

Letter to the Editor

Nasal filters for the treatment of allergic rhinitis: A randomized, double-blind, placebo-controlled crossover clinical trial

To the Editor:

Allergic rhinitis (AR) is clinically defined as a symptomatic disorder of the nose induced after allergen exposure by IgE-mediated inflammation.¹ Conservatively, it is estimated that more than 500 million people worldwide have AR.¹

Allergen avoidance continues to be at the forefront of guidelines for AR treatment,²⁻⁵ although it is typically considered difficult to implement.^{2,5} As a practical method of allergen avoidance, nasal filters have generally yet to prove that they are useful when their benefits are weighed against their disadvantages. In particular, efficacy, unimpeded nasal breathing, low visibility, and comfortableness are important for patient compliance to this strategy in the management of AR. Therefore this randomized clinical trial (RCT) sought to investigate the efficacy, safety, and usability of a new nasal filter, Rhinix (Rhinix ApS, Aarhus, Denmark), which was constructed to ensure comfort and minimize airway resistance and visibility when in use.

A detailed methodology is provided in the **Methods** section in this article's Online Repository at www.jacionline.org. Briefly, this trial was a single-center, randomized (1:1), double-blind, placebo-controlled crossover clinical trial (clinicaltrials.gov ID: NCT01699165) conducted in an environmental exposure unit (EEU) in Denmark from December 2012 to February 2013, avoiding the normal grass season (June-August). Twenty-four adult subjects with a history of grass pollen-induced AR confirmed based on positive specific IgE levels and a positive skin prick test response were included (see **Table E1** in this article's Online Repository at www.jacionline.org).

The active nasal filter (Rhinix) consists of a membrane that removes particles by means of interception and impaction. The membrane is placed in each nostril's anterior vestibule and kept in place by a copolymer frame (see **Fig E1**, A, in this article's Online

Repository at www.jacionline.org). The level of air resistance across the filtering membrane had been determined before study commencement, and it was concluded that the increase in resistance was less than the level of perception⁶; thus no difference was expected in the perceived air resistance between the active and placebo devices (unpublished data).

Subjects were exposed to grass pollen for 210 minutes and rated their nasal symptoms at baseline (time = 0), every 30 minutes in the EEU (until 180 minutes), shortly after exiting the EEU (at approximately 220 minutes), and 3 hours later (at 390 minutes) (for a trial overview, see **Fig E2** in this article's Online Repository at www.jacionline.org). Assessments were made by using a total nasal symptom score (TNSS) consisting of nasal congestion, nasal discharge, nasal itching, and sneezing. The primary outcome measure was the difference between placebo and active nasal filters evaluated by using maximum TNSSs (the highest score of the 9 ratings). Differences in daily TNSSs (the sum of all 9 ratings) were also evaluated as a prespecified outcome measure. Exploratory analyses on individual nasal symptoms, as well as ocular symptoms, throat irritation, and objectively measured intranasal volume, were also performed. Finally, the device was evaluated on usability and tolerance, and measurements of oral fraction of exhaled nitric oxide and spirometry served as safety measures. All analyses of symptoms were done with Wilcoxon signed-rank tests. Reductions (**Tables I** and **II**) were calculated as follows:

$$\frac{\text{Rhinix} - \text{Placebo}}{\text{Placebo}} \times 100.$$

A significant *P* value of less than .05 was used in all analyses. *P* values of .10 or less indicated tendencies.

Detailed results are available in the **Results** section in this article's Online Repository at www.jacionline.org. Briefly, 24 subjects were randomized. Of these, 3 subjects were excluded from the analyses: 1 was excluded because of a septal deviation that went unnoticed on screening, and 2 were excluded because their

TABLE I. Daily and maximum TNSSs and daily and maximum values for all 4 individual nasal symptoms

Outcome measure‡	Rhinix vs Placebo										Relative difference (%)†	
	Rhinix	Placebo	Rhinix		Placebo		Absolute difference*			P value§	Mean	Median
	Mean	Mean	Median	Range (25% to 75%)	Median	Range (25% to 75%)	Mean	95% CI	Median			
TNSS, maximum (12)	4.67	5.43	4	4 to 6	6	4 to 7	0.76	−0.13 to 1.66	2	.140	14	33
TNSS, daily (108)	20.67	26.19	19	14 to 25	25	17 to 35	5.52	0.59 to 10.46	6	.049	21	24
Itch, maximum (3)	0.67	1.24	1	0 to 2	1	0 to 2	0.57	0.26 to 0.88	0	.004	46	—
Itch, daily (27)	2.76	4.33	2	0 to 4	3	1 to 8	1.57	−0.27 to 3.41	1	.234	36	33
Runny nose, maximum (3)	1.86	1.90	2	1 to 2	2	2 to 2	0.05	−0.19 to 0.29	0	.706	3	—
Runny nose, daily (27)	9.10	10.29	7	6 to 12	10	7 to 13	1.19	−0.51 to 2.89	3	.174	12	30
Sneeze, maximum (3)	0.95	1.52	1	1 to 1	2	1 to 2	0.57	0.20 to 0.94	1	.006	38	50
Sneeze, daily (27)	2.86	5.19	2	1 to 5	6	3 to 7	2.33	0.88 to 3.78	4	.011	45	67
Blocked nose, maximum (3)	1.43	1.43	1	1 to 2	2	1 to 2	0.00	−0.47 to 0.47	0	.928	—	50
Blocked nose, daily (27)	5.95	6.38	5	2 to 9	6	3 to 10	0.43	−2.12 to 2.98	1	.702	7	17

*Absolute difference calculated as placebo − Rhinix for means and medians. Surrogate 95% CIs are calculated by using a bootstrap method in STATA software with 1000 repetitions.

†Relative difference calculated as absolute difference divided by placebo.

‡Numbers in parentheses indicate highest possible scores for each outcome measure. *Daily* indicates the sum of all 9 scores throughout a study day. *Maximum* indicates the highest individual score of the 9 possible scores.

§*P* value for the nonparametric Wilcoxon signed-rank test of no difference between placebo and Rhinix nasal filters.

TABLE II. Symptom scores for each nasal symptom at all recorded time points

Outcome measure‡	Rhinix	Placebo	Rhinix		Placebo		Absolute difference*			P value§	Relative difference (%)†		
	Mean	Mean	Median	Range	Median	Range	Mean	95% CI	Median		Mean	Median	
				(25% to 75%)		(25% to 75%)							
Itching													
At baseline: before exposure	0.05	0.05	0	0 to 0	0	0 to 0	0	−0.13 to 0.13	0	1.00	—	—	
At 30 min: during exposure	0.38	0.38	0	0 to 1	0	0 to 1	0	−0.35 to 0.35	0	.85	—	—	
At 60 min: during exposure	0.38	0.48	0	0 to 1	0	0 to 1	0.10	−0.15 to 0.34	0	.47	21	—	
At 90 min: during exposure	0.38	0.57	0	0 to 1	0	0 to 1	0.19	−0.13 to 0.51	0	.29	33	—	
At 120 min: during exposure	0.38	0.71	0	0 to 1	1	0 to 1	0.33	−0.06 to 0.73	1	.15	47	100	
At 150 min: during exposure	0.38	0.57	0	0 to 1	0	0 to 1	0.19	−0.13 to 0.51	0	.41	33	—	
At 180 min: during exposure	0.38	0.71	0	0 to 1	0	0 to 1	0.33	−0.09 to 0.76	0	.19	47	—	
At 220 min: after exposure	0.33	0.71	0	0 to 1	0	0 to 1	0.38	0.03 to 0.73	0	.05	54	—	
At 390 min: after exposure	0.10	0.14	0	0 to 0	0	0 to 0	0.05	−0.12 to 0.21	0	.56	34	—	
Blocked nose													
At baseline: before exposure	0.1	0.1	0	0 to 0	0	0 to 0	−0.05	−0.21 to 0.11	0	1.00	—	—	
At 30 min: during exposure	0.29	0.38	0	0 to 1	0	0 to 1	0.19	−0.08 to 0.46	0	.21	50	—	
At 60 min: during exposure	0.71	0.57	1	0 to 1	1	0 to 1	−0.14	−0.60 to 0.31	0	.55	−25	—	
At 90 min: during exposure	1.05	0.71	1	0 to 2	1	0 to 1	−0.33	−0.81 to 0.15	0	.23	−47	—	
At 120 min: during exposure	0.95	0.81	1	0 to 1	1	0 to 1	−0.14	−0.69 to 0.40	0	.64	−17	—	
At 150 min: during exposure	0.86	1.00	1	0 to 1	1	0 to 2	0.14	−0.35 to 0.64	0	.52	14	—	
At 180 min: during exposure	1.00	1.14	1	0 to 2	1	0 to 2	0.14	−0.40 to 0.69	0	.60	12	—	
At 220 min: after exposure	0.67	1.10	1	0 to 1	1	0 to 2	0.43	0.04 to 0.82	0	.07	39	—	
At 390 min: after exposure	0.33	0.48	0	0 to 1	0	0 to 1	0.14	−0.10 to 0.38	0	.26	29	—	
Runny nose													
At baseline: before exposure	0.38	0.29	0	0 to 1	0	0 to 1	−0.10	−0.35 to 0.16	0	.48	−33	—	
At 30 min: during exposure	0.86	0.95	1	0 to 1	1	0 to 1	0.10	−0.29 to 0.52	0	.48	10	—	
At 60 min: during exposure	1.29	1.38	1	1 to 2	1	1 to 2	0.10	−0.29 to 0.48	0	.50	7	—	
At 90 min: during exposure	1.38	1.24	1	1 to 2	1	1 to 2	−0.14	−0.49 to 0.20	0	.63	−11	—	
At 120 min: during exposure	1.24	1.29	1	1 to 2	1	1 to 2	0.05	−0.21 to 0.30	0	.71	4	—	
At 150 min: during exposure	1.24	1.62	1	1 to 2	2	1 to 2	0.38	0.00 to 0.76	1	.10	24	50	
At 180 min: during exposure	1.29	1.71	1	1 to 2	2	1 to 2	0.43	0.10 to 0.76	1	.03	25	50	
At 220 min: after exposure	0.95	1.33	1	0 to 1	1	1 to 2	0.38	−0.10 to 0.86	0	.07	29	—	
At 390 min: after exposure	0.48	0.48	0	0 to 1	0	0 to 1	0	−0.19 to 0.19	0	1.00	—	—	
Sneezing													
At baseline: before exposure	0.05	0	0	0 to 0	0	0 to 0	−0.05	−0.13 to 0.04	0	.32	—	—	
At 30 min: during exposure	0.24	0.38	0	0 to 0	0	0 to 1	0.14	−0.10 to 0.39	0	.26	38	—	
At 60 min: during exposure	0.33	0.52	0	0 to 1	0	0 to 1	0.19	−0.06 to 0.44	0	.16	37	—	
At 90 min: during exposure	0.52	0.76	1	0 to 1	1	0 to 1	0.24	−0.05 to 0.52	0	.15	32	—	
At 120 min: during exposure	0.48	0.67	0	0 to 1	1	0 to 1	0.19	−0.09 to 0.47	1	.21	28	100	
At 150 min: during exposure	0.48	0.81	0	0 to 1	1	0 to 1	0.33	−0.08 to 0.75	1	.10	41	100	
At 180 min: during exposure	0.52	1.14	0	0 to 1	1	1 to 2	0.62	0.11 to 1.12	1	.03	54	100	
At 220 min: after exposure	0.19	0.67	0	0 to 0	1	0 to 1	0.48	0.16 to 0.79	1	.01	72	100	
At 390 min: after exposure	0.05	0.24	0	0 to 0	0	0 to 0	0.19	0.02 to 0.36	0	.047	79	—	

Time points of 30 to 180 minutes are while exposed to pollen in the EEU.

*Absolute difference calculated as placebo − Rhinix for means and medians. Surrogate 95% CIs are calculated by using a bootstrap method in STATA software with 1000 repetitions.

†Calculated as the absolute difference divided by placebo.

‡Highest score at each time point is 3: 0, absent symptoms; 1, mild symptoms; 2, moderate symptoms; 3, severe symptoms.

§P value for the nonparametric Wilcoxon signed-rank test of no difference between placebo and Rhinix nasal filters.

nasal cavities proved too small for the sizes available (size medium). For all 3 subjects, the unintended consequence was that the devices came into continuous contact with the mucosal membrane. A diagram of the study flow and information on study subjects is shown in Fig E3 and Table E2, respectively, in this article's Online Repository at www.jacionline.org. The mean grass exposure was 1066 grains/m³ (SD, 237 grains/m³), see Fig E4 in this article's Online Repository at www.jacionline.org.

The maximum TNSS was insignificant ($P = .14$), with mean and median reductions at 14% and 33%, respectively, for Rhinix when compared with placebo (Table I). The difference in daily TNSSs was significantly reduced for Rhinix when compared

with placebo ($P = .049$), with mean and median reductions of 21% and 24%, respectively (Table I). Maximum nasal itching ($P = .004$) and maximum ($P = .006$) and daily ($P = .011$) sneezing were all significantly reduced with Rhinix versus placebo (Table I). Analyses at each time point revealed that the difference between Rhinix and placebo became significant or tended to become significant toward the end of the exposure period. For individual symptoms, see Table II, and for TNSSs, see Fig E5 and Table E3 in this article's Online Repository at www.jacionline.org. Throat irritation was significantly decreased with Rhinix versus placebo at 220 minutes ($P = .037$), with a mean reduction of 75% (see Table E4 in this article's Online Repository at www.jacionline.org).

[jacionline.org](http://www.jacionline.org)). No difference between treatments in ocular symptoms, intranasal volume, or any of the safety measures could be detected. Three subjects experienced mild treatment-related adverse events of unspecified nasal irritation (2 for Rhinix and 1 for placebo). No other treatment-related adverse events were recorded. Most subjects quickly stopped noticing that they were wearing the device, and no difference in increased breathing resistance between treatments could be detected (see Fig E6, A and B, respectively, in this article's Online Repository at www.jacionline.org). Of the 21 subjects, 19 were interested in using the device, and all subjects felt completely safe with Rhinix (see Fig E6, D).

The results of this trial demonstrated that Rhinix was significantly more effective than placebo in alleviating nasal symptoms in adults with seasonal allergic rhinitis (SAR), primarily through its effect on nasal itching, sneezing, and nasal discharge. These results are consistent with the preventive effect of nasal filters suggested in other studies,^{7,8} although it must be noted that direct comparison of different nasal filters is difficult because the filtration mechanism, retention rates, air flow rates, and overall designs deviate substantially. Furthermore, Rhinix was well tolerated and safe to use.

In regard to limitations, this study was conducted in a clinical setting and was not designed to answer questions on long-term compliance, safety, or long-term treatment effects during natural pollen seasons. Furthermore, the study did not show significance on the primary outcome measure. This could be due to the small sample size or the limited symptom severity among subjects in the trial, which again might have been caused by our choice of exposure level, the out-of-season setting, and lack of priming. As indicated in the time point analyses, differences tended to become apparent near the end of the exposure sessions. This suggests that the length of exposure and exposure levels might have been too short and too low, respectively, to show the true difference between treatments.

Interestingly, throat irritation was decreased with Rhinix compared with placebo, with a mean reduction of 75% at 220 minutes. Although the overall severity of throat irritation was perceived as low (only 10 subjects were mildly symptomatic to throat irritation at any one point), this finding was surprising because it could be speculated that the active nasal filter would increase throat irritation as a result of a potentially increased tendency to breathe orally (thus allowing for more particles to bypass the nasal filtration system). This finding and the findings of no difference in breathing resistance between the devices suggest that the active device did not increase the tendency to breathe orally. Further discussions are available in this article's Discussion section in the Online Repository at www.jacionline.org.

In conclusion, although maximum TNSS showed no statistically significant difference, statistically significant and clinically

relevant reductions were achieved with Rhinix nasal filters in daily TNSS, as well as in a subset of individual symptoms for patients with SAR. Furthermore, it would seem that this nasal impaction filter is acceptable to wear and has negligible airway resistance.

On the basis of the findings of this small, limited in length and exposure levels EEU trial conducted in a clinical setting, Rhinix appears useful in the treatment of SAR, although in-season studies on efficacy and usability (particularly concerning convenience, comfort, and treatment costs) in larger populations are needed to verify this.

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Disclosure of potential conflict of interest: P. Kenney is a board member for, is employed by, has a patent with, and has stock/stock options in Rhinix ApS. The rest of the authors declare that they have no relevant conflicts of interest.

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METHODS

Elaboration on the clinical trial design

No changes to the trial protocol were made after enrollment of trial subjects had begun. The regional ethics committee approved all relevant trial material, including the protocol and informed consent form. The trial was conducted in accordance with the Helsinki Declaration, the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice, the European standard “Clinical investigation of medical devices for human subjects—good clinical practice (ISO 14155:2011),” and the requirements of the Danish Health and Medicines Authority, as well as the Danish Data Protection Agency. Written informed consent was obtained from all subjects before study entry. The trial report was written according to the guidance provided in the Consolidated Standards of Reporting Trials (CONSORT) statement.^{E1}

Trial population

The full list of inclusion and exclusion criteria is provided in [Table E1](#).

Subjects were recruited for screening by using posters at Aarhus University and on Facebook. Screening visits, including physical examinations, vital signs, and evaluation of inclusion and exclusion criteria, were performed only after written informed consent had been given. The trial’s principal investigator (T.S.) enrolled eligible subjects.

Trial setting and protocol

The trial took place in an EEU at the Department of Environmental and Occupational Medicine, Aarhus University School of Public Health. This EEU was a 4.15 m × 2.9 m × 2.7 m (length × width × height) room made of stainless steel. Two tables with 4 chairs (numbered 1-4) were placed at optimum positions in regard to securing an even distribution of pollen.

An overview of the trial protocol is presented in [Fig E2](#).

Subjects were called one by one into a separate room, where they were blind to device allocation and assigned their treatment for the day (placebo or active). After assignment, subjects entered the EEU as a group. Subjects were monitored at all times during exposure by an EEU technician. Subjects wore disposable coveralls, shoe covers, and nurse caps to eliminate contamination. All material (eg, books and paper) that entered the EEU was cleaned before and after exposure either by vacuuming it or wiping it clean. The same operator performed all objective recordings to eliminate interindividual variations.

Trial intervention

The placebo and active nasal filters, including the standardized method of insertion, are depicted in [Fig E1](#). In the placebo filters the membrane was omitted from the frame ([Fig E1, A](#)).

Subjects were blind to the intervention allocation and had no prior experience with the devices. They were not told by which mechanism the device was supposed to work and therefore had no knowledge that would make it possible for them to identify which device (placebo or active) they were wearing on a given day.

The devices were inserted by using a standardized method that was identical for both the placebo and active filters ([Fig E1, B](#)). During this procedure, study subjects were blind with a standard sleep mask. They were told to tilt their heads backward, and an operator then inserted the device in a manner similar to [Fig E1, B](#). The crossbar was used to adjust the height to the most comfortable and most appropriate position in terms of filtration.

Two sizes (medium and large) were used in the study to accommodate size variations in the subjects.

Grass exposure

The dispersion of pollen (*Phleum pratense*) was done with a modified small-scale powder dispenser (model 3433; TSI Incorporated, Shoreview, Minn). Second-by-second online particle measurements (Solair 3100; Light-house Worldwide Solutions, Fremont, Calif) and 30-minute pollen counts

(Personal volumetric air samplers; Burkard Manufacturing Co Ltd, Hertfordshire, United Kingdom) were used as feedback information to continuously check that the pollens were dispersed evenly. Both of these measurements were done in actual time. The target pollen concentration was 1000 grains/m³.

Elaboration on outcome measures

Acoustic rhinometry was used to assess mucosal swelling measured as changes in intranasal volume.^{E2} Differences between treatments in change in intranasal volume between baseline and 220 minutes and baseline and 390 minutes were evaluated as the trials’ secondary outcome measure.

The 2 remaining outcome measures were exploratory: a total ocular symptom score (TOSS) was rated at identical time points to the TNSS and with an identical scale. The TOSS rated itchy, swollen, and watering eyes. Only differences in maximum and daily TOSSs were evaluated. Throat irritation was rated at baseline and at 220 and 390 minutes on a continuous visual analog scale ranging from no symptoms (0) to severe symptoms (100).

The usability and tolerance of the device were evaluated by using a product evaluation questionnaire. Subjects rated the device after its removal at approximately 220 minutes.

Oral fraction of exhaled nitric oxide with an NO Vario Analyser (Filt Lungen- und Thoraxdiagnostik GmbH, Berlin, Germany) measured at baseline and 220 and 390 minutes plus assessment of FEV₁ with a spirometer (Micro DL spirometer; Micro Medical, Hoechnberg, Germany) at baseline, 220 minutes, 390 minutes, evening, bedtime, and the following morning served as safety measures.

Determination of sample size

The power of the study was calculated based on including 24 study participants, of whom 18 were expected to have different reactions when using active and placebo filters. We expected that 85% of the 18 would react more with placebo filters compared with active filters in a way that would be possible to see in the TNSS. With a significance level of 5%, the power of the study was calculated to be 92%.

Randomization, assignment to interventions, and blinding

A statistician generated the randomized allocation sequence for study subjects using a computerized block method (1:1) and assigned study subjects to their order of intervention. Each study day included 2 subjects with filters and 2 with placebo filters. Both study subjects, care providers, EEU technicians, and study investigators were blind to the allocations. The devices were kept in coded boxes that stated the study day (1/2), subject ID, study group (1-6), and the subject’s unique seat in the EEU (1-4). The same operator handled the insertion and removal of the devices for all subjects. The operator who handled the devices did not participate in any other investigational activities during the course of the trial.

Statistics

The secondary outcome measure was analyzed by using a Student *t* test after having checked that data followed a normal distribution. In all analyses the null hypothesis was “no difference” between the paired treatments. A bootstrap method with 1000 repetitions was used to calculate surrogate 95% CIs.

All statistical analyses were performed with STATA 12 software (StataCorp, College Station, Tex). All graphic work was done with Prism 6.0 software (GraphPad Software, La Jolla, Calif).

RESULTS

The study population was composed of 13 male and 11 female subjects ([Table E2](#)). The mean age of the subjects was 24.7 years

(SD, 3.6 years), and the mean specific IgE level was 41.7 kU/L (SD, 34.4 kU/L; Table E2).

The mean grass pollen exposure counted at 30-minute intervals was 1066 grains/m³ (SD, 237 grains/m³; Fig E4). The EEU was kept at a slight positive pressure (range, 0–10 Pa) with a humidity of 35% (SD, 5%) and an air change cycle rate of 8.5 times per hour.

Efficacy

The secondary outcome of difference between Rhinix and placebo in change in nasal volume, as measured by using acoustic rhinometry, was insignificant at both 220 minutes ($P = .85$) and 390 minutes ($P = .78$). No difference in maximum TOSS ($P = .35$) or daily TOSS ($P = .59$) was observed between the 2 treatments.

Device evaluation

Most subjects were aware of wearing the device immediately after insertion; however, within 10 minutes, less than half reported noticing the device, and at 60 minutes, only 2 of 21 were aware of wearing the active nasal filter (Fig E6, A). Thirteen subjects reported increased breathing resistance (for both Rhinix and placebo); however, the number who noticed it decreased quickly during the experiment (Fig E6, B).

DISCUSSION

This article is the first report comparing the newly developed Rhinix nasal filter with a placebo nasal filter on subjects with SAR in a double-blind, single-center crossover RCT in the controlled environment of an EEU.

Rhinix nasal filters are solely intended to be in contact with unbroken epidermal skin, and because that could not be achieved in 3 of the 24 subjects, they were excluded from the analyses. In everyday use we would expect these subjects to either switch to a smaller filter size or discontinue use entirely because of a suboptimal effect or mucosal irritation. We did not exclude subjects with nasal cavities larger than the largest size (size large). In daily use we expect that gaps will arise because of anatomic variations or grimacing. Therefore small gaps were not considered grounds for exclusion as long as the device was positioned as intended.

We conducted this RCT in the rigorously controlled setting of an EEU. The merits of EEUs as effective, reproducible, safe, and suitable settings for single-center clinical studies evaluating treatments for SAR are generally acknowledged,^{E3,E4} and more than 40 peer-reviewed trials concerning AR in EEUs have been published.^{E4} Moreover, US Food and Drug Administration authorities have endorsed EEUs as valid models for investigating the time to onset and duration of action plus short-term effects of antiallergic drugs.^{E5} However, EEU trials are not without limitations. Most notably, the clinical setting means that subjects are not in their normal habitat, and therefore EEUs are inadequate when testing actual use over a prolonged period. In our specific setting subjects wore scrubs and nurse caps to prevent contamination. This might also have promoted the feeling of being in a clinical setting in comparison with a situation in which subjects are free to wear their own clothes.

Two other common critiques of EEU SAR trials are that subjects are exposed to unnaturally high concentrations of pollen and the role of priming during an EEU trial.^{E4} In this study we

exposed subjects to *P. pratense*. Because pollens have different allergenic properties, thereby complicating the use of pollen levels from other EEU pollen studies,^{E4} and because we lacked sufficient information on exposure levels in EEUs for *P. pratense*, we decided to err on the side of caution regarding our subjects' safety and chose a low target exposure level of 1000 grains/m³ (this was calculated by using a reported height-to-ground ratio from Danish settings^{E6} and seasonal pollen reports from the Danish Meteorological Institute).

This low exposure level compared with other EEU trials^{E4,E7} must be regarded as one of the primary limitations of this study, and it probably had a key influence on the low symptom severity that was apparent in both of the treatment arms.

This study was conducted during the Danish winter, during which ambient pollen levels are zero. The subjects were carefully chosen to be asymptomatic at the start of the trial so that any change in symptoms could be associated with the actual exposure. However, we did not use a run-in priming period, which is typically recommended to increase the study subjects' level of sensitivity to a specific allergen.^{E4}

Our choice of exposure level, the out-of-season setting, and lack of priming might account for the generally low symptom scores. The maximum theoretic average TNSS was 12, which would imply severe symptoms in all 4 categories at all 9 time points. In this trial the mean TNSS fluctuated around 3 while the subjects were in the EEU (see Table E2). This is comparable with symptom scores in reports on outpatient sublingual immunotherapy trials,^{E8,E9} and to follow their argumentation, we recommend that focus be kept on the differences between the treatment arms because this should be the key output from double-blind, placebo-controlled RCTs.^{E9}

In regards to the size of the study population, our power calculation proved to be too optimistic, at least with the chosen study design and exposure levels. We assumed that 18 of the 24 included subjects would show at least a 50% reduction in symptoms with the active device compared with placebo; however, this proved difficult to show, perhaps because of the limitations discussed in the previous section.

The crossover design assumes that disease severity is balanced between the 2 treatments.^{E10} In this regard a potential priming effect from visit 1 to visit 2 could prove a problem. However, several reports have shown that priming is reversible within 2 weeks.^{E11–E13} Therefore this study's use of a washout period of at least 16 days between visits was likely to minimize the effects of priming on observed differences in treatment effects.

Nasal congestion showed the least difference between treatment arms, with a trend toward a difference only immediately after exposure (Table II). This corresponded with the lack of effect on objectively measured changes in intranasal volume by using acoustic rhinometry. On this matter, it is noteworthy that a recent study on antihistamines did not show an objective difference between treatment arms with acoustic rhinometry, even though nasal congestion was reduced.^{E14}

Finally, we observed a buildup of symptoms during the pollen exposure in both the placebo and Rhinix groups, with a time lapse before any difference in treatment results became evident (eg, Table II). The reason for this lack of initial effect is unclear. It might relate to the fact that impaction filters only remove a fraction of the particles but that their effectiveness increase over time as particles are deposited in the mesh. Another possibility is simply that the number of subjects included was too low to show

subtle differences in low-level symptoms when exposing unprimed asymptomatic subjects to pollen in an EEU. A final possibility, and perhaps the most plausible, is the fact that our exposure level was low and that it was only after being exposed for almost the entire period that meaningful effects became apparent and thus the possibility of separating the 2 treatments became possible.

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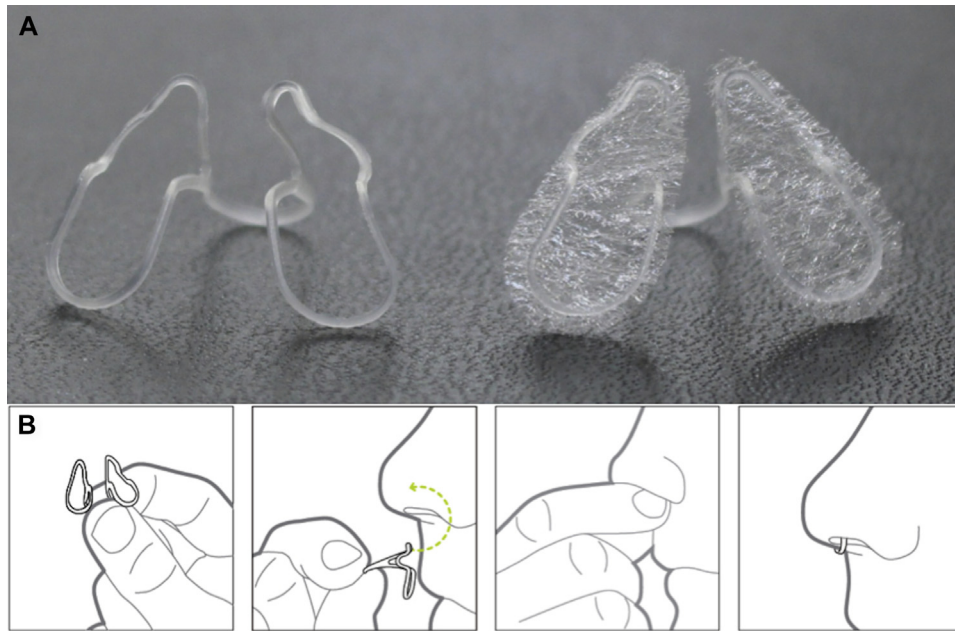


FIG E1. A, The devices. *Left*, Placebo. *Right*, Rhinix nasal filter. B, Standardized method of insertion. Please note that the illustration depicts how a user would insert it. In the study an operator inserted and removed all devices using a similar standardized method. This was done to ensure blinding.

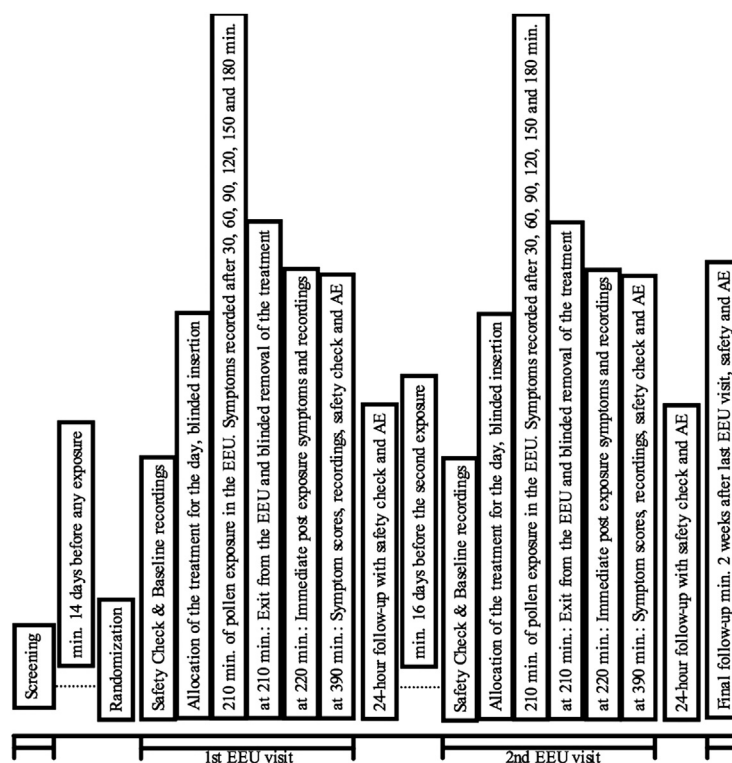


FIG E2. Trial protocol. Safety check included blood pressure, pulse, temperature, and physical examination results. Recordings at baseline and 220 and 390 minutes included symptoms (TNSSs, TOSSs, and throat irritation), acoustic rhinometry, FEV₁, and nitrogen oxide in exhaled air. During exposure, TNSSs and TOSSs were obtained every 30 minutes. The devices were evaluated on usability at 220 minutes. AE, Adverse event.

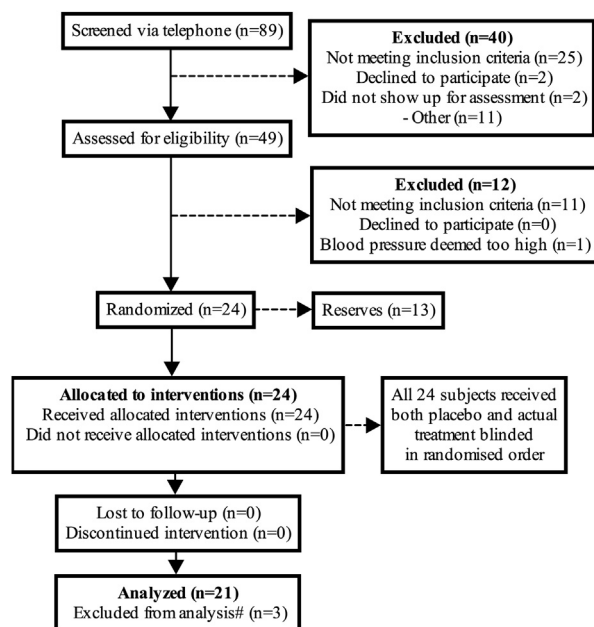


FIG E3. Study flow diagram. #Three subjects were excluded from the analyses (see text for details).

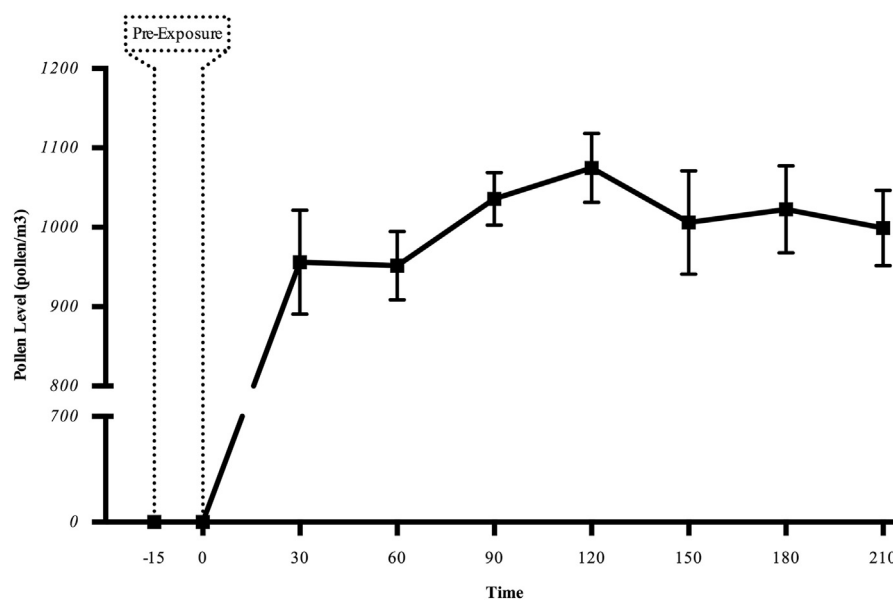


FIG E4. Pollen exposure levels in the EEU in grains per cubic meter with SEMs as error bars. Note that 15 minutes before each EEU session, pre-exposure recordings were performed. The exposure sessions ended at 210 minutes when participants left the EEU. Pollen levels were counted every 30 minutes.

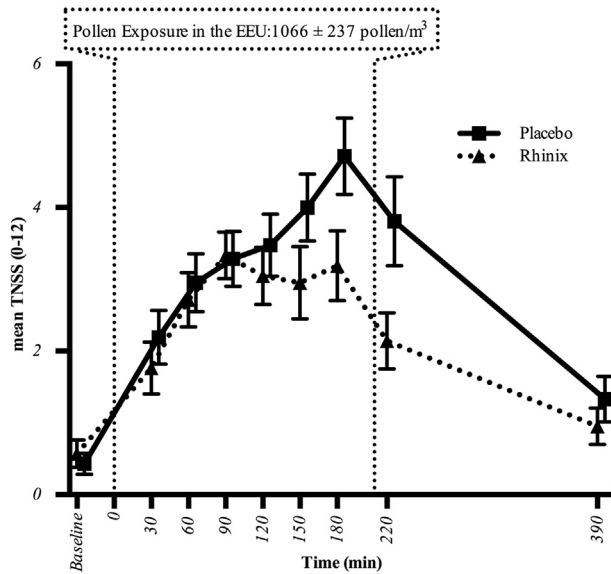


FIG E5. Mean TNSSs with SEMs as error bars. Note that exposure in the EEU was from time point 0 to 210 minutes. Symptoms at baseline and 220 and 390 minutes were recorded outside of exposure. Exposure levels are presented as means $\pm$ SDs.

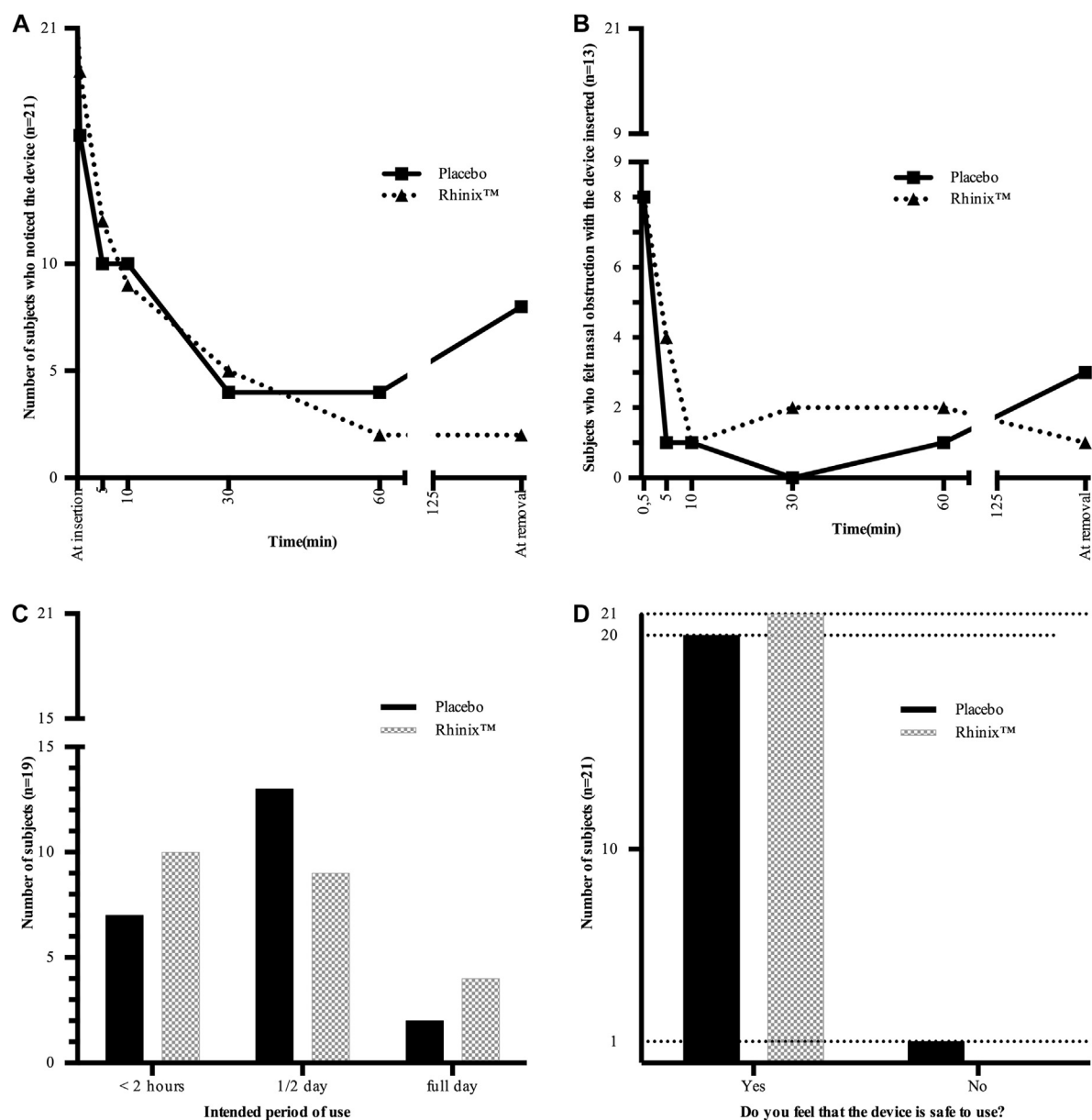


FIG E6. Device evaluation. **A**, Proportion of subjects aware of wearing a device. **B**, Time points for noticing breathing resistance in the 13 of 21 subjects who felt increased resistance. **C**, Intended period of use for the 19 of 21 subjects who wanted to use the device. **D**, Proportion of subjects who believed the device was completely safe to use.

TABLE E1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age of 18-65 y	Positive pregnancy test for fertile women or women currently breast-feeding
Positive history of SAR for a minimum of 2 y before study entry documented by a positive skin prick test response to <i>P pratense</i> (wheal diameter >3 mm) within 12 mo of study entry	Inadequate washout periods regarding EEU appointments for the following medications: intranasal or systemic corticosteroids (1 mo), intranasal cromolyn (2 wk), intranasal or systemic decongestants (3 d), intranasal or systemic antihistamines (3 d), loratadine (10 d), long-acting antihistamines or any other medication related to controlling or alleviating symptoms related to AR
Specific IgE for timothy grass pollen (>3.5 kU/L, CAP Class ≥ 3 ; <i>Phleum pratense</i> ; Phadia AB, Uppsala, Sweden)	Asthma unless mild and only occurring in relation to the grass pollen season, as assessed by the investigator
Written informed consent	Rhinitis medicamentosa
Reliable method of birth control for fertile women	Documented evidence of acute or chronic sinusitis, as determined by the investigator
Ability to be present as required during the trial period	FEV ₁ <70% of predicted value
	Subjects with perennial AR (eg, house dust mites, cats, dogs, or molds) unless symptom free
	AR requiring medication caused by allergens other than grass unless symptom free
	Subjects with nasal conditions likely to affect the outcome of the study in the opinion of the investigator (ie, anterior nasal septal deviation, nasal septum perforations, nasal polyps, chronic nasal obstruction, or other nasal diseases)
	Receipt of immunotherapy with grass pollen within the previous 10 y

TABLE E2. Information on study subjects

Randomization no.	Age (y)	Height (cm)	Weight (kg)	Sex	SPT maximum wheal (mm)	PP IgE (kU/L)
1	22	181.2	82.6	Male	12.0	43.6
2	23	171.0	57.6	Female	10.8	57.0
3	22	162.9	55.4	Female	11.0	37.2
4	31	178.0	74.5	Male	14.9	9.5
5	27	177.2	72.1	Male	22.5	14.6
6	23	183.6	75.6	Male	5.2	9.4
7	36	173.4	72.2	Female	9.5	15.8
8	22	168.7	68.5	Female	10.0	86.9
9	23	182.4	88.9	Male	16.0	10.7
10	30	170.0	74.2	Female	9.0	33.9
11	24	182.3	73.3	Male	16.5	31.9
12	22	183.6	64.9	Male	9.0	16.9
13	20	171.3	69.0	Female	11.0	4.3
14	25	171.3	80.8	Male	13.5	33.3
15	28	173.5	68.2	Male	18.0	67.6
16	23	165.3	67.6	Female	7.0	101.0
17	27	178.1	68.9	Male	11.0	11.6
18	23	169.0	54.0	Female	9.5	15.2
19	23	172.4	74.1	Female	15.5	101.0
20	24	188.1	79.7	Male	10.0	87.1
21	24	182.3	73.3	Male	12.0	12.6
22	24	174.4	75.8	Male	16.2	84.2
23	24	169.2	62.0	Female	13.5	101.0
24	22	171.9	73.9	Female	13.1	15.2

PP, *P pratense*; SPT, skin prick test.

TABLE E3. TNSSs at all recorded time points

Outcome measure [‡]	Rhinix	Placebo	Rhinix		Placebo		Absolute difference*			P value [§]	Relative difference (%) [†]	
	Mean	Mean	Median	Range (25% to 75%)	Median	Range (25% to 75%)	Mean	95% CI	Median		Mean	Median
TNSS												
At baseline: before exposure	0.57	0.43	0	0 to 1	0	0 to 1	−0.14	−0.52 to 0.23	0	.63	—	—
At 30 min: during exposure	1.76	2.19	1	1 to 2	1	1 to 3	0.43	−0.38 to 1.24	1	.26	20	50
At 60 min: during exposure	2.71	2.95	2	2 to 4	3	2 to 4	0.24	−0.62 to 1.10	1	.87	8	33
At 90 min: during exposure	3.33	3.29	3	2 to 4	4	2 to 4	−0.05	−0.84 to 0.74	1	1.00	−2	25
At 120 min: during exposure	3.05	3.48	4	1 to 4	4	2 to 5	0.43	−0.44 to 1.30	0	.39	12	—
At 150 min: during exposure	2.95	4.00	3	1 to 4	4	2 to 5	1.05	−0.04 to 2.13	1	.14	26	25
At 180 min: during exposure	3.19	4.71	3	1 to 4	5	2 to 6	1.52	0.28 to 2.77	2	.03	32	40
At 220 min: after exposure	2.14	3.81	2	1 to 3	3	1 to 6	1.67	0.55 to 2.79	1	.01	44	33
At 390 min: after exposure	0.95	1.33	1	0 to 2	1	0 to 2	0.38	−0.05 to 0.82	0	.13	29	—

Time points of 30 to 180 minutes are while exposed to pollen in the EEU.

*Absolute difference calculated as placebo − Rhinix for means and medians. Surrogate 95% CIs are calculated by using a bootstrap method in STATA software with 1000 repetitions.

†Calculated as the absolute difference divided by placebo.

‡Highest score at each time point is 12. The TNSS is a composite of the individual symptoms of sneezing and blocked, itchy, and runny nose.

§P value for the nonparametric Wilcoxon signed-rank test of no difference between placebo and Rhinix nasal filters.

TABLE E4. Throat irritation

Outcome measure†	Rhinx	Placebo	Rhinx		Placebo		Absolute difference*			P value§	Relative difference (%)†	
	Mean	Mean	Median	Range (25% to 75%)	Median	Range (25% to 75%)	Mean	95% CI	Median		Mean	Median
Throat irritation (n = 21)												
At baseline	1.68	3.93	0	0 to 0	0	0 to 0	2.25	−2.80 to 7.30	0	.676	57	—
At 220 min	2.01	7.96	0	0 to 0	0	0 to 15	5.95	0.70 to 11.20	0	.037	75	—
At 390 min	0.40	4.73	0	0 to 0	0	0 to 0	4.34	−2.63 to 11.31	0	.526	92	—
Throat irritation (n = 10)												
At baseline	3.54	8.26	0	0 to 5.7	0	0 to 10.8	4.72	−5.94 to 15.38	0	.640	57	—
At 220 min	4.23	16.73	0	0 to 0.7	15.3	3.5 to 29	12.5	2.87 to 22.13	15.3	.051	75	100
At 390 min	0.83	9.94	0	0 to 0	0	0 to 6.7	9.11	−5.05 to 23.27	0	.482	92	—

Data are presented for the whole population (n = 21) and the subset who at any one rating point scored higher than zero on at least one of the 2 study days (n = 10).

*Absolute difference calculated as placebo − Rhinx for means and medians. Surrogate 95% CIs are calculated by using a bootstrap method in STATA software with 1000 repetitions.

†Calculated as the absolute difference divided by placebo.

‡Outcome measure rated on a visual analog scale: 0 = symptom is absent; 100 = symptom is severe.

§P value for the nonparametric Wilcoxon signed-rank test of no difference between placebo and Rhinx nasal filters.