placebo group ($p = 0.005$). The response rate elevated steadily and was 55.4% on day 5, when the response rate in the placebo group was only half as high ($p = 0.009$). The number needed to treat (NNT) is 5.4 for an early response and 3.5 for a response within five days. The

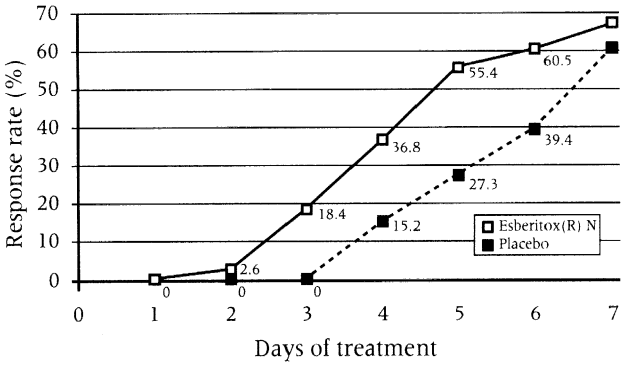



**Figure 2. Time to response defined as at least 50% improvement of the global score. Results are shown for ITT patients with at least moderate complaints at day 1 ($n$ = 71). The difference between the treatment groups was significant ($p_{overall}$ = 0.022; $p_{day\ 5}$ = 0.009; $p_{day\ 4}$ = 0.033; $p_{day\ 3}$ = 0.005)**

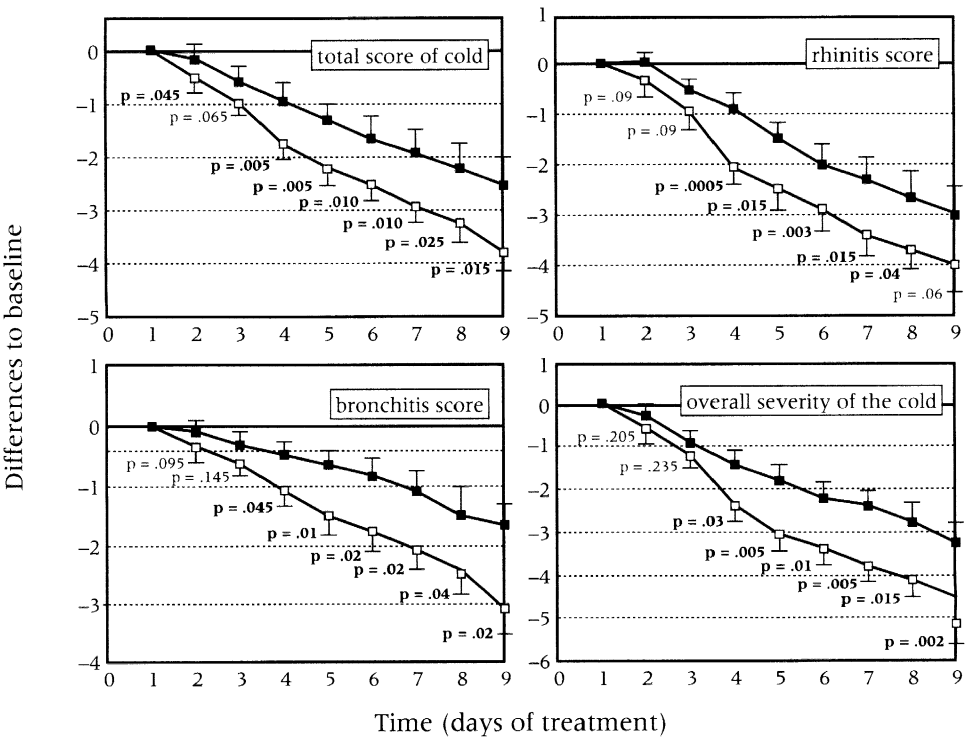



**Figure 3. Improvement of symptom scores (individual differences to baseline). Mean scores and SEM are shown for placebo (■) and the herbal remedy ( ). $p$-values ($t$-test) for the differences between treatment groups are given for the patients who started therapy in an early phase of their cold ($n$ = 62). Note the first differences between treatment groups already manifest on day 2, reaching significance from day 4 onwards**

mean time to response was 4.8 days. In the placebo group the corresponding value was 46% longer (7.0 days).

The subgroup of patients who started therapy early in their individual cold was also analysed. With respect to the primary endpoint, the herbal remedy was significantly better than placebo ($p = 0.017$), as shown in Table 5. The effect size in these patients was 49% of the standard deviation (90% CI: 11–87%). This superiority was most prominent with respect to the rhinitis score, and the other three endpoints all showed effects in the same direction. The changes with time in the total score of cold, rhinitis score, bronchitis score and overall severity of the cold are shown in Figure 3. This provides an impression of the clinical relevance of the superior effect of the herbal remedy when compared with placebo. The clinical benefit of the active treatment was already seen on the first two days after the start of treatment (days 2 and 3) and reached statistical significance at day 4, until the end of treatment. From this time until the end of observations equal levels of improvement were reached three days earlier in the active treatment group than in the placebo group. Fever score and pain score showed a minor but insignificant superiority of the herbal remedy over the placebo (data not shown). The clinically relevant differences between the treatment groups in this subgroup were, to a greater extent, due to the rhinitis and bronchitis symptoms (Figure 3). The baseline data of the symptom scores were balanced between the treatment groups, in the 'early therapeutic intervention' subgroup (data not shown) as well as in the total ITT population.

Results for the clinical global impression (estimated by the investigator) are not shown. CGI-1 (severity of cold), CGI-2 (changes compared with cold at baseline) and CGI-3 (overall estimation of efficacy) were all too insensitive for the detection of statistically significant differences between the treatment groups.

## Compliance

Compliance, determined by pill counting, was 99.7% at day 4 and 100.7% at the final visit (mean, range 63.3–158.7%). One patient took less than 80% and five patients took more than 120% of the planned dosage. During the blind review of data, these facts were classified as minor protocol violations and no exclusions were made from the VC population for this reason.

**Table 6. Overall tolerability estimated at the end of treatment; frequency (relative frequency)**

| | Tolerability | Herbal remedy ($n = 131$) | Placebo ($n = 132$) | $U$-test ($p$-value) |
|---|---|---|---|---|
| Investigator | Very good | 101 (78.3%) | 99 (76.2%) | |
| | Good | 24 (18.6%) | 27 (20.8%) | |
| | Moderate | 3 (2.3%) | 3 (2.3%) | 0.694 |
| | Bad | 0 | 0 | |
| | Very bad | 1 (0.8%) | 1 (0.8%) | |
| | Missing value | 2 | 2 | |
| Patient | Very good | 114 (92.7%) | 112 (88.9%) | |
| | Good | 6 (4.9%) | 14 (11.1%) | |
| | Moderate | 3 (2.4%) | 0 | 0.339 |
| | Bad | 0 | 0 | |
| | Very bad | 0 | 0 | |
| | Missing value | 8 | 6 | |

Interestingly, the number of patients with missing values was lower with regard to the Welzel-Kohnen colour scales (about 6%) for assessment of general well-being compared with the line scales for the cold items (about 10%).

## Safety

The overall tolerability was good or very good in most of the patients as assessed by both the investigator and the patient at the end of the treatment (Table 6). Investigators did not document either a 'bad' tolerability or a 'very bad' tolerability in any of the cases. In each group one patient reported a 'very bad' tolerability, but without any details. No differences between the treatment groups could be detected.

The number of patients with adverse events (AEs), for which a causal relationship to the study medication was not excluded, is listed in Table 7. Most of the AEs (65 AEs in 49 patients) were not related to the study medication and were equally distributed between both treatment groups. Adverse drug reactions (AEs with questionable, possible or probable relationships to the study medication) were suspected in five patients in the placebo group and in two patients in the active treatment group, respectively. Serious adverse events did not occur.

No clinically relevant changes in safety laboratory data were detected. Laboratory values outside the normal range at the end of the study occurred six times in the active treatment group and nine times in the placebo group.

# Discussion

The results of this study show that the herbal remedy is an efficacious and safe treatment for the common cold. In short, the efficacy has been detected confirmatorily for the primary endpoint in the ITT population (Table 4 and Figure 1). The optimal efficacy was shown in patients who started treatment early on in the course of their

**Table 7. The number of patients with adverse events for which a causal relationship to the study medication was not excluded. Investigators estimated the causal relationship with either the herbal remedy or placebo using a modification of the algorithm by Karch and Lasagna[14]; no = no causal relationship (not shown); quest. = questionable causal relationship; poss. = possible causal relationship; prob. = probable causal relationship. Figures give the absolute number of patients**

| Adverse event | Causal relationship | | | | | |
|---|---|---|---|---|---|---|
| | To the herbal remedy | | | To placebo | | |
| | Quest. | Poss. | Prob. | Quest. | Poss. | Prob. |
| Vertigo | | | | 1 | | |
| Bitter taste | | | | | | 1 |
| Insomnia | | 1 | | | | |
| Diarrhoea | | | | 1 | | |
| Pressure over the stomach | | | | | 1 | |
| Nausea | 1 | | | | | |
| Stomatitis | | | | 1 | | |
| Tachycardia | 1 | | | 1 | | |
| Total number of patients | 1 | 1 | 0 | 3 | 1 | 1 |

cold, before their symptoms had reached a maximum (cf. Figure 1 and Table 5). The phytocombination leads to an early response (Figure 2) and a more rapid improvement from all symptoms than in patients receiving placebo (Figure 3). Recovery of all major cold symptoms is affected. The first effects were already detected one day after the start of treatment and reached statistical significance from day 4 onwards. Bearing in mind the high degree of safety observed, the effect size found is considered to be clinically relevant. Both cold-specific questions as well as questions about the general well-being were sensitive for the detection of therapeutic effects. The Welzel-Kohnen colour scales seem to be a quick and convenient scheme for measuring general well-being relevant to the quality of life.

Although common colds heal spontaneously, effective treatment is desirable because cold symptoms impair patients' activities of daily living, including participation in sports and their individual capacity for either work or school. The clinically relevant efficacy should include an early improvement of all symptoms as shown in this study, confirming recent reports on the efficacy of the herbal remedy[5,6]. Adverse events were distributed equally in both treatment groups. Specific adverse drug reactions were not reported (Table 7). Overall tolerability was equal in both treatment groups (Table 6). All data stress the safety of the herbal remedy.

This clinical trial emphasises the clinical efficacy under conditions of daily life in general practice. The design and conduct of clinical trials are often artificial to a certain extent. Generalisation is a major aspect of the interpretation of study results. The current study may therefore be important because the study population consisted of typical outpatients. Moreover, response factors such as initial intensity of symptoms and phase of the cold were found. In particular, patients starting the therapeutic intervention at an early phase of their cold were identified by the course of an indicator symptom during the first three days of observation. This method probably results in the discarding of rapid responders to early intervention. However, rapid responders to early intervention cannot be divided from late-phase beginners by using an indicator symptom algorithm. Therefore the size of the early intervention group reported here underestimates the number of patients who obtained therapeutic benefit. When treatment decisions have to be made at the time of a patient visit, the course of clinical symptoms cannot be foreseen accurately. Therefore because of the very good safety data, therapy with the herbal remedy would be a reasonable choice for all patients attending GPs with symptoms of the common cold. This is confirmed by the overall results of this study.

If patients with colds were able to start the application of the herbal remedy immediately after the start of the first symptoms, the benefit would be expected to be even greater (e.g. patients could be supplied with the herbal remedy in advance of any manifestations of cold symptoms). This conclusion is supported by a recent report about clinical efficacy of an Echinacea-derived herbal remedy against the common cold in patients who started therapy within 24 hours after the occurrence of the initial symptoms[20].

Most treatments for the common cold are aimed at reducing rhinitis symptoms[21]. Conventional remedies can actually prolong viral shedding and the duration of the disease[21]. Neuramidase inhibitors, a new class of possible antiviral agents, are in clinical development[22]. Data about the efficacy of zinc in the treatment of the common cold are controversial[23,24]. Active ingredients of the herbal remedy have been shown to modulate immunological pathways with respect to extracts of echinacea purpurea radix[8,9,11,25], baptisia

tinctoria radix[25,26] and thuja occidentalis herba[27]. Thus clinical efficacy of the herbal remedy shown in this and recent studies is probably due to its immunomodulatory properties. This mode of action should be a matter of future research and may explain the broad influence on all cold symptoms. Therefore the herbal remedy seems to be an efficacious and safe therapeutic agent against the common cold.

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