Butterbur Ze339 for the Treatment of Intermittent Allergic Rhinitis

Dose-Dependent Efficacy in a Prospective, Randomized, Double-blind, Placebo-Controlled Study

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Objectives: To investigate whether the efficacy and safety of Butterbur extract Ze339 are related to dosage when administered to patients with intermittent allergic rhinitis.

Design: Prospective, randomized, double-blind, placebo-controlled, parallel-group comparison.

Setting: Multicenter, including 6 outpatient general medicine and allergy clinics.

Patients: One hundred eighty-six patients were randomized (Butterbur Ze339 high dose, 60; low dose, 65; and placebo, 61 patients). Established diagnostic criteria for intermittent allergic rhinitis were confirmed by skin allergy tests in all patients.

Interventions: High-dose group, 1 tablet 3 times daily; low-dose group, 1 tablet twice daily; or matching placebo. All groups were treated for 2 consecutive weeks.

Main Outcome Measures: The main efficacy variable was change in symptoms from baseline to end point during the daytime. The secondary efficacy variables were Clinical Global Impression score, change in symptoms from baseline to treatment day 7, and responder rates. Statistical analysis was prospective, on an intention-to-treat basis.

Results: Improvement in the main efficacy variable was significantly superior in the Butterbur Ze339 groups, relative to placebo, and a significant dose relationship was observed between the 2 Butterbur doses. The clinicians’ assessment of efficacy and the overall responder rates were significantly superior for the active groups compared with placebo. The incidence and type of adverse events were indistinguishable across the herbal treatment and placebo groups.

Conclusions: Butterbur Ze339 is an effective treatment for intermittent allergic rhinitis symptoms and is well tolerated. The effects of this herbal medicine are clear to patients and physicians in a double-blind evaluation against placebo.

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Allergic rhinitis, intermittent or persistent, is caused by the deposition of allergens on the nasal mucosa, a process that is followed by a hypersensitivity reaction (type I allergy). The intermittent and persistent types differ in terms of duration of illness and causative allergens: in most parts of the world, the most common allergens for intermittent allergic rhinitis are grass, tree, and weed pollens, while the most common allergens for persistent allergic rhinitis are house dust mites and domestic animals. The condition is characterized by sneezing, rhinorrhea, obstruction of the nasal passages, lacrimation, and nasal, conjunctival, and pharyngeal itching.

Butterbur is an Asteraceae herbaceous plant native to Europe, northern Africa, and southwestern Asia. The leaves and roots of butterbur contain a mixture of eremophilane-type sesquiterpenes (petasins) as pharmacologically active compounds. Two chemovarieties are reported, namely, petasin and furanopetasin chemovarieties, both of which can be distinguished by chemical analysis. The Ze339 extract derives solely from the leaves of the petasin chemovariety. Extracts from roots with a mixture of both chemovarieties have been used in bronchial asthma, smooth muscle spasms, and headache, and studies have shown that petasins inhibit the biosynthesis of leukotrienes, which may be associated with spasmyloytic activity and the therapeutic action in type I hypersensitivity.

Butterbur Ze339 is a special extract obtained from the leaves of the butterbur plant (Petasites hybridus, butter dock, bog rhubarb, and exwort). The leaves and roots contain a mixture of eremophilane-type sesquiterpenes (petasins) as pharmacologically active compounds.
into small pieces less than 125 μm in length, followed by extraction with liquid carbon dioxide. Compared with extraction with conventional solvents, this method has many advantages. Carbon dioxide prevents oxidation, can be used several times, and is not retained within the extract. Its major advantage is to minimize the extraction of hepatotoxic pyrrolizidine alkaloids. Remaining pyrrolizidine alkaloids are eliminated in one step during the extraction by using the thin-layer alkaloid-absorption method.

The effects of Butterbur Ze339 on seasonal allergic rhinitis have been shown to be significant under methodologically controlled study conditions. In that evaluation of butterbur, we found the treatment advantageous relative to a commonly used antihistamine (cetirizine hydrochloride). Symptomatic treatments such as antihistamines are effective in reducing rhinorrhea and sneezing but are less effective for nasal congestion. Most antihistamines can be obtained over the counter in pharmacies for the symptomatic treatment of allergic rhinitis, although some of them may cause drowsiness, interact with alcohol, and decrease ability to drive or operate machines.

Our aim in the present study was to evaluate whether the effects of Butterbur Ze339 extract tablets are dose-dependent when tested in a prospectively planned, randomized, placebo-controlled trial and conducted in a sufficiently large number of patients to yield meaningful results.

### METHODS

#### PROTOCOL AND BLINDING

All subjects were outpatients attending 6 general medicine and allergy clinics in Switzerland and Germany between April 4, 2001, and March 26, 2002. All physicians were experienced in using the instruments of assessment and underwent a training on the scales (Clinical Global Impression and visual analog scale instructions to patients) to enhance intercenter and intracenter consistency. In each clinic, all assessments were made by the same individual.

Study medication consisted of Butterbur (Petasites leaves carbon dioxide extract Ze339, standardized to 8.0 mg of total petasin per tablet), administered at a high-dose (HD) rate of 1 tablet 3 times daily, at a low-dose (LD) rate of 1 tablet twice daily, or as placebo (1 tablet 3 times daily). The LD group received a placebo tablet at the midday dosing to maintain study blindness, so all patients received 3 tablets daily. Blinding was ensured by blister packing with preassigned printed weekly calendar carbonates marked as “early morning,” “middle of day,” and “late evening” doses for all tablets, which were identical in size, color, and smell and were to be taken with a little liquid at the assigned times.

The study was performed according to current International Conference on Harmonization and European Union guidelines on Good Clinical Practice and the Declaration of Helsinki on Human Rights. The study was approved by each clinic’s local ethics committee, in Switzerland and Germany.

### PATIENT SELECTION

All patients were 18 years or older, had a history of intermittent allergic rhinitis for at least 2 seasons in consecutive years, and fulfilled intermittent allergic rhinitis diagnostic criteria for enrollment (Table 1) required for trials regarding this condition. Exclusions from enrollment included alcohol or substance abuse, pregnant or nursing mothers, parasitic disease causing an increase in IgE or eosinophil levels, use of corticosteroids (systemic or nasal) in the previous 2 months, use of antihistamines in the previous 6 weeks, use of anti-inflammatory agents in the previous 2 weeks, persistent (nonintermittent) rhinitis, prior organ transplantation and serious concomitant disease, or concomitant use of α- or β-blockers, sympathomimetics, cromoglycates, azelastine hydrochloride, levocabastine hydrochloride, and antidepressants.

Baseline assessment was made at the referral consultation (screening), when the inclusion and exclusion criteria were checked. All patients underwent skin allergy tests, and all were allergic to pollen. Among them, 3 patients were allergic to birch (Betula and Prunus) pollen, 1 patient was allergic to mugwort (Artemisia) pollen, and all others were allergic to grass pollen. Because of the acute nature of the illness and as per guidelines, the initial screening phase was kept short, typically 1 day before starting treatment. At baseline, patients also underwent full medical examination and laboratory tests (hematology, biochemistry, electrocardiogram, and pregnancy test, if female), after which they were given sufficient trial medication for 2 weeks. An intermediate visit after 1 week was optional, in case of adverse events or deterioration. A visit at the end of week 2 (end point) was mandatory, when patients underwent full medical examination, laboratory tests (identical to the screening workup), compliance checks, and adverse events monitoring. Exposure to pollen was confirmed for each patient through cross-checking each individual’s treatment period with the regional online pollen count service. Patients’ self-assessments were recorded in diaries at 3 preassigned daily times, just before taking medication.

### STATISTICS, ASSIGNMENT, AND ANALYSIS

All analyses were prospectively planned, and the data were processed and analyzed by the University of Giessen’s Department of Medical Information Technology, Giessen, Germany. Randomization was provided centrally and was computer generated in blocks of 6. Analysis was on an intention-to-treat basis, defined as all randomized patients who had at least the baseline and 1 postbaseline value and took any medication. The
planned sample size was a minimum of 60 patients per group, based on previous literature on this condition,13 with a 10% expected withdrawal rate and an assumed effect size of 0.5. According to current guidelines,11 the main efficacy variable prospec-tively sought in the protocol was self-assessment (intraindividual change from baseline to end point, referred to in the guidelines as a reflective score, as an evaluation of overall symptom severity) of the 4 main symptoms (rhinorrhea, nasal congestion, itching, and sneezing) through a visual analog scale in which symptoms were presented in lay terms (“runny nose,” “blocked nose,” “itchy nose or eyes,” and “sneezing”). The scores were subsequently combined for analysis as single scores, as an evaluation of over-all symptom severity) of the 4 main symptoms (rhinorrhea, nasal congestion, itching, and sneezing) through a visual analog scale in which symptoms were presented in lay terms (“runny nose,” “blocked nose,” “itchy nose or eyes,” and “sneezing”). The scores were subsequently combined for analysis as single scores, as an evaluation of over-all symptom severity) of the 4 main symptoms (rhinorrhea, nasal congestion, itching, and sneezing) through a visual analog scale in which symptoms were presented in lay terms (“runny nose,” “blocked nose,” “itchy nose or eyes,” and “sneezing”). 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the most frequent being rhinorrhea (Table 2), as previ-

ously observed.8 Sneezing, nasal congestion, and itchy eyes

or nose had similar frequency and severity across the treat-

ment groups. One patient in each group used antihista-

amines during the study, but, despite this being a protocol

exclusion, all were included in the analysis.

Efficacy Results

The results at the end of the treatment period are dis-
played in Tables 3, 4, and 5. Analysis of the main ef-

ficacy variable confirmed that Butterbur Ze339 is dose-

dependently superior to placebo in relieving the 4 main

symptoms of intermittent allergic rhinitis (Tables 3 and

4 and Figure 2). Although both doses were individu-

ally significantly (P < .001) superior to placebo, the HD

group was also significantly (P = .02) superior to the LD

group.

Analysis of the second efficacy variable, Clinical Global

Impression 3-item score (1, severity; 2, global improve-

ment; and 3, risk-benefit), yielded results similar to those

of the main variable, with the 2 active groups being sig-

nificantly superior to placebo in all 3 items. However, dif-

ferences between the 2 active dose groups were present

only in item 2 (global improvement), favorable to the HD

group. Regarding the instantaneous symptoms scores

(evaluated immediately before the next dosing), the HD

group was significantly superior to placebo, but the LD

group was only marginally superior to placebo (signifi-
cantly on day 5), failing to reach significance at day 7. The

significant improvements in the HD group were consis-
tently present from day 3 onward. Responder rates were

also significantly higher for the 2 active dosing groups rela-
tive to placebo.

Safety Results

The overall incidence of adverse events and treatment with-

drawals was low (Table 6). The most commonly reported

event (gastrointestinal upset) was present similarly across
active and placebo groups. There was no evidence to suggest an event that could be considered as typically associated with active treatment, with most events being reported once or twice only. Events causing treatment withdrawal also had similar incidence across all groups.

The large number of antihistamines and corticosteroid nasal sprays, available without prescription, and their wide use in the spring and early summer highlight the dimension of the problems caused by intermittent allergic rhinitis in patients, as evidenced by most physicians involved in primary care and by allergy specialists. Yet, methodologically robust studies are difficult to conduct in intermittent allergic rhinitis, in part because of the acute nature of the illness and wide scope of access to antiallergic treatments by patients. Although regulatory guidelines exist on the criteria for selection and evaluation of patients in intermittent allergic rhinitis trials, the inclusion of a placebo group can be problematic, because of possible contamination of results by the use of other treatments readily available to ameliorate unpleasant symptoms such as runny nose, sneezing, itching, and congestion. We monitored our patients closely and allowed them to visit the clinics whenever they thought their condition needed further intervention; hence, our control subjects exhibited the level of treatment of the illness and wide scope of access to antiallergic treatments by patients. Yet, methodologically robust studies are difficult to conduct in intermittent allergic rhinitis, in part because of the acute nature of the illness and wide scope of access to antiallergic treatments by patients. Although regulatory guidelines exist on the criteria for selection and evaluation of patients in intermittent allergic rhinitis trials,11 the inclusion of a placebo group can be problematic, because of possible contamination of results by the use of other treatments readily available to ameliorate unpleasant symptoms such as runny nose, sneezing, itching, and congestion. We monitored our patients closely and allowed them to visit the clinics whenever they thought their condition needed further intervention; hence, our control subjects exhibited the level of treatment failures and interruptions that would be expected in a 2-week treatment, as in our experience patients with intermittent allergic rhinitis do not tolerate ineffective treatments for longer periods. The length of treatment was also chosen according to regulatory guidelines. Treatment compliance was monitored and was identical for all treatment groups. We considered the addition of an active comparator but decided against it as this comparison had already been conducted with a similar design8 and the addition of a further treatment group would delay completion by another season (year), with a consequent increase in variability of the data. We excluded the use of corticosteroids of any kind (including nasal) 2 months before and during the study. We then formulated the hypothesis of whether this herbal treatment was superior to placebo in a dose-dependent manner, prospectively in the protocol, and tested the hypothesis hierarchically so that the analysis would stop if any of the tested items of the patients’ self-assessment showed the herbal drug to be similar to placebo. Finally, we confirmed patients’ exposure to the allergens through regional pollen counts for each patient’s treatment period and by checking each patient’s days’ exposure indoors and outdoors, all of which were similar across groups, with 98% of allergens being grass pollen.

The use of herbal treatments in the last decade has increased tremendously, often by physicians’ recommendation and frequently after requests from patients; consequently, the number of published randomized controlled trials with herbal medicines has increased substantially.8,16-18 Although the effects of butterbur on the preclinical and clinical pathogenesis of allergen hypersensitivity have also increased substantially,18-21 we set out to test Butterbur Ze339 in a methodologically robust, controlled design in which a dose relationship of its clinical effects in intermittent allergic rhinitis could be tested against placebo and judged separately and blindly by patients and their physicians. The results showed that both doses of this herbal drug are significantly and increasingly effective relative to dose, similar to traditional synthetic medicines. The clinical benefit can be detected rapidly, usually within a few days’ treatment. With regard to safety, Butterbur Ze339 was well tolerated.

We collected data on overall effects throughout the dosing period (also referred to as reflective in the guide-

Table 6. Adverse Events and Withdrawals From Treatment*

<table>
<thead>
<tr>
<th>Variable</th>
<th>HD</th>
<th>LD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All events (regardless of relationship to treatment)</td>
<td>9 (15)</td>
<td>1 (2)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Adverse events (possibly, probably, or definitely related to treatment)</td>
<td>7 (12)</td>
<td>1 (2)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Events causing temporary treatment interruption</td>
<td>4 (7)</td>
<td>1 (2)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Events causing treatment withdrawal</td>
<td>2 (3)</td>
<td>0</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>

List of all events (regardless of relationship to treatment), No.

<table>
<thead>
<tr>
<th>Gl upset, 3</th>
<th>Nausea, 2</th>
<th>Skin rash, 1</th>
<th>Hot flushes, 1</th>
<th>Diarrhea, 1</th>
<th>Influenza, 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza, 1</td>
<td>Nausea, 1</td>
<td>Skin rash, 1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Gl, gastrointestinal; HD, high dose; LD, low dose.

*Data are given as number (percentage) unless otherwise indicated. Sixty patients were randomized to the HD group, 65 to the LD group, and 61 to the placebo group.
lines), as well as trough effects (also referred to as instantaneous in the guidelines), the latter showing that, although the LD improves overall symptoms, the effects do not last until the next dosing.

### CONCLUSIONS

This prospective, randomized, double-blind, placebo-controlled study demonstrated that Butterbur Ze339 extracted from leaves of the petasin chemovariety is effective in treating the symptoms of intermittent allergic rhinitis in a dose-dependent manner. This treatment raised no tolerability concerns regarding adverse events. The effects of this herbal extract were confirmed by patients and physicians who were blinded to treatment codes during the study, in the presence of a control group receiving placebo. Butterbur Ze339 should be considered for treating intermittent allergic rhinitis in patients in whom antihistamines are not indicated or when sedation is to be avoided.

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Disclaimer: Dr Schapowal is the principal investigator and guarantor of the article. He had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis, which was conducted by Joachim Dudeck, PhD (Department of Medical Information Studies, University of Giessen), who also conducted data audit and management. The analysis was conducted independently by the University of Giessen, and the interpretation of the results was the prerogative of Dr Schapowal and the Petasites Study Group.

### REFERENCES


