Safety and efficacy of Nasya/Prevalin in reducing symptoms of allergic rhinitis

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Abstract

Background: Nasya/Prevalin is a natural, drug-free nasal spray for treatment and prevention of allergic rhinitis. Because of its thixotropic property, it forms a barrier on the nasal mucosa, preventing allergen contact. This study assesses the clinical efficacy and safety of Nasya/Prevalin in a nasal provocation test with house dust mite allergens.

Methodology/Principal: In this randomised, double-blind, placebo-controlled trial, 20 subjects suffering from allergic rhinitis because of house dust mite allergens received a single dose of Nasya/Prevalin or saline spray before allergen challenge. Total nasal symptom score and total ocular symptom score were assessed 15, 30, 60, 75, 90, 120 and 240 min after challenge. Further, the appearance of the mucosa was examined by rhinoscopy.

Results: A single treatment with Nasya/Prevalin led to a significant reduction of TNSS at 60, 75 and 90 min after dust mite allergen challenge as compared with placebo ($p_{VCAS} = 0.021$, $p_{VCAS} = 0.035$, $p_{VCAS} = 0.036$, respectively). Mucosa changes assessed by the rhinoscopic score (on swelling, secretion and colour) were significantly worse in the placebo group compared with the Nasya/Prevalin group ($P = 0.033$). Nasya/Prevalin was well tolerated, and the safety was comparable with placebo.

Conclusions: Treatment with Nasya/Prevalin was effective in preventing allergic reactions induced by dust mite allergen challenge.

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Key words
allergic rhinitis – allergy prevention – clinical trial – placebo-controlled – randomised

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Authorship and contributorship
This manuscript was drafted and finalised by Katharina Stoelzel and Gordana Bothe. Pee Win Chong and Minoo Lenarz reviewed the manuscript before submission.

Ethics
The study was approved by the Ethics Committee of the Charité, Charitéplatz 1, 10117 Berlin, Germany.

Conflict of interest
This study was sponsored by InQpharm Europe. The investigators of this clinical trial, Minoo Lenarz and Katharina Stoelzel (employees of the Charité Berlin) and Gordana Bothe (project manager at the CRO), declared no conflict of interest.

Introduction

Allergic rhinitis is a common allergic condition mainly affecting the nasal mucosa (rhinitis) and the eyes (conjunctivitis). The prevalence of allergic rhinitis has increased within the last 50 years. The reason for this increase might be related to the increase of air pollution and an actual increase in airborne quantities of allergenic pollen (1). In some countries, over 50% of the adolescents are affected by symptoms [for review, see Bousquet *et al.* (2)]. Within Germany, the prevalence is between 13.3% and 23.0%, depending on the region (3, 4). It is caused by sensitization to one or more allergens such as pollen, animal dander or dust mites. This leads to an immunoglobulin E-mediated inflammatory reaction after allergen exposure. The main symptoms of allergic rhinitis include nasal itching and sneezing, runny nose, nasal obstruction, as well as ocular symptoms. Allergic rhinitis has also been associated with asthma by some researchers (5–7).

With allergic rhinitis, the quality of life of the patients is hampered, as well as their productivity in school and job [for review, see Mosges and El Hassan (8)].

Besides desensitisation (allergen-specific immunotherapy), there is no cure of allergic rhinitis. Therefore, the therapy is symptom related. Increased histamine release has been reported to be mainly responsible for sneezing, itching nose and rhinorrhoea; only in very high concentrations, it induces obstruction (mainly as a result of interleukin activation). Therefore, antihistamines or leukotriene receptor antagonists are used (9). Further, nasal glucocorticosteroids are frequently prescribed, as they have a known effect on inflammatory mediators (8). However, those treatment methods are associated with side effects.

The most effective and safest way to decrease the allergic symptoms is to eliminate exposure to the allergens. Avoidance or elimination of allergens present in the breathing air is, in most cases, not possible. An alternative option is to create a physical barrier within the nose to prevent contact between allergens and the nasal mucosa. There are several products on the market that act by creating a barrier for allergens such as creams or cellulose powder (10–12). All of these products have in common the problem of distribution within the nasal caverns and sinuses, leading mostly to unsatisfactory clinical results (13).

In this clinical trial, the barrier function of Nasya/Prevalin (containing the technomarker ThixoPro, InQpharm Europe Ltd, Hitchin, Hertfordshire, UK) on dust mite allergens was investigated. Nasya/Prevalin is a natural, drug-free nasal spray for prevention and treatment of allergic rhinitis, currently marketed as a medical device in Europe. It is a thixotropic gel that turns into sol state when shaken or sprayed, and returns to solid phase when settled (14). After the nasal spray is applied, it turns back into gel state, forming a protective layer/'mechanical' barrier on the surface of the nasal mucosa. When the barrier is established, the allergens no longer come in contact with the nasal mucosa and the mast cells, which, when triggered, contribute to allergy symptoms.

This present study was designed for the first time to assess the safety and efficacy of Nasya/Prevalin in subjects suffering from allergic rhinitis because of house dust mite allergens.

Materials and methods

This clinical investigation was performed according to EN ISO 14155:2011 for medical device. The clinical investigation was based on the principles of the World Medical Association (Declaration of Helsinki) and the European Union recommendations for Good Clinical Practice (CPMP/ICH/135/95). It was approved by the Ethics Committee of the Charité (Berlin, Germany) and registered at ClinicalTrials.gov (NCT01503957).

Study design

In accordance with the recommendations in the General Considerations for Clinical Trials (ICH E8), the present study was designed as a randomised, placebo-controlled, double–blind, clinical trial. The study was designed to, for the first time, assess the safety and efficacy of Nasya/Prevalin in subjects suffering from allergic rhinitis because of house dust mite allergens.

Study data were collected at two regular visits. The first visit (V1) was held for screening, randomisation and to obtain baseline values for the defined measurement parameters, including a pretest of nasal provocation test (NPT) and total nasal symptom score (TNSS) after NPT to determine individual allergen concentration. The second visit (V2; 7–10 days after V1) was the treatment visit. At this visit, subjects were administered with either Nasya/Prevalin or placebo before the allergen provocation. Thereafter, the assessment of TNSS and other study parameters followed.

Study population

Twenty adult subjects of both genders suffering from allergic rhinitis because of house dust mite allergens were enrolled in the study (Fig. 1). They had to comply with the inclusion criteria (main criteria: age 18–60 years; history of persistent allergic rhinitis to house dust mite allergy ≥2 years; TNSS ≤3 at screening and before application of device; subject's written informed consent) and were not allowed to violate any of the exclusion criteria (main criteria: besides allergy, no other respiratory tract diseases or other severe diseases; known sensitivity to any of the constituents of treatment product; pregnancy or nursing). In addition to the inclusion criteria, a TNSS >6 after NPT was required for randomisation.

Randomisation and blinding procedure

Subjects were assigned to one of the two study treatments according to the randomisation code provided by an independent statistician. Treatment assignment occurred when all inclusion/randomisation criteria, and none of the exclusion criteria had been fulfilled.

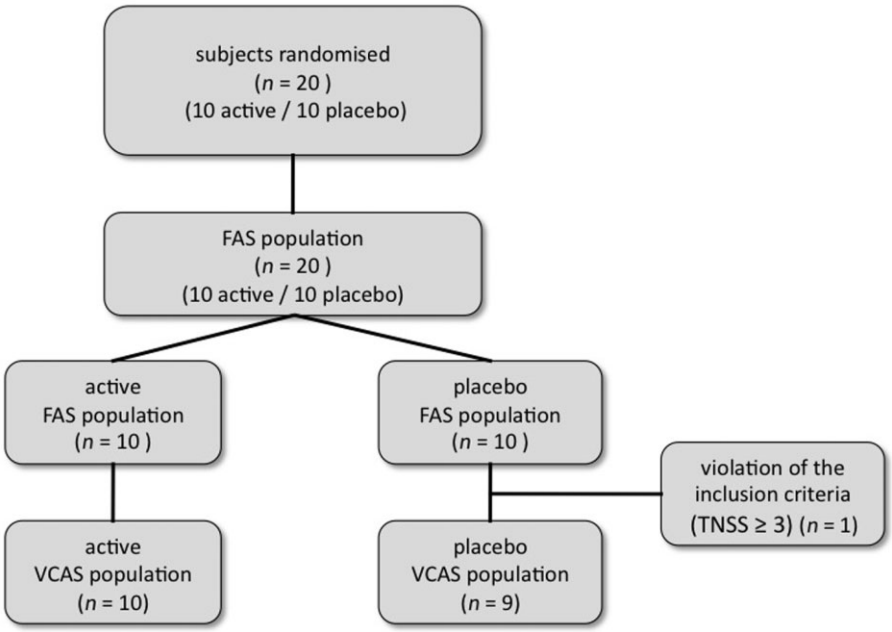

Figure 1. Flowchart of the study population. FAS, full analysis set; TNSS, total nasal symptom score; VCAS, valid case analysis set.

Intervention

The investigational study device was Nasya/Prevalin (a thixotropic nasal gel composed of water for injection, bentonite, xanthan gum, glycerol monostearate, monopotassium phosphate, dipotassium hydrogen phosphate, glycerol anhydrous, sesame oil and spearmint oil; InQpharm). The placebo was a commercially available isotonic seawater nasal spray. Both applicators were identical in appearance and design, and were indistinguishable from each other by participants and investigators.

The subjects had to apply two sprays (2×0.14 mL) of their assigned product into each nostril, directly before the NPT with the dust mite allergen (15) at the investigational site.

The minimal individual allergen concentration for each subject sufficient to achieve a TNSS >6 was determined by the NPT before subject randomisation.

NPT

The NPT was performed according to Riechelmann *et al.* (15) and as described by the manufacturer (ALK-Abelló Arzneimittel GmbH, Hamburg, Germany; test solution: ALK freeze-dried mite allergen, *Dermatophagoides farinae*, allergen concentration of the stock solution: 100.000 standardised quality units/mL). In brief, after acclimatization for 15 min, the patient was examined by rhinomanometry and endoscopy, and the symptom score was determined. The required allergen solution (dilution of the stock solution: 1:10) was applied by a pump spray applicator into the nostril with the higher flow rate. After a 15-min incubation period, the different measurements as described later were undertaken at 15, 30, 60, 75, 90, 120 and 240 min after allergen application.

Measurements/Objectives

Primary outcome

The primary outcome was defined as the difference in TNSS at 75 min after application of the NPT. This time point was determined based on the experiences from the pollen allergen challenge studies (16). The TNSS was calculated by the scores obtained from the individual symptoms rhinorrhoea, nasal pruritus, sneezing and nasal congestion. Subjects had to rate the intensity of the symptoms by a 4-point scale: 0 = no, 1 = mild, 2 = moderate, 3 = severe symptoms. Baseline TNSS was assessed before the nasal provocation at all visits.

Secondary outcomes

The main secondary outcome criteria were: TNSS at 15, 30, 60, 90, 120 and 240 min, and the individual scores for rhinorrhoea, nasal pruritus, sneezing and

nasal congestion at 15 and 75 min, after challenge; total ocular symptom score (TOSS) at 15, 30, 60, 75, 90, 120 and 240 min, respectively, after challenge; rhinoscopy score at 15 and 75 min; the global rating of treatment efficacy and symptom relief; and the use of rescue medication.

TOSS was used for assessment of the symptoms itching/burning eyes, tearing/watery eyes and redness of eyes. Subjects had to rate the symptoms on a 4-point scale: 0 = no, 1 = mild, 2 = moderate, 3 = severe symptoms.

Conventional anterior rhinoscopy with a nasal speculum and headlight was performed to assess any swelling of the mucosa, secretion or change in colour. Rhinoscopy score was assessed as follows: secretion (0 = no, 1 = clear, low viscosity, 2 = thick, high viscosity); swelling and colour change (0 = no, 1 = mild, 2 = severe), respectively.

For the determination of the global assessment of efficacy, subjects and investigators evaluated the benefit of the investigational product or placebo with 'very good', 'good', 'moderate' or 'poor' at the end of the study.

Safety assessment

At the end of the study, subjects and investigators evaluated the tolerability of the investigational product with 'very good', 'good', 'moderate' or 'poor'. The adverse events (AEs) occurred during the study were documented and judged by the investigator regarding intensity and causality with the investigational product.

Statistical methods/sample size calculation

Sample size was defined based on the study data reported by Emberlin and Lewis (10), at a significance level of 5.0% and power of 80%.

The primary end point {TNSS change from baseline, with reference from 75 min after NPT [TNSS(T_{75})] to baseline [TNSS(T_0)]} was analysed by the non-parametric Wilcoxon test. All secondary variables were examined by exploratory data analysis and descriptively evaluated with mean value ± standard deviation (metrically scaled variables) and were analysed using parametric or non-parametric statistical tests (qualitative data: Fisher's exact test; quantitative data: independent *t*-test or Mann–Whitney *U*-test for independent groups, and paired *t*-test or Wilcoxon test for paired observations).

Table 1. Characteristics of the participants at baseline (FAS)

Baseline characteristics	Nasya/Prevalin (n = 10) mean ± SD	Placebo (n = 10) mean ± SD	*P* value
Age (years)	29.2 ± 11.8	39.5 ± 12.7	0.063
BMI (kg/m^2)	23.3 ± 3.2	26.0 ± 5.5	0.218

BMI, body mass index; FAS, full analysis set; SD, standard deviation.

Results

Study population

All randomised subjects (n = 20) were included in the full analysis set (FAS). Only one subject was excluded from the valid case analysis set (VCAS) because of violation of the inclusion criteria (TNSS ≥ 3). There were no dropouts (Fig. 1).

The baseline characteristics of the two study groups are given in Table 1. There was no statistically significant difference between the two study groups.

Both study groups had comparable baseline values of TNSS before (P = 0.503) and after (P = 0.657) allergen challenge at V1 prior to randomisation (Table 2).

Primary outcome

TNSS 75 min after challenge

As the primary outcome, the difference in TNSS at 75 min after application of the NPT was calculated. The TNSS values before and after allergen challenge (FAS population) are given in Table 3.

At baseline, before the NPT, the two study groups did not differ in the TNSS, neither in the FAS nor in the VCAS population. 75 min after the NPT challenge, however, there was a statistically significant difference between the two treatment groups (p_{FAS} = 0.039; p_{VCAS} = 0.042). In the placebo group, the TNSS value increased by 2.0 points from 1.60 ± 1.58 to 3.60 ± 2.99

Table 2. Baseline mean values of TNSS before and after NPT (FAS population)

	TNSS (mean ± SD) (points)		
Study treatment	Baseline before NPT	Baseline after NPT	Changes after NPT
Nasya/Prevalin (n = 10)	1.50 ± 1.27	7.20 ± 2.10	5.70 ± 2.45
Placebo (n = 10)	1.10 ± 1.29	6.90 ± 0.99	5.80 ± 1.48
P value	0.503	0.657	0.635

FAS, full analysis set; NPT, nasal provocation test; SD, standard deviation; TNSS, total nasal symptom score.

Table 3. Mean TNSS (at Visit 2) before, 75 min after NPT and changes of TNSS (FAS and VCAS population)

	TNSS (mean ± SD) (points)		
Study treatment	Before NPT	After NPT	Increase after NPT
FAS population			
Nasya/Prevalin ($n = 10$)	1.50 ± 1.27	1.90 ± 2.78	0.40 ± 2.91
Placebo ($n = 10$)	1.60 ± 1.58	3.60 ± 2.99	2.00 ± 2.67
P value	1.000	0.039	0.099
VCAS population			
Nasya/Prevalin ($n = 10$)	1.50 ± 1.27	1.90 ± 2.78	0.40 ± 2.91
Placebo ($n = 9$*)	1.22 ± 1.09	3.67 ± 3.16	2.44 ± 2.40
P value	0.699	0.042	0.035

*One subject was excluded from VCAS because of the violation of an inclusion criterion (TNSS ≤ 3 before application of device).
FAS, full analysis set; NPT, nasal provocation set; SD, standard deviation; TNSS, total nasal symptom score; VCAS, valid case analysis set.

(FAS population), whereas the TNSS values in the Nasya/Prevalin group increased only slightly by 0.4 points (from 1.50 ± 1.27 to 1.90 ± 2.78; $p_{FAS} = 0.099$ for difference between Nasya/Prevalin and placebo). These differences were even more pronounced and statistically significant in the VCAS population, where the TNSS value increased by only 0.4 points in the Nasya/Prevalin group but by 2.44 points in the placebo group ($p_{VCAS} = 0.035$).

Secondary outcomes

Time course of TNSS after challenge

The TNSS was determined before and at 15, 30, 60, 75, 90, 120 and 240 min after the allergen challenge. This time course is shown in Fig. 2. In both treatment groups, the dust mite challenge led to an increase of the TNSS after 15 min. The increase was less pronounced in the Nasya/Prevalin group than in the placebo group. Thirty minutes after challenge, the Nasya/Prevalin group showed already an obvious reduction of the TNSS [Nasya: 2.7 points (pts); placebo 4.3 pts]. This value significantly reduced to 2.1 pts after 60 min in the Nasya/Prevalin group but remained high (4.1 pts) in placebo ($P = 0.026$). At the end of the observation time (after 240 min), the Nasya/Prevalin group had already reached baseline values of TNSS, whereas the values of the placebo group were still elevated. A nearly identical time course has been found in the VCAS population.

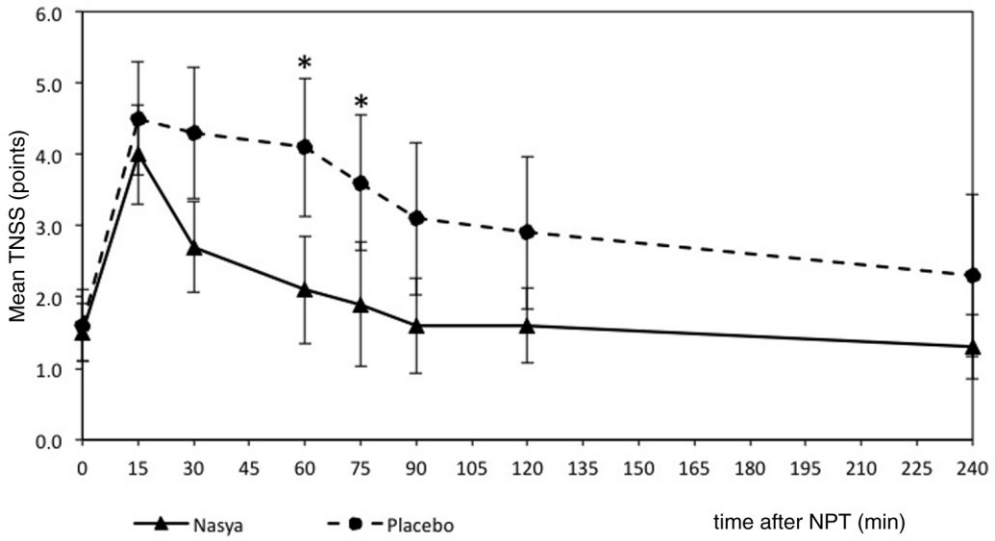

Figure 2. Mean total nasal symptom score (TNSS) (at Visit 2) before and after the allergen challenge (full analysis set population); error bars represent standard error of the mean; *indicate statistically significant differences. NPT, nasal provocation test.

Table 4. Mean changes (differences to baseline) in TNSS after NPT at Visit 2 (FAS and VCAS population)

	Changes in TNSS (mean ± SD) (points)					
	FAS population			VCAS population		
Time points (min)	Nasya/Prevalin ($n = 10$)	Placebo ($n = 10$)	*P* value	Nasya/Prevalin ($n = 10$)	Placebo ($n = 9$)	*P* value
15	2.50 ± 2.55	2.90 ± 2.38	0.696	2.50 ± 2.55	3.33 ± 2.06	0.480
30	1.20 ± 2.25	2.70 ± 2.71	0.193	1.20 ± 2.25	3.22 ± 2.28	0.077
60	0.60 ± 2.55	2.50 ± 2.99	0.074	0.60 ± 2.55	3.00 ± 2.69	0.021
90	0.10 ± 2.23	1.50 ± 2.95	0.116	0.10 ± 2.23	1.89 ± 2.85	0.036
120	0.10 ± 1.73	1.30 ± 3.16	0.235	0.10 ± 1.73	1.78 ± 2.95	0.085
240	–0.20 ± 1.55	0.70 ± 3.16	0.658	–0.20 ± 1.55	1.00 ± 3.20	0.418

FAS, full analysis set; SD, standard deviation; TNSS, total nasal symptom score; VCAS, valid case analysis set.

The TNSS changes compared with baseline are presented for the Nasya/Prevalin and placebo groups (Table 4). Sixty minutes after challenge, the increase in TNSS for the Nasya/Prevalin group was significantly less than for the placebo group in the VCAS population ($p_{VCAS} = 0.021$). Differences between the two groups remained significant even after 90 min ($p_{VCAS} = 0.036$). The same tendency could be observed in the FAS population, however, only with trends of significance.

Individual TNSS scores

For the individual TNSS scores (rhinorrhoea, nasal pruritus, sneezing and nasal congestion) at 15 and 75 min, there were no statistically significant differences between the study groups. A *post-hoc* analysis (FAS) of TNSS individual scores at the remaining time points after NPT revealed a statistically significant difference in favour of Nasya/Prevalin for the TNSS nasal pruritus score at 60 min after NPT ($p_{exF} = 0.023$) and 120 min after NPT ($p_{exF} = 0.013$); a trend in favour of verum was observed at 75 min ($p_U = 0.096$).

Time course of TOSS after challenge

The TOSS was determined before and at 15, 30, 60, 75, 90, 120 and 240 min after the allergen challenge. The results are shown in Fig. 3.

Because of the NPT, the TOSS increased in both treatment groups. Even though the curves of TOSS for the Nasya/Prevalin and the placebo groups are different, no statistical significance for differences in ocular symptoms could be achieved. In the Nasya/Prevalin group, the ocular symptoms were less pronounced and achieved a peak after 15 min before they decreased,

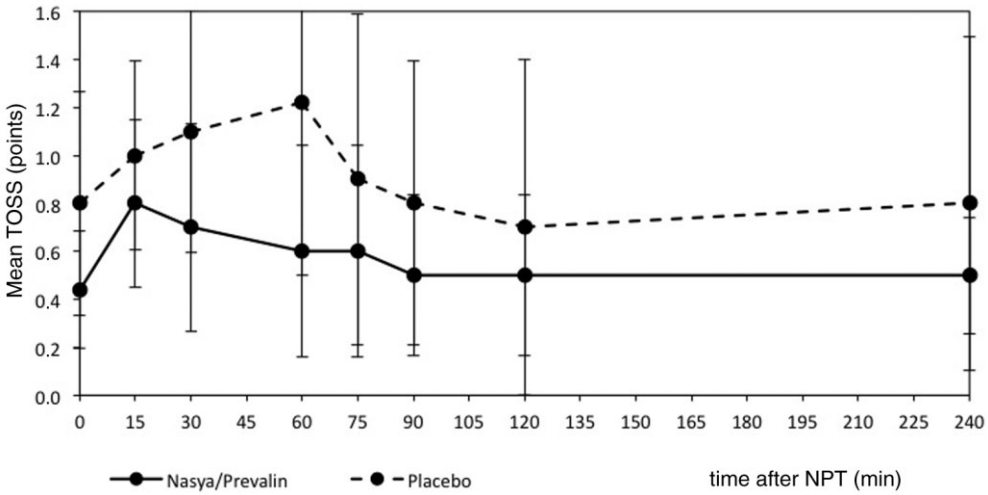

Figure 3. Mean total ocular symptom score (TOSS) (at Visit 2) before and after the allergen challenge (full analysis set population); error bars represent standard error of the mean. NPT, nasal provocation test.

whereas in the placebo group, the symptoms peaked 60 min after the allergen challenge.

Rhinoscopy score at 15 and 75 min

Conventional anterior rhinoscopy with a nasal speculum and headlight was performed by the investigator. The swelling of the mucosa, secretion or change in colour was judged in a rhinoscopy score at baseline, and 15 and 75 min after the allergen challenge.

At baseline, there was no difference in the appearance of the nasal mucosa (concerning swelling, secretion or colour) in the Nasya/Prevalin group compared with the placebo-treated subjects (Nasya/Prevalin: 0.40 ± 0.7 pts; placebo 0.60 ± 0.97 pts; $P = 0.777$). Because of the NPT, the macroscopic appearance of the mucosa deteriorates in both groups (increase of rhinoscopy score). However, the nasal mucosa irritation 15 min after the NPT, stated by the rhinoscopy score, were significantly worse in the placebo group compared with the Nasya/Prevalin group (Nasya/Prevalin: 1.60 ± 1.17 pts; placebo 3.00 ± 1.25 pts; $P = 0.033$). At this time point in all of the placebo subjects (100%), but only in 60% of the Nasya/Prevalin subjects, the score increased. After 75 min, the scores were decreased in both treatment groups; however, the recovery from allergen challenge was more pronounced in the Nasya/Prevalin group than in the placebo group (Nasya/Prevalin: 1.00 ± 0.82 pts; placebo 2.00 ± 1.05 pts; $P = 0.054$).

Global rating of treatment efficacy and symptom relief

To determine the global assessment of benefit, subjects and investigators evaluated the benefit of the investigational product with 'very good', 'good', 'moderate' or 'poor' at the end of the study.

There was no difference between the two treatment groups regarding the global assessment of efficacy provided by the investigators ($P = 0.554$) or by the subjects ($P = 0.389$). Zero per cent of the investigators and 10% of the patients rated the Nasya/Prevalin treatment as being poor, whereas in the case of placebo, 20% of the investigators and 20% of the patients rated the efficacy as being poor.

Rescue medication

No rescue medication was used for any of the subjects during the study.

Safety evaluation

Assessment of AEs

During the study, three mild AEs were documented in two subjects in the verum group (swallowing difficulties, nasal airways obstruction and headache); none related to the application of the investigational product. None of the AEs was classified as serious.

Global evaluation of tolerability

There was no difference between the two treatment groups regarding the global assessment of tolerability provided by the investigators ($P = 0.582$) or by the subjects ($P = 1.000$). In 100% of the cases, the investigators rated the tolerability of Nasya/Prevalin or placebo with 'very good' or 'good'. Similar judgment was given by the subjects (Nasya/Prevalin: 90% 'very good' or 'good'; placebo: 100% 'very good' or 'good').

Discussion

The results of this placebo-controlled study demonstrate that application of Nasya/Prevalin before a challenge with dust mite allergens was associated with a reduction of the allergic rhinitis symptoms. The primary end point has been reached with statistical significance in VCAS population and a trend in the FAS population. This indicates the prophylactic effect of Nasya/Prevalin.

The difference in the intensity of allergic rhinitis symptoms, as assessed per TNSS, was statistically significant at 75 min, as well as at 60 and 90 min after allergen provocation in favour of Nasya/Prevalin. The TNSS showed a reduced peak and a faster return to baseline in the Nasya/Prevalin group compared with placebo. The same has been observed for the TOSS. The results of these two scores were further underlined by the outcome of the rhinoscopic evaluation by the investigator. The mucosa of both treatment groups showed visible irritation after NPT, which, however, were significantly less pronounced and decreased faster because of Nasya/Prevalin treatment.

Before randomisation, all patients had to achieve a TNSS score >6 pts after NPT (mean TNSS at randomisation 7.20 pts). In this study, a single application of Nasya/Prevalin was sufficient to reduce this reaction. The TNSS in the Nasya/Prevalin group reached only 4.0 points 15 min after NPT. This makes it obvious that Nasya/Prevalin has established a barrier in the nasal mucosa and was able to reduce the allergen contact.

However, the placebo product (saline spray) also showed some positive effects. Like the Nasya/Prevalin subjects, subjects treated with the placebo did not reach the TNSS they had at randomisation (TNSS at randomisation: 6.9 pts; with saline spray treatment: 4.5 pts). It was shown earlier, in an open-label study that 4 weeks of treatment with salt water sprays resulted in a significant reduction of the observed symptoms in acute, chronic, atrophic or allergic rhinitis, as well as in rhinitis sicca (17). The protective effect of hypertonic salt solutions on allergic rhinitis has further been shown by Cordray *et al*. (18). The authors claimed that intranasal saline might be as effective as H1 receptor antagonists in patients with mild allergic rhinitis. The mechanism behind saline spray is probably an intensive humidification of the mucosa, which stimulates mucociliary clearance. It has been shown that application of sodium chloride leads to increased ciliary beat frequency, that improves mucociliary clearance (19). Further, it has been shown that salt water sprays have anti-inflammatory and antiswelling effects.

This probably explains the positive effects of the placebo in this trial. Without these positive effects of the saline spray, the obtained difference between Nasya/Prevalin and the placebo would have probably been even more pronounced.

Based on the results obtained in this placebo-controlled study, the barrier function of the thixotropic nasal spray has been confirmed. The barrier is effective in minimizing the early-phase immune response (2–4 h after allergen contact). Therefore, to prevent the initiation of the late-phase response, Nasya/Prevalin has to be applied every 4–6 h.

The use of Nasya/Prevalin in the presented clinical investigation can be considered as safe as placebo. None of the reported AEs were related to the application of the product. Further the tolerability of Nasya/Prevalin was rated as 'very good' or 'good' by 90% of the subjects and for 100% of the subjects by the investigator.

In conclusion, in this clinical trial, the efficacy of Nasya/Prevalin on allergic rhinitis because of house dust mite allergens has been shown. However, in view of the few patients treated in that study, together with the single application of the investigational product, further studies will be necessary to prove efficacy under real-life conditions and daily use.

Acknowledgement

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