

# Open, Multicenter Study to Evaluate the Tolerability and Efficacy of Echinaforce Forte Tablets in Athletes

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## ABSTRACT

This open, multicenter study investigated the tolerability and efficacy of a new tablet formulation of *Echinacea purpurea* extract (Echinaforce Forte; A. Vogel, Bioforce AG, Roggwil, Switzerland) in 80 subjects actively involved in sports. Most investigators (97.5%) rated the treatment as having "very good" or "good" tolerability. About 75% of patients and investigators rated its efficacy during a common cold as "very good" or "good," and 71% of subjects were free of cold episodes. This study is the first to suggest that Echinaforce is effective in the prophylaxis, as well as the treatment, of the common cold in persons who actively participate in sports.

**Keywords:** Echinaforce; *Echinacea purpurea*; sport; common cold; prophylaxis; treatment; efficacy; safety

## INTRODUCTION

Among athletes, coaches, and team physicians, the general perception is that athletes are susceptible to infectious illnesses, in particular, upper respiratory tract infections (URTIs). When athletes exceed individual training thresholds, immune suppression may result, which may increase the risk of catching the common cold.<sup>1</sup> The influence of nutritional supplements, such

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as zinc, vitamins A, C, and E, glutamine, fatty acids, and carbohydrates, on immune function in athletes has been investigated in trials, but the results remain contradictory.<sup>2</sup> One treatment option for this population with a higher infection risk is herbal remedies, which have traditionally been used in the treatment and prophylaxis of URTI.

Preparations from the red coneflower, *Echinacea purpurea*, are used for treatment and prophylaxis of colds. They are among the best-selling herbal products in the United States, with an annual turnover of more than \$300 million.<sup>3</sup>

*Echinacea* supports the immune system and is seen today as an immune modulating agent. In vitro investigations have demonstrated stimulatory effects on macrophages,<sup>4</sup> activation of natural killer cells,<sup>5</sup> and modulated production of cytokines in monocytes and macrophages.<sup>6,7</sup> Recently, a molecular mechanism of action for this immune modulation has been described with a standardized tincture of 95% *Echinacea purpurea herba* and 5% *Echinacea purpurea radix* (Echinaforce). This preparation selectively induced production of tumor necrosis factor-alpha (TNF- $\alpha$ ) mRNA and, under the influence of bacterial lipopolysaccharides, led to modulated production of the TNF- $\alpha$  protein. The main active constituents, the alkylamides, were responsible for this effect, which resulted from interaction with the endocannabinoid receptor CB2.<sup>8</sup> Ex vivo studies have demonstrated the ability of *Echinacea purpurea* extracts to stimulate macrophages, to engulf particles, and to secrete cytokines.<sup>6,9,10</sup> These effects on immune modulation have not been confirmed in human clinical trials from which conflicting results have been obtained.<sup>9,11</sup> However, a series of controlled studies have clearly demonstrated the efficacy and tolerability of *Echinacea purpurea* extracts in the treatment of patients with URTI.<sup>12-16</sup>

*Echinacea* preparations are generally known to have a very good safety profile. No deaths and few significant adverse effects have been reported in widespread use, indicating a favorable overall risk ratio.<sup>17</sup>

The current study was designed to evaluate the tolerability and efficacy of a new tablet formulation (Echinaforce Forte tablets, 750 mg [marketed as Echinaforce Forte or Echinaforce Protect 750-mg tablets] of the extract Echinaforce, which is a fresh plant tincture made from *Echinacea purpurea* (95% herba, 5% radix). This extract has been sold worldwide for more than 50 years, with usage of more than 2.6 billion 2-mL daily doses. This study was carried out in athletes, a population often affected by the common cold during the winter months. The aim was to provide an informative basis for the prophylactic use of Echinaforce Forte tablets and for establishment of their acute efficacy and safety in this population.

## PATIENTS AND METHODS

### Ethical Issues

The protocol, informed consent form, and product information were submitted to the responsible local ethics committees in Switzerland; written approval was sent to the regulatory authority (Swissmedic) in February 2004. This study was carried out in compliance with Good Clinical Practice and the ethical obligations of the Declaration of Helsinki (revised version of Edinburgh, 2000), as required by the Swiss government for clinical trials with pharmaceutical products and by current

medicinal regulations. Each subject was provided with oral and written information about the study and was required to give written consent before he or she could participate in the study.

### Study Design

This was an open, phase 4, multicenter study undertaken to investigate the tolerability and efficacy of Echinaforce Forte tablets given to athletes twice daily for 8 wk. An open-label observation study was considered adequate to judge the tolerability of this treatment because the safety profile of various *Echinacea* products is well documented in the Western literature. To minimize center-specific bias, subjects were recruited from 10 investigational sites.

The primary objective of the study was to investigate the tolerability of the study product, as assessed by the investigator, when taken as prophylaxis by volunteers who were actively involved in sports. The secondary objectives were to investigate the following: tolerability, as assessed by volunteers, adverse events, changes in blood parameters, efficacy of prophylaxis, as assessed by investigators and subjects, efficacy during episodes of the common cold, as assessed by investigators and subjects, and subjects' acceptance of the therapy and compliance with the regimen.

### Study Subjects

Eligible subjects were those aged 18 to 75 y who participated regularly (3 times/wk) in sports activity for at least 30 min and were able to complete the diary correctly after giving their written informed consent. Subjects were recruited through general practitioners or sports physicians. Study subjects with a chronic intolerance to products of the Composita family or to any of the excipients in the tablet, as well as subjects with a chronic disease that could affect one of the variables under assessment (eg, diabetes, asthma, autoimmune disease), were excluded from the study. Subjects who were receiving antimicrobial or antiviral drugs were also excluded because these may have had an effect on the immune system. Subjects could choose to discontinue the study for any reason. Furthermore, those who failed to comply with the study medication or who failed to complete the cold diary for any reason over the duration of the study were withdrawn.

## METHODS

At baseline (visit 1), after the consent form had been signed, demographic data (date of birth, weight, sex) and concomitant treatments were recorded, and the eligibility of each subject to participate in the study was checked. A blood sample was drawn so that the following hematologic and clinical chemistry variables could be evaluated: creatinine, cholesterol, hematocrit, hemoglobin, leukocytes, thrombocytes, bilirubin, transaminases, erythrocytes, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.

Subjects were supplied with 1 bottle that contained 145 Echinaforce Forte tablets; this was sufficient for 8 wk of treatment. Each 750-mg tablet contained 1200 mg of tincture mass of Echinaforce, which corresponded to 18.6 mg dry mass of *Echinacea purpurea* (drug extract ratio of the 95% herba=1:12; ratio of the 5% radix=1:11).

Subjects were instructed to take 1 tablet in the morning and 1 in the evening with some water. Unused tablets were to be returned at the end of the study and were counted to determine compliance with the medication regimen.

Subjects were supplied with a diary in which they were instructed to record cold symptoms. The diary was to be completed for the full 8-wk duration of the study. Subjects were required to answer the question, "Do you think you have a cold today?" and to record on a daily basis the occurrence of the following cold symptoms: headache, joint pain, drowsiness, sneezing, sore throat, cough, fever. The severity of all symptoms was recorded on a 4-point scale: 0=none, 1=mild, 2=moderate, and 3=severe.

Details of all concomitant medications taken during the study were recorded. The intake of medications that had an influence on the immune system was to be avoided during the study. These included, in particular, corticosteroids, antibacterial and antiviral drugs, cytostatics, and vaccinations.

Visit 2 took place 8 weeks after visit 1. An additional blood sample was drawn for evaluation of any changes in tested laboratory parameters. All adverse events reported during the study were recorded, as were any changes in concomitant medications and treatments. Investigators and subjects were asked to rate the tolerability of the study medication as "very good," "good," "moderate," or "poor." Investigators and subjects also assessed the efficacy of prophylaxis for the entire treatment period and the efficacy of the study medication during cold episodes, using the same 4-point scale. Finally, subjects used the same 4-point scale to rate overall acceptability of the study therapy after the 8-wk treatment period had ended. Compliance was based on the assessment of the investigator and by a count of the returned study tablets.

## STATISTICAL ISSUES

Data are presented descriptively, and no formal statistical analysis was planned. Sample size was planned for this study with consideration given to the requirements in Swissmedic's "Guidance for Submission of Registration Applications for Medicines With Known Active Ingredients, Jan 31, 2002," which stipulates that data from at least 50 evaluable patients are needed.

Study populations consisted of (1) the safety population, which included all patients who took the medication at least once, (2) the intent-to-treat population (ITT), for whom at least 1 documented value under therapy was available, and (3) the per protocol population, who completed the study within a duration of  $56 \pm 5$  days and had a complete follow-up according to the "cold diary." In this study, the safety population is equivalent to the ITT population, which is the primary population for analysis.

## RESULTS

### Baseline Characteristics and Study Conduct

A total of 80 patients (39 male, 41 female) from 10 centers in the east of Switzerland were included in this study from February to May 2004. Mean age was 40.5 y (range, 18–75 y), and mean weight was 68.2 kg (range, 48.0–94.0 kg). Subjects each participated in up to 4 different activities, the most common of which were cycling (24% of subjects) and jogging (19%). Other common sporting activities included fitness training, skiing, and walking. The mean duration of training time per week was  $4.3 \pm 2.3$  h

(range, 1.5–15.0 h). Average temperatures in this region were 0.6°C (February), 2.8°C (March), and 7.7°C (April), and rainy days averaged about 13 per month.

Five patients (6.25%) were protocol violators—1 because of unplanned surgery, 1 as the result of an adverse event (allergic reaction), and 3 who received treatment for less than 51 d. Mean duration of treatment was 58.8±8.7 d. All 80 subjects are included in the ITT and safety analyses. No subjects took prohibited concomitant medications during the course of the study. Investigators judged compliance as very good in 92.5% of subjects (Table 1).

Table 1. Baseline Demographic Characteristics (ITT population, N=80)

Total number of patients (ITT)	80
Male, n (%)	39 (48.8)
Age, mean y, SD	40.5±12.5
Weight, mean kg, SD	68.2±11.8
Mean weekly training duration, h	4.3±2.3
Average treatment duration, d	58.8±8.7
Use of allowed concomitant medication during trial, n (%)	20 (25)
Very good compliance in the judgment of the investigator, n (%)	74 (92.5)

## Safety Evaluation

### *Adverse Events*

Adverse events were recorded at each study visit, whether or not they were considered related to the study medication. Sixty-nine subjects (86.3%) reported no adverse events during the course of the study. Eleven subjects (13.7%) reported adverse events; all were mild or moderate in nature. Details of the events, including body system, severity, and relationship to study medication, are shown in Table 2. Three adverse events—swelling of the nasal mucous membranes, headache, and skin rash—resulted in discontinuation of study treatment and withdrawal from the study. Only 2 events—1 gastrointestinal complaint and a skin rash that appeared 51 days after initiation of treatment—were related to the study medication. One subject discontinued therapy because of the need to undergo previously unplanned surgery.

### *Laboratory Parameters*

No clinically significant changes were observed between visits 1 and 2 in the laboratory variables measured. Mean values remained within normally defined ranges.

### *Tolerability Assessments*

Tolerability ratings provided by subjects and investigators are shown in Figure 1. Tolerability was assessed by investigators as “very good” in 68 subjects (85%),

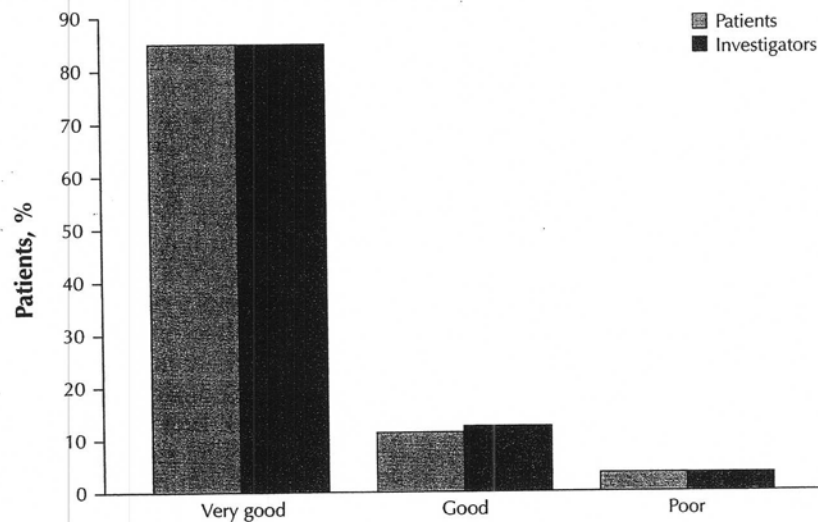
Table 2. Listing of All Adverse Events Reported During the Trial

Description	Body System	Severity	Onset	Duration	Causality	Study Termination
Exanthema	Skin	Mild	After 28 days	28 days	Possible	No
Conjunctivitis, itching in the eyes, rhinitis, sneezing	Eye Respiratory	Moderate	After 40 days	16 days	Possible	No
Flatulence	GI	Mild	Day 1	7 days	Probable	No
Intense thirst	GI	Mild	Day 1	14 days	Possible	No
Swelling of the nasal mucous membranes	Respiratory	Moderate	After 21 days	1 day	Possible	Yes
Flatulence	GI	Mild	Day 1	56 days	Possible	No
Itching of the scalp	Skin	Mild	After 28 days	28 days	Possible	No
Flatulence	GI	Mild	From begin	56 days	Definitely	No
Nausea, indisposition	GI	Moderate	After 28 days	28 days	Possible	No
Headache	CNS	Moderate	After 7 days	ns	Possible	Yes
Skin rash	Skin	Moderate	After 51 days	ns	Definitely	Yes

GI=gastrointestinal; CNS=central nervous system; ns=not specified.

"good" in 10 subjects (12.5%), and "poor" in only 2 subjects (2.5%). Subject assessments were very similar in that 68 subjects (85%) rated tolerability as "very good" and 9 (11%) as "good."

Fig 1 Assessment of tolerability by patients and investigators (N=80)



## EFFICACY EVALUATION

Twenty patients (25%) did not report any cold symptoms over the duration of therapy; 60 subjects reported a phase during which they experienced 1 or more symptoms. The highest mean symptom scores per subject per day of illness were recorded for rhinitis and headache (0.7 and 0.4, respectively). Total mean score for the 4 variables, "headache/joint pain/cold/sore throat," was 1.5.

Because a cold generally lasts for several days, an analysis for defined "cold episodes" was carried out. A cold episode was defined as a period characterized by symptoms for more than 3 consecutive days, with symptom-free periods of longer than 7 days between episodes. In addition, a total symptom score for the common cold (drowsiness, sneezing, fever, joint pain, headache, sore throat, cough) of greater than 9 had to be achieved on 7 subsequent days, according to Jackson et al.<sup>18</sup> Most subjects (57; 71%) had no cold episodes during the treatment period; about 26% had 1 episode, and about 3% had 2 episodes.

### *Global Efficacy Conclusions*

Prophylactic efficacy as assessed by investigators and subjects is shown in Figure 2. Investigators rated prophylactic efficacy of the tablets as "very good" (n=44; 55%) or "good" (n=15; 18.8%) when taken twice daily for 8 wk; subjects' assessment of prophylactic efficacy was similar (42 [52.5%] "very good" and 19 [23.8%] "good").

The efficacy of tablets during episodes of the common cold was similarly judged as "very good" or "good" by investigators in 75% of cases, and by subjects in 73.4% of cases (Fig 3).

Fig 3. Assessment of efficacy by patients and investigators (n=50)

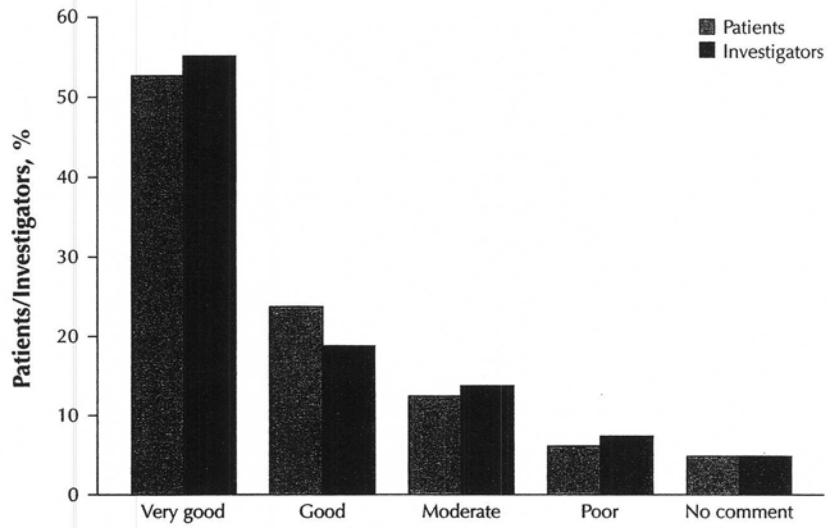
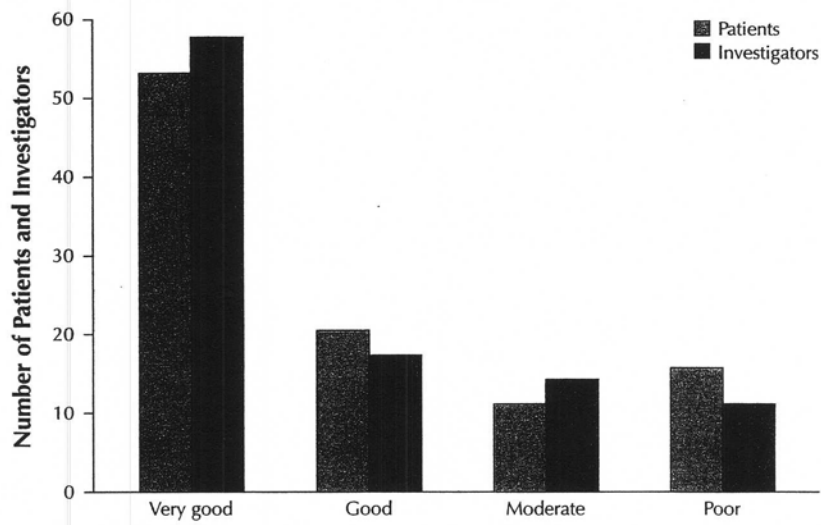


Fig 4. Assessment of efficacy by patients and investigators (n=64)





### Acceptability of Treatment

In assessing the acceptability of treatment, 65 subjects (81.3%) rated it as "very good," 7 (8.8%) as "good," 4 (5%) as "moderate," and 3 (3.8%) as "poor." One subject did not provide an assessment.

## DISCUSSION AND CONCLUSIONS

Athletes as a population have a greater susceptibility to infectious illnesses such as URTI.<sup>1</sup> The incidence of infection seems to increase with the intensity of the sporting activity, that is, moderate training has a favorable effect on the immune system, and intensive training and overtraining lead to higher infection rates.<sup>19,20</sup> The threshold of training intensity that leads to immune suppression must be individually identified for any subject.<sup>21</sup> It has been proposed that the relationship between exercise and URTI may be modeled in the form of a "J" curve.<sup>22,23</sup>

It has been proposed that several possible mechanisms may lead to an increased risk of URTI among athletes. Most prominent is the "open window" theory,<sup>24</sup> which suggests that intensive exercise causes initial stimulation of the immune system that is followed by longer-lasting immune suppression ranging from 3 to 72 h, depending on the immune measure.<sup>25</sup> During this period of the open window, the athlete is at higher risk of contracting infection. Other possible factors include the alteration of mucosal surfaces and immunity by high ventilatory flow rates, particularly during sporting activities in wintertime, the depletion of important factors required for immune function, and the additive effects of psychological stress.<sup>1</sup>

*Echinacea*, with its known immune modulatory properties and effectiveness in the treatment of common colds,<sup>17</sup> is therefore a valuable treatment option in prophylaxis and acute treatment of URTIs in athletes. One clinical trial has so far been carried out with an *Echinacea* preparation in athletes: 42 triathletes were randomly administered magnesium, placebo tablets, or *Echinacea purpurea* pressed juice (8 mL) during 28 days of training and directly before and after competition.<sup>26</sup> Blood and urine samples were taken at the beginning and at the end of treatment, and several immune parameters were determined. Although the authors claimed that changes in urinary soluble interleukin-2 receptor (sIL-2R), interleukin (IL)-6, and cortisol were different in the *Echinacea* group, close inspection of the results shows no real difference between placebo and magnesium. The most interesting result is that none of the athletes in the *Echinacea* group developed a URTI, whereas 3 of 13 in the magnesium group and 4 of 13 in the placebo group caught a cold.

The study reported here is the second trial known by the authors that was undertaken to investigate the efficacy and safety of an *Echinacea* preparation in individuals who actively participate in sports. The primary objective of this study was to assess the tolerability of Echinaforce Forte (750 mg), 1 tablet twice daily, taken for 8 wk. Study results clearly show that treatment was well tolerated, with a rating of "very good" or "good" by 97.5% of investigators. This finding is supported by a similar rating for tolerability in the volunteers' assessment (96.3%) and acceptability of treatment (90%). The most commonly reported adverse effects involved the gastrointestinal system and were mild to moderate in nature; only 2 were clearly related to the study medication. Of the laboratory values assessed, none changed significantly during the treatment period. These results underline the excellent safe-

ty profile of *Echinacea*, as already documented in the literature in terms of its traditional use.<sup>27</sup>

As has already been described, athletes are often affected by coughing and sneezing during the winter season; in this study, Echinaforce Forte was found to be effective in the prevention of episodes of the common cold. Most subjects (71%) reported no cold episode during the treatment period, and only 3% had 2 episodes. On average, people experience 2 to 4 episodes of the common cold during a winter season,<sup>28</sup> so these results indicate good prophylactic efficacy.

About 75% of patients and investigators rated treatment efficacy during a common cold as "very good" or "good." These results compare favorably with those of a large, randomized study that focused on early intervention at onset of symptoms; 71% of patients rated treatment with Echinaforce as effective.<sup>13</sup> Its efficacy is also confirmed by low mean symptom scores during an episode of the common cold. A review from Gwaltney et al shows that generally during a common cold, total symptom severity scores are higher.<sup>29</sup>

This study is the first to suggest that Echinaforce is effective in the prophylaxis and treatment of the common cold in persons who actively participate in sports; this fact is underlined by the subjects' high acceptance rating. Additional studies in athletes, particularly those with high exercise frequencies, are needed to confirm these data.

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