

Preventive effect of nasal filters on allergic rhinitis: A randomized, double-blind, placebo-controlled crossover park study

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Background: A recently reported small, out-of-season environmental exposure unit study found nasal filters to be efficacious in preventing seasonal allergic rhinitis (AR). However, nasal filters still need to show efficacy in a natural setting in a regular pollen season.

Objective: We sought to evaluate the efficacy of nasal filters (Rhinix; Rhinix ApS, Aarhus, Denmark) for the prevention of symptoms related to seasonal AR.

Methods: The trial was a single-center, randomized (1:1), double-blind, placebo-controlled crossover clinical trial (NCT02108574) conducted over 2 days in the main grass pollen season in June 2014 in Aarhus, Denmark, on 65 adults with proven grass allergy. A total nasal symptom score (TNSS) consisting of blocked nose, runny nose, nasal itching, and sneezing was used to evaluate symptoms. The difference in daily Σ TNSS (the sum of 13 ratings) was the primary outcome measure. The difference in maximum TNSS (highest score, 13 ratings) was also evaluated.

Results: The nasal filters significantly reduced daily Σ TNSSs ($P = .03$) and maximum TNSSs ($P = .03$) compared with placebo. Median relative reductions were 40% for daily Σ TNSSs ($P = .02$), 43% for maximum TNSSs ($P = .004$), 83% for daily Σ sneezing ($P = .001$), 75% for daily Σ watery eyes ($P = .02$), and 53% for daily Σ runny nose ($P = .005$) when compared with placebo. The nasal filters were well tolerated, and no serious adverse events were recorded.

Conclusion: Statistically significant and clinically relevant reductions were achieved for the primary outcome measure of daily Σ TNSS, for maximum TNSS and for a subset of individual symptoms. The results support the preventive role of nasal

filters for managing seasonal AR. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: Seasonal allergic rhinitis, nasal filter, placebo controlled, randomized controlled trial, total nasal symptom score, total ocular symptom score, pollen, efficacy, allergen avoidance, prevention

Allergic rhinitis (AR), a symptomatic disorder of the upper airway tract affecting more than 500 million persons globally, occurs when exposure to environmental allergens triggers IgE-mediated inflammation.¹ AR has been linked to a general impairment in quality of life,^{2,3} emotional problems and poorer mental well-being,³ daytime sleepiness,⁴ and loss of productivity.^{5,6} Consequently, AR is associated with significant direct and indirect costs to an economy.⁷

As part of an overall management strategy for AR, allergen avoidance is indicated for all patients,^{8,9} although it has generally been considered difficult to implement.^{9,10} Recently, a study on a new impaction nasal filter showed promising results as an effective and wearable device for the prevention of nasal and throat allergy symptoms during exposure to pollens.¹¹ However, because that study was conducted out of season in an exposure unit environment, it is essential to investigate the efficacy of the nasal filters in a regular pollen season and in natural settings. This is in line with the US Food and Drug Administration's recommendations for AR clinical trials.¹² One in-season method for achieving this is a park study.¹² Park studies have previously been used to study the in-season effect of antiallergenic treatments under controlled natural settings.^{1,13,14}

Also, supporting the relevance of this current study, the exposure unit study did not meet its primary end point. It was argued that this could have been due to a small sample size or a limited symptom severity as a result of the study's out-of-season setting or the lack of priming or because of the choice of pollen levels.¹¹ Therefore this randomized controlled trial sought to investigate the efficacy, safety, and usability of the nasal filter in a larger population during a regular pollen season in a natural park setting.

METHODS

Clinical trial design

A detailed methodology is given 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: NCT02108574) conducted over 2 days (day 1 on June 4th and day 2 on June 16th) in 2014 during the main grass pollen season in a park in Aarhus, Denmark. Seventy-six adults with a history of grass pollen-induced AR confirmed by a positive specific IgE level and a positive

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Supported by Rhinix ApS, Aarhus, Denmark, and designed to be consistent with recommendations provided in the US Food and Drug Administration document for clinical development of drug products for allergic rhinitis (Guidance for Industry, US Department of Health and Human Services, US Food and Drug Administration Center for Drug Evaluation and Research, April 2000).

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

Received for publication February 4, 2015; revised April 30, 2015; accepted for publication May 13, 2015.

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0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2015.05.015>

Abbreviations used

AR: Allergic rhinitis
 daily Σ : Sum of ratings from minute 90 to minute 450
 SAR: Seasonal allergic rhinitis
 TNSS: Total nasal symptom score
 TOSS: Total ocular symptom score

skin prick test response were included (see [Table E1](#) in this article's Online Repository at www.jacionline.org).

The nasal filters (RhiniX; RhiniX ApS, Aarhus, Denmark), placebo filters, and method for insertion are described in the [Methods section](#) in this article's Online Repository.

Trial protocol

An overview of the trial protocol is presented in [Fig 1](#). Both days, subjects arrived at the park before 9 AM and left just after 5 PM. Baseline was recorded at 9 AM. The run-in period started at 9:30 AM, and the assessment period started at 11 AM. Assessments were made every 30 minutes by using a total nasal symptom score (TNSS) consisting of blocked nose, runny nose, nasal itching, and sneezing.¹² The primary outcome measure was the difference between placebo and the nasal filter evaluated by the difference in daily Σ TNSS (the sum of the 13 ratings from minute 90 to minute 450). Difference in maximum TNSS (the highest score of the 13) was also evaluated. Other prespecified secondary and tertiary analyses included difference in daily Σ throat irritation and difference in daily Σ total ocular symptom score (TOSS).

Exploratory analyses were performed for the groups with a baseline TNSS of 0 or 1 and the groups with a baseline TOSS of 0 or 1. Also, exploratory analyses of drowsiness and global discomfort were performed. Finally, the device was evaluated on usability, and FEV₁ served as a safety measure.

All crossover analyses were done with Wilcoxon rank sum tests for 2-period crossover studies.¹⁵ For each of the 2 study days individually, reductions ([Tables I-IV](#)) were calculated as follows:

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

Also, statistical analyses for each day individually were carried out for the parallel groups by using Wilcoxon rank sum tests. All analyses, including exploratory analyses, were prepared before unblinding. A *P* value of less than .05 was used to measure significance in all analyses. *P* values of .10 or less were considered to indicate tendencies. For information on sample size determination, randomization, blinding, and pollen measurements, see the [Methods section](#) in this article's Online Repository.

RESULTS

A total of 76 subjects were randomized. Of these, 7 did not show up at all, 3 were discontinued after day 1 for reasons unrelated to the study, and 1 was excluded because of an inappropriate nasal filter fit. This left 65 subjects for the analyses. See [Fig 2](#) for a diagram of the study flow.

The study population was comprised of 34 male and 31 female subjects. Mean age was 24.8 years (SD, 6.1 years), mean wheal diameter for the *Phleum pratense* response was 8.0 mm (SD, 3.4 mm), and mean specific IgE level was 21.7 kU/L (SD, 22.4 kU/L). Five subjects reported having had asthma attacks within the last 12 months.

Grass pollen levels varied substantially between days 1 and 2. Thus the mean pollen level on day 1 was 56.12 grains/m³ (SD, 56.60 grains/m³), and the mean level on day 2 was 140.19 grains/m³ (SD, 115.23 grains/m³; [Fig 3](#)). Mean temperatures between 9 AM and 5 PM were 17.0°C and 17.4°C for days 1 and 2, respectively.

Efficacy

The primary outcome measure of difference in daily Σ TNSS was significantly reduced for the nasal filter when compared with placebo (*P* = .03), with median reductions on day 2 of 40% (*P* = .02, [Table I](#)). Difference in maximum TNSS was also significantly reduced (*P* = .03), with median reductions of 43% on day 2 (*P* = .004, [Table I](#)). Sneezing, itching, and runny nose symptoms contributed to the overall differences ([Table I](#)).

Restricting the analyses to the groups with a baseline TNSS of 0 or 1 on each study day (33 subjects on day 1 and 22 subjects on day 2), daily Σ TNSS was reduced by 62% (*P* = .012) on day 2 for the nasal filter compared with placebo ([Table II](#)). Also, symptom severity in the nasal filter groups was close to identical for the 2 study days ([Table II](#)).

Difference in daily Σ TOSS was insignificant (*P* = .12), with median reductions on day 2 of 47% (*P* = .076, [Table III](#)). Daily Σ watering eyes was significantly reduced (*P* = .03), with reductions of 75% on day 2 (*P* = .016, [Table III](#)). For subjects with a baseline TOSS of 0 or 1 on each study day (56 subjects on day 1 and 41 subjects on day 2), daily Σ TOSS was reduced by 73% (*P* = .031) on day 2 ([Table IV](#)).

The difference in daily Σ throat irritation was insignificant (*P* = .43, [Table III](#)) for days 1 and 2, respectively.

Drowsiness was not significant when evaluated by using the crossover design (*P* = .24). However, on day 2, the nasal filter significantly reduced drowsiness by a median reduction of 54% (*P* = .046) compared with placebo ([Table III](#)). Global discomfort was significantly decreased overall for the nasal filter (*P* = .037) compared with placebo, with day 2 reductions of 42% (*P* = .071). For subjects with a baseline TNSS of 0 or 1, global discomfort was reduced by 82% (*P* = .005) and drowsiness by 83% (*P* = .076) on day 2 for the nasal filter compared with placebo ([Table IV](#)).

For all outcomes, the overall significant differences, as outlined above, were almost entirely a result arising from differences between treatments on day 2 ([Tables I-IV](#)).

No difference between placebo and the filter could be detected for the FEV₁ safety measure. Three subjects experienced device-related transient adverse events: a mild nasal burning sensation (placebo), a mild unspecified nasal irritation (placebo), and a moderate nasal itch (the nasal filter). No other device-related adverse events were recorded. For a summary of the usability results and time-point specific mean TNSSs, see the Results section and [Figs E1](#) and [E2](#) in this article's Online Repository at www.jacionline.org.

DISCUSSION

This is the first report of an in-season natural exposure randomized controlled trial comparing this impaction nasal filter with a placebo filter in adults with seasonal allergic rhinitis (SAR).

Results of this trial demonstrated that the nasal filter was significantly more efficacious than placebo in preventing symptoms associated with SAR. These results expand on the suggested preventive effects of the nasal filter found in a small out-of-season environmental exposure unit study,¹¹ thus strengthening arguments for the filters' relevance in preventing symptoms of SAR during a regular pollen season.¹² Their relevance is also supported by the current body of evidence related to other nasal filters, especially an earlier randomized, double-blind, placebo-controlled

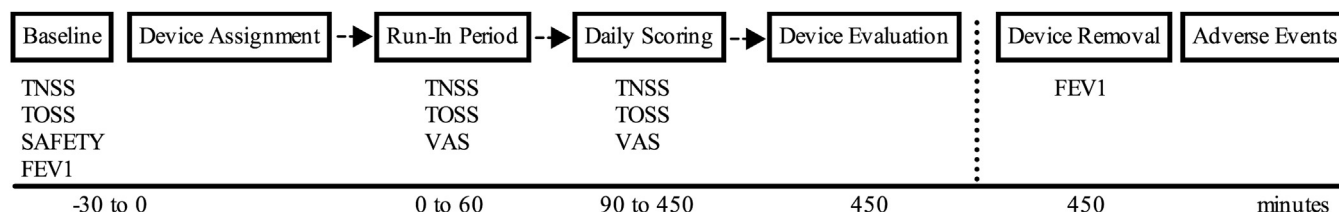


FIG 1. Trial protocol. Baseline scoring, FEV₁ measurement, and safety checks were performed before blind device insertion. TNSSs and TOSSs were evaluated every 30 minutes. Visual analog scale (VAS) ratings were evaluated at hourly intervals from minute 60. The devices were removed after the final ratings at minute 450. FEV₁ was recorded immediately thereafter, and adverse events were noted.

TABLE I. Daily Σ and maximum TNSSs and daily Σ and maximum values for all 4 individual nasal symptoms by study day

Outcome measure†	Nasal filter		Placebo		Absolute difference*		Relative difference (%)‡
	Median	Range (25%-75%)	Median	Range (25%-75%)	Median	P value§	Median
Day 1							
TNSS, daily Σ (156)	17	8-35	21.5	10-30	4.5	.713	21
TNSS, maximum (12)	3	2-5	3.5	2-5	0.5	.729	14
Itch, daily Σ (39)	7	2-13	8	4-13	1	.449	13
Runny nose, daily Σ (39)	5	2-11	5	1-10	0	.493	—
Sneeze, daily Σ (39)	0	0-2	0	0-2	0	.876	—
Blocked nose, daily Σ (39)	1	0-12	3	0-12	2	.707	67
Itch, maximum (3)	1	1-2	1	1-2	0	.305	—
Runny nose, maximum (3)	1	1-2	1	1-2	0	.654	—
Sneeze, maximum (3)	0	0-1	0	0-1	0	.815	—
Blocked nose, maximum (3)	1	0-1	1	0-1	0	.761	—
Day 2							
TNSS, daily Σ (156)	29.5	16-44	49	33-67	19.5	.019	40
TNSS, maximum (12)	4	3-6	7	5-8	3	.004	43
Itch, daily Σ (39)	10	3-16	15	7-24	5	.057	33
Runny nose, daily Σ (39)	9	2-15	19	9-23	10	.005	53
Sneeze, daily Σ (39)	1	0-5	6	3-10	5	.001	83
Blocked nose, daily Σ (39)	7	0-16	7	0-17	0	.528	—
Itch, maximum (3)	1.5	1-2	2	1-3	0.5	.038	25
Runny nose, maximum (3)	1	1-2	2	2-3	1	.002	50
Sneeze, maximum (3)	1	0-1	1	1-2	0	.001	—
Blocked nose, maximum (3)	1	0-2	1	0-2	0	.573	—

*Absolute difference calculated for medians as follows: Placebo – Nasal filter.

†Calculated as the absolute difference divided by placebo.

‡Numbers in parentheses indicate the highest possible scores for each outcome measure. Daily Σ indicates the sum of all 13 scores from minute 90 through minute 450. Maximum indicates the highest individual score of the 13 possible scores.

§P value for the 2-sample Wilcoxon rank sum (Mann-Whitney) test of no difference between placebo and the nasal filter within the study day (parallel groups).

park study¹⁴ and, to a lesser degree, the effect suggested by 2 non-randomized open-label studies.^{16,17} However, it is important to note that the filters used in these studies differ substantially from this nasal filter in design and filtration mechanisms, thus making direct comparison difficult. Furthermore, this trial supported the fact that the nasal filter was well tolerated and safe to use, although it should be noted that prolonged periods of use might lead to more significant side effects.

Daily Σ TNSS included the ratings from minute 90 to study's end. This was chosen to minimize any effect of pollen exposure before having the devices inserted. Because the filters work by preventing allergen inhalation, any allergens that had been inhaled before insertion could potentially induce symptoms and obscure a treatment difference between placebo and the nasal filter. Optimally, in evaluating the prophylactic effect of the filters, subjects should be asymptomatic or have only mild rhinitis symptoms before device insertion.¹² This is apparent when looking solely at the subjects with a baseline TNSS of 0 or 1. Among these

subjects, the differences between placebo and the nasal filter became even greater (the median relative reduction for daily Σ TNSS changed from 40% to 62%). Also, interestingly, when comparing the nasal filter group on day 2 with the nasal filter group on day 1, there was no difference in symptom severity (Table II), even though the pollen levels on day 2 were markedly higher than those on day 1. This emphasizes the added benefit of initiating use of the filters before symptom onset and also suggests that the filters will become increasingly beneficial as pollen levels increase.

The lack of significant differences between placebo and the nasal filter when looking solely at day 1 was most probably a consequence of the low pollen levels and thus mild symptom severity. The maximum theoretic median for TNSS was 12, which would imply maximum scores for all 4 nasal symptoms at all 13 ratings. On day 1, the median TNSS fluctuated around 1.31 for the nasal filter and 1.65 for placebo, thus being considerably lower than scores reported in the out-of-season study.¹¹ The sample size in this study was not large enough to show significant

TABLE II. Daily Σ and maximum TNSSs for the subjects with a baseline TNSS score of 0 or 1 by study day

Outcome measure†	Nasal filter		Placebo		Absolute difference*		Relative difference (%)‡	
	Median	Range (25%-75%)	Median	Range (25%-75%)	Median	P value§	Median	
Day 1								
TNSS, daily Σ (156)	13	6-24	14.5	5-24	1.5	.899	10	
TNSS, maximum (12)	2	1-3	2	1-5	0	.941	—	
Itch, daily Σ (39)	4	1-10	8.5	3-13	4.5	.186	53	
Runny nose, daily Σ (39)	4	1-8	2	0-8	−2	.351	−100	
Sneeze, daily Σ (39)	0	0-2	0	0-2	0	.921	—	
Blocked nose, daily Σ (39)	1	0-8	0	0-4	−1	.553	—	
Itch, maximum (3)	1	1-2	1	1-2	0	.282	—	
Runny nose, maximum (3)	1	1-2	1	0-2	0	.563	—	
Sneeze, maximum (3)	0	0-1	0	0-1	0	.984	—	
Blocked nose, maximum (3)	1	0-1	0	0-1	−1	.436	—	
Day 2								
TNSS, daily Σ (156)	16	8-25	42	30-49	26	.012	62	
TNSS, maximum (12)	3	2-4	5	4-7	2	.002	40	
Itch, daily Σ (39)	4	0-15	13	6-14	9	.227	69	
Runny nose, daily Σ (39)	3	0-6	19	9-21	16	.010	84	
Sneeze, daily Σ (39)	0	0-1	6	3-9	6	.032	100	
Blocked nose, daily Σ (39)	0	0-4	5	2-11	5	.226	100	
Itch, maximum (3)	1	0-2	2	1-2	1	.152	50	
Runny nose, maximum (3)	1	0-1	2	2-3	1	.010	50	
Sneeze, maximum (3)	0	0-1	1	1-2	1	.050	100	
Blocked nose, maximum (3)	0	0-2	1	1-2	1	.309	100	

*Absolute difference calculated for medians as follows: Placebo − Nasal filter.

†Calculated as the absolute difference divided by placebo.

‡Numbers in parentheses indicate highest possible scores for each outcome measure. *Daily Σ* indicates the sum of all 13 scores from minute 90 through minute 450. *Maximum* indicates the highest individual score of the 13 possible scores.

§P value for the 2-sample Wilcoxon rank sum (Mann-Whitney) test of no difference between placebo and the nasal filter within the study day (parallel groups).

TABLE III. Daily Σ TOSSs, daily Σ values for all 3 individual ocular symptoms, and daily Σ VAS ratings by study day

Outcome measure†	Nasal filter		Placebo		Absolute difference*		Relative difference (%)‡	
	Median	Range (25%-75%)	Median	Range (25%-75%)	Median	P value§	Median	
Day 1								
TOSS, daily Σ (117)	4	0-13	3.5	1-13	−0.5	.771	−14	
Eye itch, daily Σ (39)	4	0-10	3	0-7	−1	.821	−33	
Watering eyes, daily Σ (39)	0	0-2	0	0-1	0	.689	—	
Swollen eyes, daily Σ (39)	0	0-0	0	0-0	0	.103	—	
Drowsiness, daily Σ (70)	2.5	1.1-12.3	4	1.5-6.9	1.5	.679	38	
Throat irritation, daily Σ (70)	3	1.3-11.9	4.9	1.4-12.3	1.9	.698	39	
Global discomfort, daily Σ (70)	5.4	2.3-11.3	6.2	2.7-11.4	0.8	.942	13	
Day 2								
TOSS, daily Σ (117)	9	3-28	17	5-47	8	.076	47	
Eye itch, daily Σ (39)	7	2-15	9	3-21	2	.169	22	
Watering eyes, daily Σ (39)	1	0-7	4	1-16	3	.016	75	
Swollen eyes, daily Σ (39)	0	0-4	0	0-9	0	.246	—	
Drowsiness, daily Σ (70)	4.3	0.8-11.6	9.3	3.1-12.5	5	.046	54	
Throat irritation, daily Σ (70)	4.3	1.1-20.2	6.5	3.9-21.8	2.2	.520	34	
Global discomfort, daily Σ (70)	10	4.7-22.5	17.3	11.8-27.3	7.3	.071	42	

VAS, Visual analog scale.

*Absolute difference calculated for medians as follows: Placebo − Nasal filter.

†Calculated as the absolute difference divided by placebo.

‡Numbers in parentheses indicate highest possible scores for each outcome measure. *Daily Σ* indicates the sum of all 13 scores from minute 90 through minute 450. Visual analog scale ratings of drowsiness, throat irritation, and global discomfort were rated 7 times in the same interval.

§P value for a 2-sample Wilcoxon rank sum (Mann-Whitney) test of no difference between placebo and the nasal filter within the study day (parallel groups).

differences between placebo and the nasal filter at such low TNSSs. However, because of a substantial filter effect on day 2, the overall results were still significant. Priming could be another contributing factor to the difference in symptom severity between days 1 and 2. The 16th of June (day 2) followed a

relatively stable period of high pollen levels (data not shown, available on www.dmi.dk). The 4th of June (day 1) at the beginning of the season followed a period with lower pollen levels. Using this knowledge when comparing the results of days 1 and 2, this study suggests why it is typically recommended to use a

TABLE IV. Daily Σ TOSSs, daily Σ values for all 3 individual ocular symptoms for subjects with a baseline TOSS score of 0 or 1, and daily Σ VAS ratings for the subjects with a baseline TNSS score of 0 or 1 by study day

Outcome measure†	Nasal filter		Placebo		Absolute difference*		Relative difference (%)‡
	Median	Range (25%-75%)	Median	Range (25%-75%)	Median	P value§	Median
Day 1							
TOSS, dailyΣ (117)	3	0-10	3	0-13	0	.848	—
Eye itch, dailyΣ (39)	3	0-9	3	0-7	0	.980	—
Watering eyes, dailyΣ (39)	0	0-1	0	0-1	0	.910	—
Swollen eyes, dailyΣ (39)	0	0-0	0	0-0	0	.175	—
Drowsiness, dailyΣ (70)	2	0.3-3.4	1.7	1-5.5	−0.3	.677	−18
Throat irritation, dailyΣ (70)	1.8	0.3-4.8	2.4	1.4-8.9	0.6	.311	25
Global discomfort, dailyΣ (70)	3.1	1.5-6.2	3.7	0.5-7.4	0.6	.718	16
Day 2							
TOSS, dailyΣ (117)	4	1.5-15	15	5-24	11	.031	73
Eye itch, dailyΣ (39)	3	1.5-7.5	9	3-12	6	.198	67
Watering eyes, dailyΣ (39)	0	0-5	4	2-11	4	.009	100
Swollen eyes, dailyΣ (39)	0	0-0	0	0-4	0	.035	—
Drowsiness, dailyΣ (70)	1.6	0.5-4.5	9.5	3.1-11.1	7.9	.076	83
Throat irritation, dailyΣ (70)	2	0.4-4.4	4.7	0.8-21.8	2.7	.367	57
Global discomfort, dailyΣ (70)	3.5	2.3-8.1	19.4	14.9-21.7	15.9	.005	82

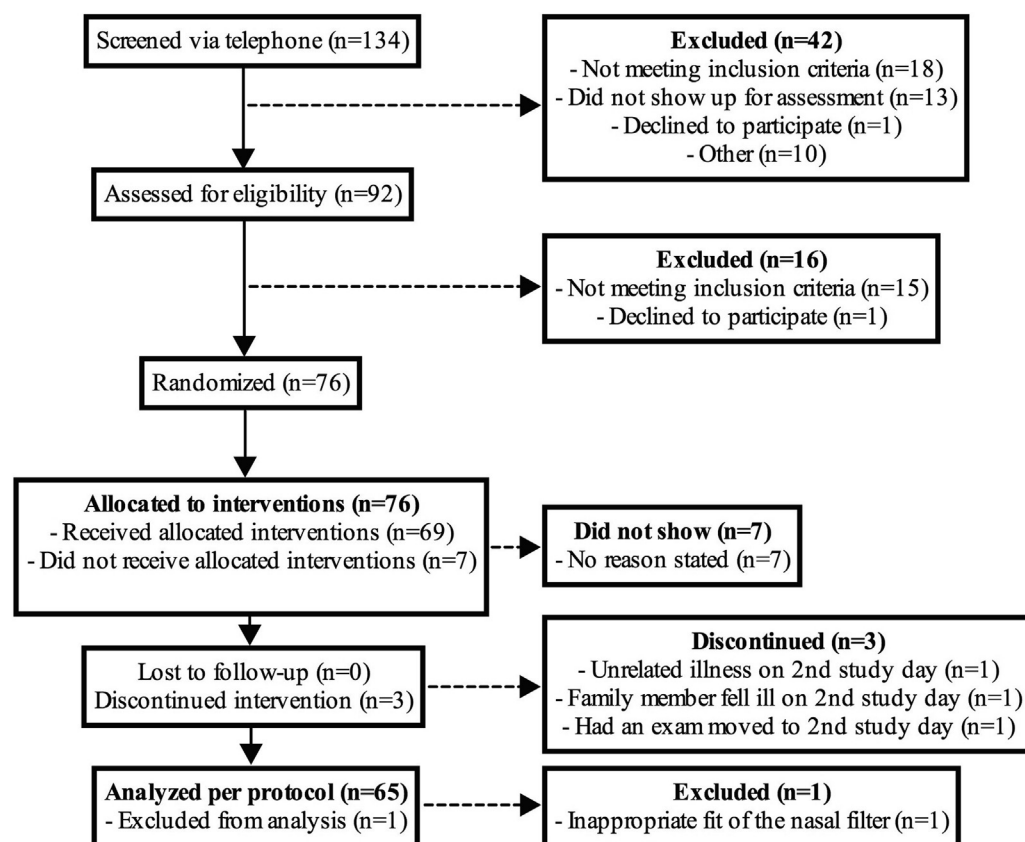
VAS, Visual analog scale.

*Absolute difference calculated for medians as follows: Placebo – Nasal filter.

†Calculated as the absolute difference divided by placebo.

‡Numbers in parentheses indicate highest possible scores for each outcome measure. Daily Σ indicates the sum of all 13 scores from minute 90 through minute 450. Visual analog scale ratings of drowsiness, throat irritation, and global discomfort were rated 7 times in the same interval.

§P value for a 2-sample Wilcoxon rank sum (Mann-Whitney) test of no difference between placebo and the nasal filter within the study day (parallel groups).

**FIG 2.** Study flow diagram.

run-in priming period before a study day to increase the subjects' sensitivity to the allergens.¹⁸

As previously described,¹¹ the crossover design assumes that disease severity is balanced between the 2 periods.¹³

A potential priming effect from day 1 on day 2 could have proved a problem; however, as is apparent from [Tables I and III](#), no difference between placebo and the nasal filter was found on day 1, and in any case, the washout period

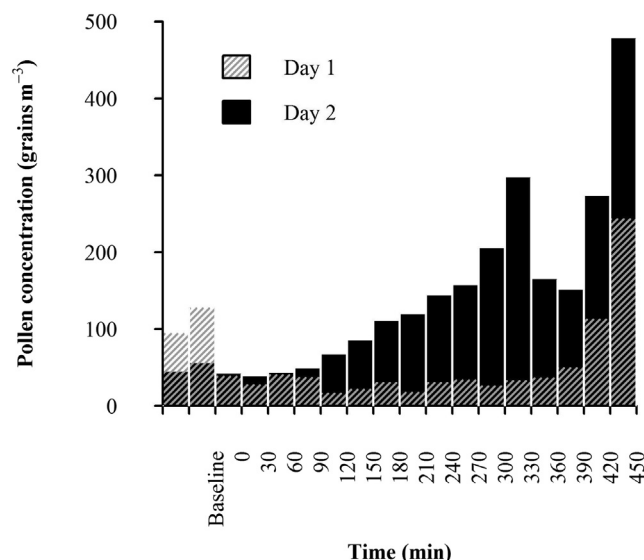


FIG 3. Diurnal changes in grass pollen concentration for the 2 study days.

between the 2 study days should be adequate to rule out such an effect.¹⁹

As regards other limitations, this study was not designed to answer questions on the overall usability of nasal filters in subjects' everyday lives. Everyday convenience, comfort, and costs will be important factors in determining the potential user uptake of nasal filters. Also, even though subjects were told not to take medications for the periods specified in Table E1 and were asked whether they had followed these instructions at the start of each study day, the investigators had no method for ensuring that subjects adhered to this. This could potentially have affected the outcome of the study. When asked, one subject admitted using eye drops once on the day before day 2. The on-call physician assessed that exclusion was not necessary, and thus the subject was included in all analyses. The analyses were repeated without this subject to ensure the reliability of the results. This did not significantly change the results of the primary outcome measure or any of the ocular symptoms.

This study was designed to overcome some of the challenges of the environmental exposure unit study,¹¹ particularly the small sample size of that study, out-of-season clinical setting, lack of priming, and limited symptom severity. An exposure unit study can be conducted under rigorously controlled and constant conditions.¹ However, in a park study pollen levels and weather conditions in general are uncontrollable,¹³ as this study shows. Even with these challenges in mind, park studies have been used and are generally recognized for use in evaluating antiallergenic treatments.^{1,12,13,20,21} Compared with outpatient studies, park studies are considered advantageous in minimizing interindividual variability in pollen exposure, in controlling exposure times, and for monitoring patients more intensely.¹³ Furthermore, it was not considered feasible to perform a double-blind placebo-controlled study if subjects were to self-administer insertion and removal of the filters, as would have to be the case in an outpatient study. First of all, such a design would allow subjects to visibly inspect the filters and placebos, thereby making the double-blind design impossible, and second, even if the study were to be carried out without blinding or with single blinding of the investigators, it would be expected that a significant share

of the placebo users would simply stop using the placebos when they learned that they were given a nonfunctioning filter. Thus the park study design was considered optimal for an in-season double-blind evaluation of the preventive effect of nasal filters.

From a clinical perspective, it is relevant to compare the efficacy of the nasal filter with the efficacies of other antiallergenic treatments. When looking at results from other park studies with similar study periods, the filters' efficacy appears to compare positively with the efficacy found for antihistamines,^{20,22} intranasal steroid sprays,^{21,23} mast cell inhibitors,²⁴ and combination therapies.^{25,26} In relation to placebo, these studies found first-day efficacies ranging from favoring placebo to roughly 50% improvements in symptoms. It is important to note that all of these studies were designed as treatment studies, as opposed to prophylaxis studies.¹² Optimally, treatment studies should enroll subjects with moderate-to-high baseline values, whereas prophylaxis studies should enroll subjects with minimal to no symptoms at baseline.¹² Typically, treatment studies will look at a treatment's efficacy in the form of a change from baseline while prophylaxis studies will look at the sum of symptoms over the study period. This complicates a direct comparison of these studies. Consider an example based on rough estimates from a park study evaluating mometasone furoate nasal spray against placebo.²³ Baseline TNSSs for both were 9.6. Mometasone furoate roughly averaged a -3 -point change from baseline from 11 AM to 5 PM, whereas placebo roughly averaged a -2.2 -point change from baseline. Comparing the relative difference in change from baseline would result in mometasone furoate performing 36% better than placebo. On the other hand, when comparing the relative reduction in the actual symptom levels after treatments (6.6 vs 7.4), mometasone furoate only performed 11% better than placebo. For a discussion of the effects of varying pollen levels on treatment and prophylaxis studies, see the Discussion section in this article's Online Repository.

The usability results were similar to those found in the out-of-season study.¹¹ Compared with that study, this study did not find any effect of the nasal filter on throat irritation. In contrast, interestingly, daily Σ TOSSs tended toward being significantly reduced with the filters on day 2 and were significantly reduced by 73% when looking at the groups with baseline TOSSs of 0 or 1, primarily through its effect on watering eyes (Tables III and IV). An earlier park study on a different nasal filter also found significant reductions for ocular symptoms compared with placebo.¹⁴ These findings support the theory that part of the ocular allergic response might be caused by reflex-generated symptoms originating from the nose.²⁷ Also, drowsiness was reduced on day 2, although the overall severity in both treatment groups was mild. This could prove important for patients because drowsiness is a well-known side effect to many antihistamines.^{20,22,25,26} The nasal filter's positive effect on drowsiness and global discomfort increased when looking solely at the groups with baseline TNSSs of 0 or 1 (Table IV). These findings further underline the added benefit of initiating use of the filters before symptom onset. It will be interesting to see whether these findings can be reproduced in future studies.

In conclusion, statistically significant and clinically relevant reductions were achieved for the primary outcome measure of daily Σ TNSS, for maximum TNSS, as well as for a subset of individual nasal and ocular symptoms. The results showed the

preventive effect of the nasal filter for SAR. Thus our findings support the preventive role of nasal filters in an overall management strategy for patients with SAR. Larger studies or clinical application will be needed for further evaluation.

We thank Michael Salomonsen and Michael Hestbæk at TV2 Østjylland for their generosity in providing access to the park area and surrounding facilities, as well as for their help in practical matters. Also, we thank Vibeke Heitmann Gutzke and Kirsten Østergaard at Aarhus University for their efforts during the screening process.

Clinical implications: The nasal filters substantially reduce symptoms of SAR. The results support the preventive role of the nasal filters for managing SAR.

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METHODS

Elaboration on the clinical trial design

No changes to the trial protocol were made after enrolment 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 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 (Torben Sigsgaard) enrolled eligible subjects. The recruitment period started in early May, and screening visits were carried out from May 26 to May 28. There was no follow-up after study’s end.

Trial intervention

The nasal and placebo filters have been described in greater detail in a previous article.^{E2} The nasal filter 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. In the placebo filters the membrane was omitted from the frame.

Laboratory tests had shown that the level of air resistance across the filtering membrane was less than the level of perception (unpublished data),^{E3} and a previous study had confirmed that in a clinical setting subjects were unable to differentiate a placebo filter from the nasal filter both in regard to breathing resistance and time points for noticing that they were wearing a device.^{E2}

Subjects were blind to the intervention allocation. They were not given any information that would make it possible for them to identify which device (the nasal filter or placebo) they were wearing on a given day. Subjects were instructed to blow their noses before insertion. They were told that they would not be able to deduce whether they had a nasal filter or a placebo filter from how the other subjects were reacting. They were neither allowed to examine each other’s nostrils nor use their fingers to feel the device. However, they were allowed to adjust the height of the device using the crossbar. They were not allowed to talk about their condition, their symptoms, pollen levels, or the devices. If they had to sneeze and did not want to or could not with the device inserted or if they wanted the device changed for any other reason, they were told to call their contact person (the students who handled insertion/removal) and have them remove and insert a new device. If they needed to sneeze or blow their nose before their contact person could come, they were to take a tissue, remove the device, place it in the tissue, and fold the tissue without looking at its contents. Subjects were observed throughout the day.

The devices were inserted by using a standardized method that was identical for both devices and also identical to the method described in a previous article.^{E2} Three sizes (small, medium, and large) were used in the study to accommodate size variations in the subjects.

Trial setting

The trial took place in a small park (56.194355N 10.186920E) in Aarhus, Denmark.

Pollen and temperature measurements

A detailed description of the pollen samplers has been presented in this recent article.^{E4} Briefly, the pollen data were collected with 2 Model 20 Rotorod samplers (Sampling Technologies, Minnetonka, Minn) powered with 12V batteries. All batteries were fully charged at the start of each sampling

day. The Rotorod rotation rates were measured at the start of each sample collection period using a digital tachometer (AT-6; Farnell, Leeds, United Kingdom), and there was no significant variation between the samplers or between the 2 study days. In all cases deviation from the prescribed rotation rate of 2400 rpm was negligible. Both samplers were placed within the area, in which subjects were examined, approximately 50 m apart. Rotorod collector rods were coated with the standard silicone grease adhesive. The rods in each sampler were changed every 30 minutes at times when symptom scores were recorded. After exposure, the rods were stained with Calberla solution and mounted on a specially designed microscope stage adapter by using the method described by the manufacturer.^{E5} Both rods from each sampler were assayed under a light microscope at $\times 400$ magnification, and counts were converted to concentrations in grass pollen grains per cubic meter by dividing the number of pollen grains by the volume of air sampled. Temperatures were recorded with a sonic anemometer (METEK USA-1; Elmshorn, Germany) powered by a 12V battery, placed halfway between the 2 pollen samplers.

Elaboration on outcome measures

TNSSs and TOSSs were evaluated on identical scales every 30 minutes from baseline until study’s end at minute 450. TOSSs consisted of itchy, swollen, and watering eyes.

Throat irritation, drowsiness, and global discomfort were rated from minute 60 at hourly intervals until minute 450. They were evaluated on continuous visual analog scales ranging from no symptoms (0) to severe symptoms (10).

Usability and tolerance of the device were evaluated by using a product evaluation questionnaire. Subjects rated the device after its removal at minute 450.

Assessment of FEV₁ with a spirometer (Micro DL Spirometer; Micro Medical Ltd, Kent, United Kingdom) at baseline and study’s end served as a safety measure.

Determination of sample size

The power of the study was calculated based on data from the recent environmental exposure unit trial on the nasal filters.^{E2} In that study TNSSs fluctuated around 3 at every time point. Thus at such a symptom level, including 80 subjects would make it possible to show a 1.2-point mean difference in TNSS with a power of 96% at a significance level of 5%. This was based on the assumption that the within-subject SD was 2. A 1.2-point mean difference would roughly equate to a clinically relevant reduction of 30% between treatments.

Randomization, assignment to intervention, and blinding

A statistician generated the randomized allocation sequence for study subjects using a computerized method (1:1) and assigned study subjects to their order of intervention. The devices were kept in concealed coded boxes that stated the study day (1/2), subject ID, and nasal filter size. The study used a crossover design in which subjects who wore a nasal filter on day 1 received a placebo filter on day 2 and *vice versa*.

Students from Aarhus University handled the blind insertion and removal of the devices for all subjects. These students were trained in the correct techniques for insertion and removal of the devices. The students were assigned to the same subjects on both study days to eliminate interindividual variations. They did not participate in any other investigational activities during the course of the trial. Study subjects, investigators, and statisticians were blind to the allocations.

Statistics

In all analyses the null hypothesis was no difference between placebo and the nasal filter. All statistical analyses were performed with STATA 12 (StataCorp, College Station, Tex). All graphic work was done with Prism 6.0 software (GraphPad Software, La Jolla, Calif).

No imputation of data was done in cases of missing data. One subject decided to withdraw after minute 240 on day 2 because of symptom severity.

The scores for minute 240 were carried forward for the remaining evaluations for this subject. We confirmed that this would result in a conservative estimate compared with the development in mean symptom severity among the remaining subjects. Following standard procedures, the blind was broken on study completion, and it was discovered that the subject wore a placebo on day 2.

RESULTS

Even though most subjects noticed wearing the devices at one point during the study (57 for placebo and 61 for the nasal filter), about two thirds of the subjects indicated that they were unaware of wearing the devices at each time point, and very few reported increased resistance to breathing (Fig E1, A and B, respectively). Of the 65 subjects, 54 were interested in using the devices, with most intending to use the filters for longer periods at a time, and 57 felt completely confident in using the devices (Fig E1, C and D, respectively).

Overall, there were 10 reinsertions/replacements on day 1 (4 placebos and 6 for the filters) and 49 reinsertions/replacements on day 2 (28 placebos and 21 for the filters). Of all 59 reinsertions/replacements (both days), 10 were ascribed to sneezing. Nose blowing was the primary reason for wanting/ needing a change/reinsertion (in total 21 of the times). On day 1, 57 subjects had no changes, 6 had 1 change, and 2 had 2 changes. On day 2, 32 subjects had no changes, 22 had 1 change, 8 had 2 changes, 2 had 3 changes (1 placebo/1 filter), and 1 had 5 changes (placebo).

Time point-specific mean TNSSs are provided in Fig E2 for the entire group (see Fig E2, A and B) and for the subjects with baseline TNSSs of 0 or 1 (see Fig E2, C and D).

DISCUSSION

The effect of pollen levels is another consequence arising from the different designs of treatment and prophylaxis studies. Both treatment and prophylaxis studies are dependent on pollen exposure to elicit an appropriate symptomatic response, but their dependence is slightly different. Treatment studies only enroll moderate to highly symptomatic subjects, and thus at baseline, the investigators know that there is pollen in the air. The pollen-related risk in treatment studies is the risk that the exposure could decrease, thus making it harder for an actual treatment to show a change from baseline that is different from what placebo-treated subjects are experiencing. On the other hand, prophylaxis studies prefer to enroll nonsymptomatic subjects at baseline. The inherent risk in this type of study is the risk of pollen levels being low or nonexistent throughout the day. Nonexistent pollen levels translate to nonexistent symptoms, and thus there is a risk that a potential prophylactic effect will not be found.

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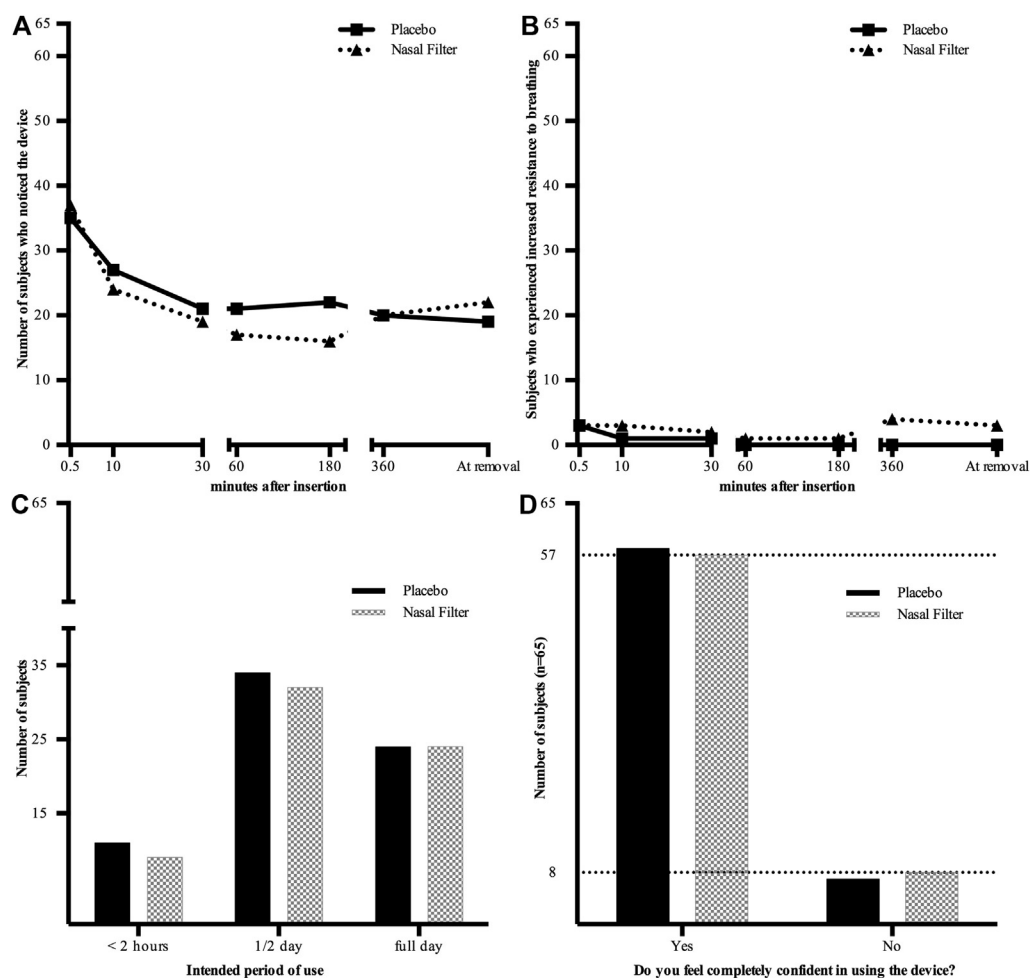


FIG E1. Device evaluation. **A**, Time points for awareness of wearing a device. **B**, Time points for noticing breathing resistance in the 10 subjects who felt increased resistance. **C**, Intended period of use for the subjects who wanted to use the device. **D**, Proportion of subjects who felt completely confident in using the device.

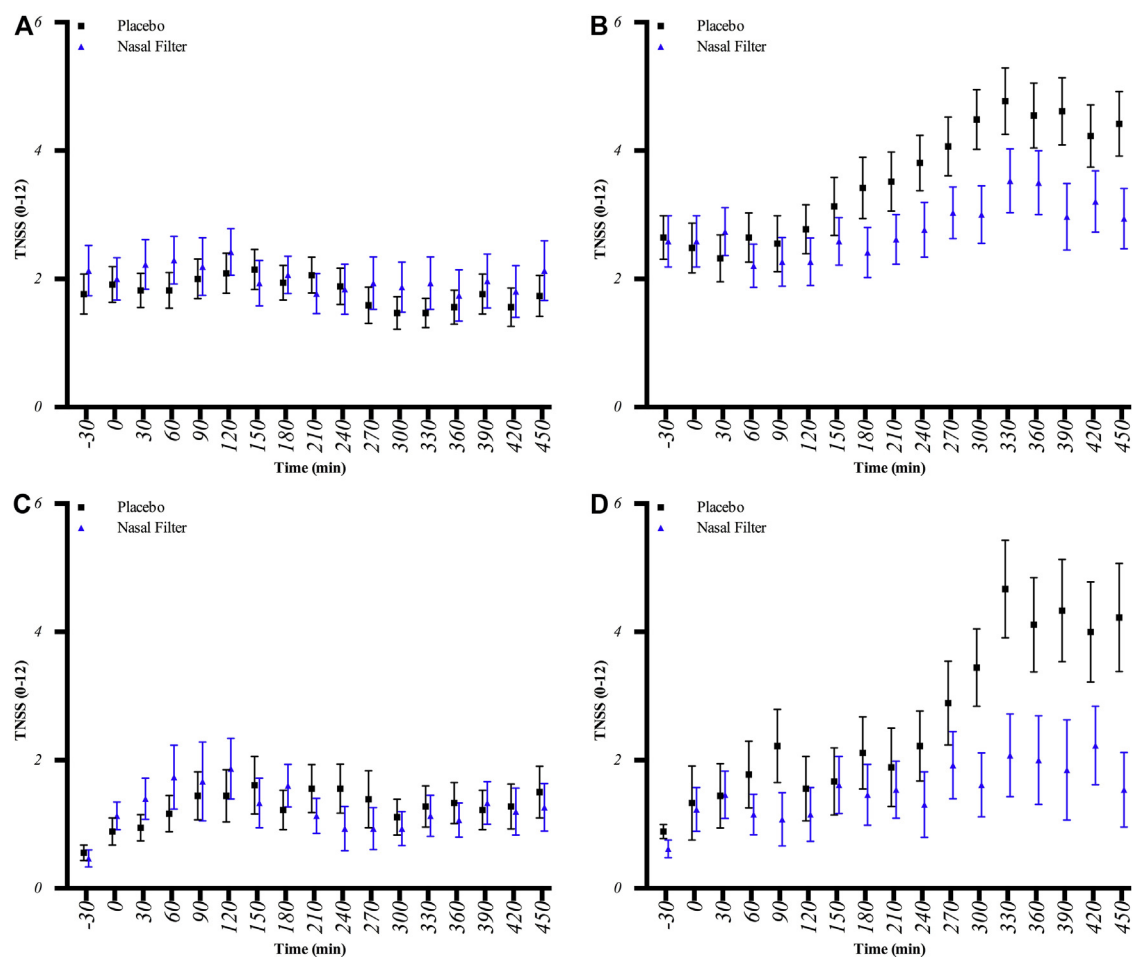


FIG E2. Mean TNSSs with SEMs as *error bars*. Devices were inserted after baseline scores (before 0 minutes). **A**, Day 1 for all 65 subjects. **B**, Day 2 for all 65 subjects. **C**, Day 1 for the 33 subjects with baseline TNSSs of 0 or 1. **D**, Day 2 for the 22 subjects with baseline TNSSs of 0 or 1.

TABLE E1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age 18-65 y	Positive pregnancy test result 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>Phleum pratense</i> (wheal diameter ≥ 3 mm) within 12 mo of study entry	Inadequate washout periods regarding park study days for the following medications: intranasal or systemic corticosteroids (1 mo), intranasal cromolyn (2 wk), intranasal or systemic decongestants (3 d), short-acting intranasal or systemic antihistamines (3 d), long-acting antihistamines (10 d), or any other medication related to controlling or alleviating symptoms related to AR
Specific IgE for timothy grass pollen (>0.70 kU/L, CAP class 2 or higher) (ALK 225 <i>Phleum pratense</i> ; ALK-Abelló, Hørsholm, Denmark)	Subjects with nasal conditions likely to affect the outcome of the study in the opinion of the investigator (ie, anterior nasal septum deviation, nasal septum perforations, nasal polyps, chronic nasal obstruction, or other nasal diseases)
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
	Improper fit of the nasal filter
	Retrospective TNSS for last summer of 0-2
	Receipt of immunotherapy with grass pollen within the previous 10 y (≥ 2 rounds of treatment)