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Two-year outcomes of radiofrequency device treatment of the nasal valve for nasal airway obstruction

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Abstract

Background: Temperature-controlled radiofrequency (TCRF) device treatment of nasal valve dysfunction (NVD) was superior to a sham procedure control in reducing the symptoms of nasal airway obstruction (NAO) in this randomised controlled trial (RCT).

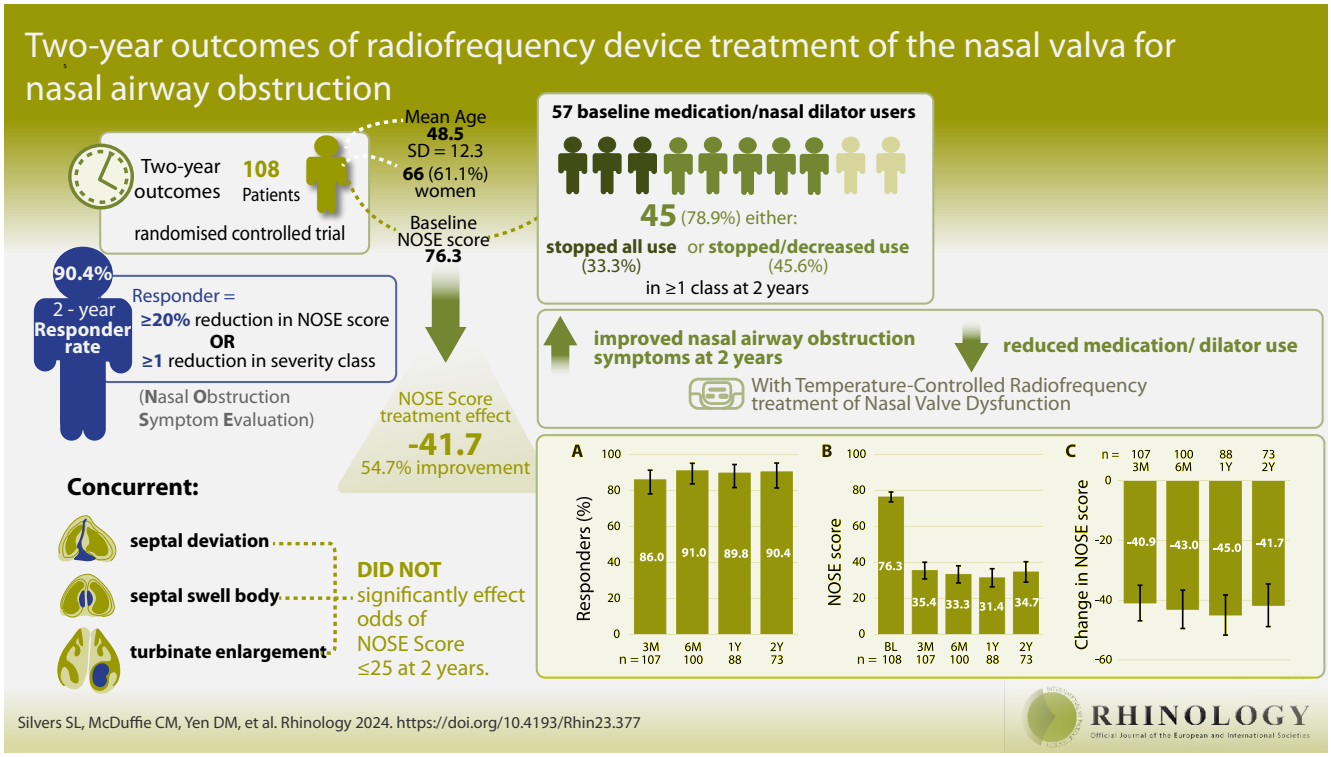
Methodology: Two-year outcomes for 108 patients actively treated in a prospective, multicenter, patient-blinded RCT were used to determine treatment effect durability and changes in medication/nasal dilator usage. A responder was defined as ≥20% reduction in NOSE score or ≥1 reduction in severity class.

Results: The mean (SD) age of patients was 48.5 (12.3) years; 66 (61.1%) women. Baseline NOSE score was 76.3. The 2-year responder rate was 90.4% and NOSE score treatment effect was −41.7; 54.7% improvement. Of 57 patients using medications/nasal dilators at baseline, 45 (78.9%) either stopped all use (33.3%) or stopped/decreased (45.6%) use in ≥1 class at 2 years. Concurrent septal deviation, septal swell body, or turbinate enlargement did not significantly affect the odds of exhibiting a NOSE score of ≤25 at 2 years.

Conclusions: TCRF device treatment of NVD resulted in significant and sustained improvements in the symptoms of NAO at 2 years, accompanied by a substantial reduction in medication/nasal dilator use.

Key words: nasal airway obstruction, nasal valve, radiofrequency, rhinoplasty, septal deviation, nasal obstruction symptom evaluation (NOSE)

Graphical abstract



Introduction

Temperature-controlled radiofrequency (TCRF) device treatment of the internal nasal valve is a minimally-invasive alternative to surgery for the treatment of nasal airway obstruction (NAO) secondary to nasal valve dysfunction (NVD) [1,2]. In this randomised controlled trial (RCT), the efficacy of the VivAer® System (Aerin Medical, Mountain View, CA, USA) was superior to a sham procedure control in treating patients with NAO and NVD at 3 months posttreatment [3]. In this report, the long-term follow-up of the patients receiving active treatment in this RCT serves to complement effectiveness study data [4,5] and feasibility/pivotal study data [6-9]. Long-term data is important for patients and providers when considering NAO treatment options, to compare the minimally-invasive approach against surgical outcomes, to evaluate the effect of symptom improvements on concomitant medication and nasal dilator usage, to support cost-effectiveness studies, and to confirm the safety profile of the device and procedure over time. NAO patients also often have septal deviation, septal swell bodies, and/or turbinate enlargement in addition to NVD. In patients with severe/extreme NAO, the prevalence of NVD+septal deviation has been reported at 14% and NVD+inferior turbinate hypertrophy at 7%; 46% exhibited NVD+septal deviation+inferior turbinate hypertrophy [10]. Therefore, the effects of these anatomical contributors to NAO on TCRF treatment outcomes were investigated.

Materials and methods

Trial design

This report describes the long-term outcomes of a prospective, single-blinded (patient), RCT with a sham procedure control arm. The RCT was a superiority trial with crossover available to eligible sham control-arm patients after 3-month follow-up and primary endpoint analysis. A 2:1 randomisation scheme was used, via a web-based randomisation module integrated into the trial's electronic data capture system. Patients were blinded to their index assignment and blindfolded during the index procedure. Patients were unblinded after the 3-month visit (primary endpoint) and index sham control arm patients underwent crossover treatment if they still met eligibility criteria and agreed to continued participation in the trial. Index sham control patients who were not eligible for crossover or did not wish to further participate in the trial were terminated from the trial. Patients who underwent additional nasal procedures at any time during follow-up were exited from the trial and therefore, no follow-up data after the additional procedure were available. This RCT was pragmatic in that medication/nasal dilator use was not dictated by the protocol. All patients who underwent active treatment (index active treatment patients and treated crossover patients) were collapsed into a single analysis group for follow-up from 3 months through 2 years. One-year outcomes have previously been described [11].

Patient population

Patients were enrolled at 16 centers in the USA and index procedures were performed between August and December 2020. WCG Institutional Review Board (IRB) (20201804) approved the trial at all enrolling centers except Eastern Virginia Medical School (EVMS), where the trial was approved by EVMS IRB (20-09-FB-0189). All center principal investigators were board certified otolaryngologists-head and neck surgeons. Patients gave written informed consent prior to enrollment.

A complete list of eligibility criteria is available in prior reports [11,12] and at clinicaltrials.gov (NCT04549545). Key inclusion criteria were aged 18-85 years, seeking treatment for nasal obstruction; a baseline Nasal Obstruction Symptom Evaluation (NOSE) score ≥55, nasal valve collapse as the primary or significant contributor to the nasal obstruction, a positive response to a temporary nasal dilation measure such as the modified Cottle manoeuvre, and patient dissatisfaction with medical management. However, no standard medication regimen prior to inclusion or intervention was dictated by the protocol. Key exclusion criteria were prior surgery of the lateral nasal wall; a severe case of septal deviation, turbinate hypertrophy, polyps, or ptotic nose tip believed to be the primary contributor to the nasal obstruction symptoms and warranting surgical intervention.

Intervention

Topical anesthesia was applied to the mucosal surface of treatment area, followed by injection of lidocaine/epinephrine. The VivAer® System consists of the Aerin radiofrequency (RF) generator and VivAer® Stylus. Patients were treated bilaterally with the VivAer® Stylus on ≤4 non-overlapping areas on the nasal mucosa at the junction of the upper and lower lateral cartilage on the lateral nasal wall. No other anatomic structures were treated. Treatment settings were temperature, 60°C; power, 4 watts; treatment time, 18 seconds; cooling time, 12 seconds. No repeat "touch-up" procedures were allowed.

Outcome measures

Efficacy outcome instruments were the NOSE Scale [13,14] and the Epworth Sleepiness Scale [15,16]. A responder was defined as ≥20% improvement (decrease) in NOSE score or ≥1 NOSE Scale severity class improvement [14] from baseline, which has also been used in the evaluation of a bioabsorbable implant for the treatment of NVD in an RCT [17]. Adverse events were recorded throughout and classified based on relationship to the device and/or procedure.

The term baseline in this report refers to the outcome measure value and medication/nasal dilator use prior to active treatment, so in the case of the crossover patients, baseline refers to the outcome measure value and medication/nasal dilator use reported at the time of requalification for crossover. The term posttreatment refers to post active treatment.

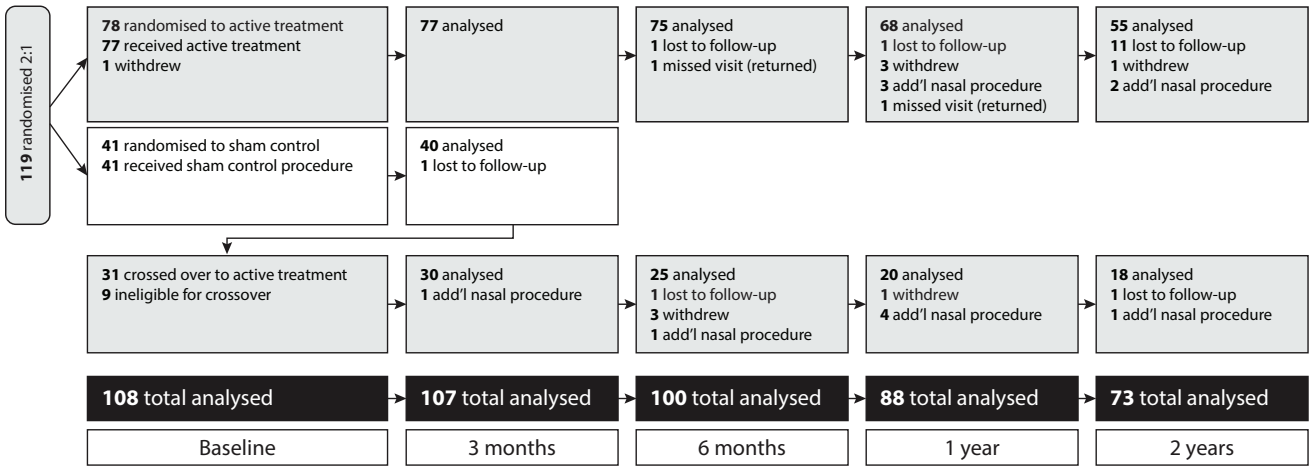


Figure 1. Patient disposition.

Subpopulation definitions

Subpopulation characteristics were chosen with consideration for potential relevance for patient selection or potential impact on treatment outcomes. All subpopulation characteristics were recorded at baseline by study investigators. Subpopulation analyses were performed based on baseline NOSE Scale severity class (severe/extreme), with/without septal deviation, prior/no prior nasal surgery (prior nasal surgeries are listed in Supplemental Table 1), with/without septal swell body, and with/without turbinate enlargement. Outcomes in patients with dynamic and static nasal valve collapse have previously been explored in this trial [11,12].

Medication and nasal dilator use analysis

Medications used to treat NAO symptoms were assessed at baseline and 2 years based on classes: antihistamines, decongestants, leukotriene inhibitors, intranasal steroids, anticholinergics, and immunotherapy. Use of nasal strips/cones (nasal dilators) was also tracked. Medication/nasal dilator use was evaluated (i) by class and then (ii) by overall use per patient (i.e., considering all medication/nasal dilator classes used by each patient). Medication/nasal dilator use was evaluated at baseline (yes/no) and then relative to baseline at 2 years (started, increased, stayed the same, decreased, stopped). Overall use for a patient was determined by evaluating all medication/nasal dilator classes used by the patient at the 2-year timepoint. Groups are also defined with result reporting (stopped all, stopped or decreased use in ≥1 medication/nasal dilator class [without increase in another class], same medication/nasal dilator use as baseline, changes in >1 medication/nasal dilator class use but with no clear overall upward or downward trend, increased/started use in ≥1 medication/nasal dilator class, not using medications/nasal dilator at baseline but started ≥1 medication/nasal dilator class). As an example, if one medication/nasal dilator class stayed the same and another medication/nasal dilator class decreased, this patient was assigned to 'stopped or decreased use in ≥1 medication/nasal dilator class (without increase in another class)'. Due to medication/mechanical nasal aid class coding and ongoing trial data monitoring, baseline medication/nasal dilator data were updated from a previous report [11].

Statistical analysis

Analysis was performed using the intention-to-treat principle. Continuous data are presented as mean and 95% confidence intervals (CI) except where noted, and categorical data as number (percentage of total). NOSE Scale and Epworth Sleepiness Scale outcomes were assessed using linear mixed effect model to test for an overall change over time; adjusted (least squares) means are presented, with Dunnett-Hsu comparisons between baseline and follow-up visits. A negative change indicates an improvement (decrease) in each measure. Generalised estimating equations were used to assess repeated binomial outcome measures (i.e., responder rate) and repeated multinomial ordered category distributions (i.e., NOSE Scale severity class).

Individual subpopulations were first examined using univariate repeated measures linear mixed model analysis based on the NOSE score with no adjustments for multiple comparisons. Multivariable logistic regression calculations were performed with the dependent variable of a NOSE score ≤25 versus >25 at 2 years (modeling the probability of achieving a 2-year NOSE score ≤25) and subpopulations as independent variables. Results are reported as odds ratios (OR) with 95% CIs. ORs with 95% CIs that did not contain 1 were considered statistically significant at the 5% level.

Statistical analysis was performed using SAS/STAT version 15.2 (SAS Institute, Inc, Cary, NC, USA).

Results

Patient disposition

A total of 119 eligible patients were randomised, and 117 (77 ac-

Table 1. Patient demographics and baseline characteristics.

Characteristic	Treated	At 2 years	Exited	p value [a]
No.	108	73	35	-
Female	66 (61.1)	44 (60.3)	22 (62.9)	0.84
Age, mean (SD), y	48.5 (12.3)	49.1 (12.0)	47.4 (13.0)	0.50
BMI, mean (SD), kg/m^2	29.0 (5.9)	29.8 (6.0)	27.2 (5.3)	0.03
Race, No. (%)				0.32
American Indian or Alaska Native	2 (1.9)	2 (2.7)	0 (0.0)	-
Asian	2 (1.9)	1 (1.4)	1 (2.9)	-
Black or African American	6 (5.6)	4 (5.5)	2 (5.7)	-
White	96 (88.9)	66 (90.4)	30 (85.7)	-
Declined choices	2 (1.9)	0 (0.0)	2 (5.7)	-
Medical history, No. (%)				
Nasal surgery [b]	31 (28.7)	22 (30.1)	9 (25.7)	0.41
Allergic rhinitis [c]	43 (39.8)	33 (45.2)	10 (28.6)	0.14
Nonallergic rhinitis [c]	15 (13.9)	10 (13.7)	5 (14.3)	>0.99
Sinus disease [d]	15 (13.9)	7 (9.6)	8 (22.9)	0.08
Obstructive sleep apnea	21 (19.4)	14 (19.2)	7 (20.0)	>0.99
NOSE score, mean (SD) [e]	76.3 (14.3)	76.8 (14.3)	75.4 (14.4)	0.65
Nasal valve collapse mechanism, No. (%)				0.68
Bilateral dynamic	51 (47.2)	37 (50.7)	14 (40.0)	-
Bilateral static	34 (31.5)	19 (26.0)	15 (42.9)	-
Bilateral static and dynamic	15 (13.9)	11 (15.1)	4 (11.4)	-
Complex [f]	8 (7.4)	6 (8.2)	2 (5.7)	-
Overall symptom management, No. (%) [e]				0.84
Medications only [g]	63 (58.3)	42 (57.5)	21 (60.0)	-
Nasal dilators only	3 (2.8)	3 (4.1)	0 (0.0)	-
Medications [g] and nasal dilators	26 (24.1)	17 (23.3)	9 (25.7)	-
No medications or nasal dilators	16 (14.8)	11 (15.1)	5 (14.3)	-
Medication/nasal dilator use, No. (%) [e]				
Antihistamines	53 (49.1)	37 (50.7)	16 (45.7)	0.68
Decongestants	28 (25.9)	22 (30.1)	6 (17.1)	0.17
Leukotriene inhibitors	14 (13.0)	9 (12.3)	5 (14.3)	0.77
Intranasal steroids	51 (47.2)	38 (52.1)	13 (37.1)	0.16
Anticholinergics	4 (3.7)	2 (2.7)	2 (5.7)	0.59
Immunotherapy	4 (3.7)	2 (2.7)	2 (5.7)	0.59
Nasal strips/cones	29 (26.9)	20 (27.4)	9 (25.7)	>0.99

Abbreviations: BMI, body mass index; NOSE, nasal obstruction symptom evaluation. [a] Comparison by t test or Fisher exact test, as applicable. [b] Includes inferior/middle turbinate reduction/excision, septoplasty, rhinoplasty, sinuplasty, functional endoscopic sinus surgery. Some patients may have undergone multiple procedures. A complete list is available in Supplemental Table 1. [c] Based on patient or provider knowledge, no tests were performed as part of the trial. [d] A combination of acute sinusitis or chronic rhinosinusitis. [e] In the case of patients originally in the index active treatment arms, baseline is prior to the active treatment procedure. In the case of patients in the crossover active treatment arm, baseline refers to the outcome measure value reported at the time of requalification for crossover. [f] Complex includes patients with a different or mixed mechanism on each side, i.e., dynamic on one side, static on the other; or static and dynamic on one side, static or dynamic on the other side. [g] Includes saline.

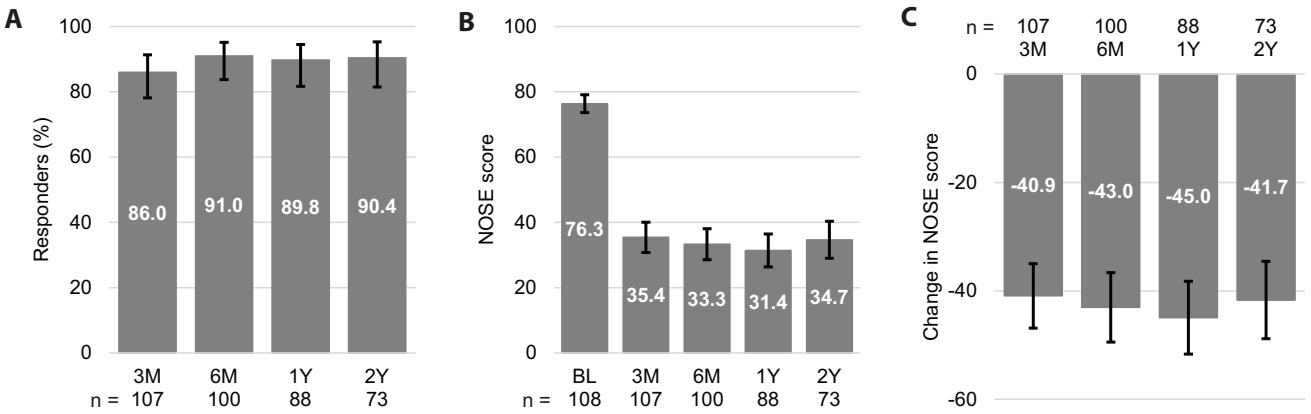


Figure 2. A) Responder rate over time. B) Adjusted mean NOSE score over time. C) Adjusted mean change in NOSE score over time, p<0.001 comparing each follow-up timepoint to baseline. Bars represent the 95% confidence interval in all panels.

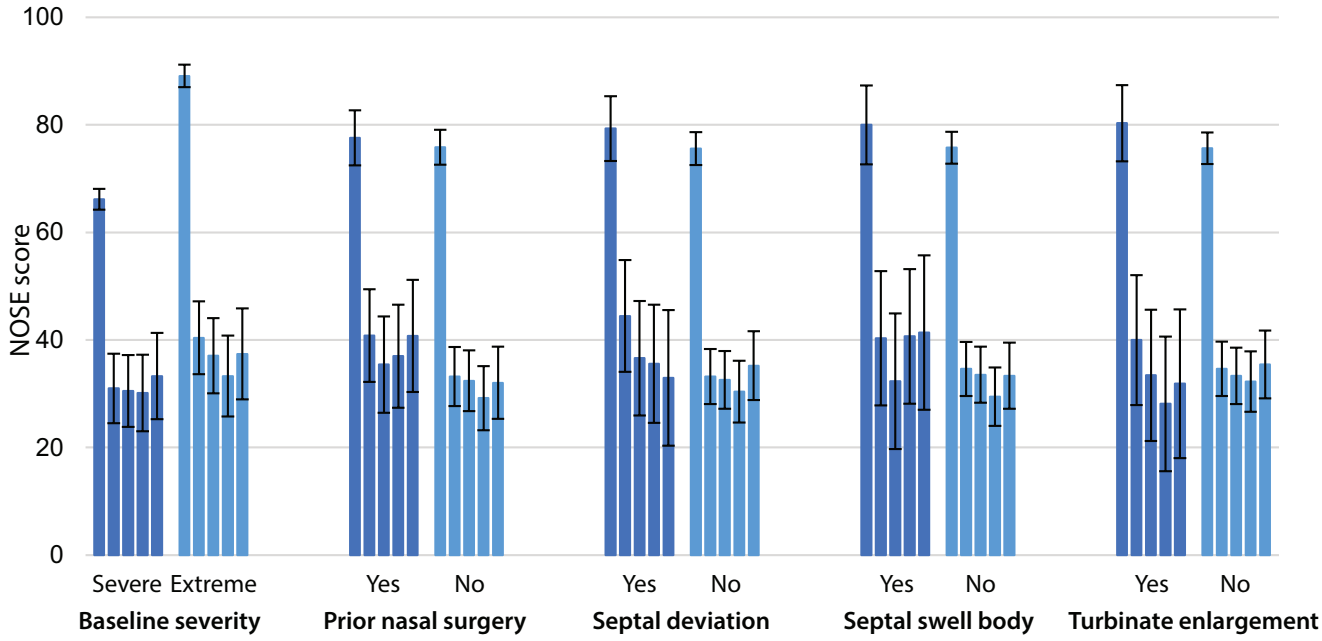


Figure 3. Adjusted mean NOSE score for each subpopulation at baseline, 3 months, 6 months, 1 year, and 2 years, p<0.001 comparing each follow-up timepoint to baseline for each subpopulation. Bars represent the 95% confidence interval.

tive treatment and 40 sham control) were included in the analysis of the 3-month primary endpoint (Figure 1) [12]. After primary endpoint analysis and unblinding, 31 patients were eligible for crossover and all elected to undergo active treatment. Two patients who crossed over were found to be ineligible during trial monitoring but were included in data analysis. Therefore, a total of 108 patients underwent active treatment in the trial (Table 1), of which 104 (96.3%) had NAO symptoms for more than 1 year prior to trial enrollment. Throughout the 2 years, 15 patients were lost to follow-up, 8 withdrew, and 12 had an additional nasal procedure (as outlined below). Of the 23 patients lost to follow-up/withdrawn, 19 (82.6%) had an improvement in NOSE score from baseline and 15 (65.2%) were responders at their last trial visit. Three patients had their additional nasal procedures between 1 and 2 years (the rest were prior to 1 year [11]), all of which were trial responders before the additional procedure: 1 patient had balloon sinuplasty for chronic sinusitis, 1 patient had bilateral functional endoscopic sinus surgery, and 1 patient had a bioabsorbable implant for NAO, drainage, and pressure and also underwent TCRF ablation of the posterior nasal nerve for chronic rhinitis.

NOSE Scale results

The mean baseline NOSE score was 76.3 (95% CI, 73.6 to 79.1). The responder rate at 3 months (86.0% [95% CI, 78.2% to 91.3%]) was sustained through 2 years (90.4% [95% CI, 81.5% to 95.3%])

Table 2. Multivariable regression analysis for a NOSE score of ≤25 at 2 years. [a]

Covariable	Comparison	Beta estimate	SE of beta	p value	Odds ratio	(95% CI)
Severity class [b]	Severe versus extreme	1.116	0.531	0.036	3.053	(1.078 to 8.645)
Prior nasal surgery	Yes versus no	−0.854	0.560	0.127	0.426	(0.142 to 1.275)
Septal deviation	Yes versus no	0.649	0.680	0.340	1.913	(0.504 to 7.256)
Septal swell body	Yes versus no	0.444	0.687	0.518	1.559	(0.406 to 5.987)
Turbinate enlargement	Yes versus no	−0.104	0.672	0.877	0.901	(0.241 to 3.368)

Abbreviations: CI = confidence interval, NOSE = nasal obstruction symptom evaluation, SE = standard error. [a] Multivariable logistic regression (full model) with the dependent variable of a NOSE score ≤25 vs >25 modeling the probability of NOSE score ≤25 at 2 years. [b] NOSE Scale severity class at baseline.

(Figure 2 and interim data in Supplemental Table 2).

The adjusted mean NOSE score was significantly improved over baseline at all follow-up timepoints (Figure 2 and Supplemental Table 2). The NOSE score treatment effect at 3 months (adjusted mean, −40.9 [95% CI, −46.9 to −35.0]; p<0.001) was sustained through 2 years (−41.7 [95% CI, −48.8 to −34.6]; p<0.001) (interim data in Supplemental Table 2). These data represent 53.6% and 54.7% improvement from baseline at 3 months and 2 years, respectively.

At baseline, 50/108 (46.3%) patients had extreme NAO and 56/108 (51.9%) had severe NAO. There was a significant shift toward lower NOSE Scale severity classes at 3 months, that was sustained through 2 years, p<0.001 comparing each follow-up timepoint to baseline (Figure 3 and Supplemental Table 2). At 2 years, more than half of the patients 41/73 (56.2%) had mild NAO or no problems.

All components of the NOSE score (nasal congestion/stuffiness, nasal blockage/congestion, trouble breathing through the nose, trouble sleeping, and unable to get enough air through the nose during exercise or exertion) had a significant and sustained improvement in mean score from 3 months through 2 years; p<0.001 comparing all follow-up timepoints to baseline for each component score (Supplemental Table 2).

To date, no NOSE score minimal clinically important differences (MCIDs) for non-surgical treatments of NVD have been derived. Anchor-based derivations of NOSE score MCIDs include 24.4 for functional, cosmetic, or combined rhinoplasty [18] and 19.4 for septoplasty [19]. Although not an endpoint in the trial protocol, for comparison, the percentage of patients with a change in NOSE score ≥24.4 from baseline to follow-up was 73.8% (95% CI, 64.8% to 81.2%) at 3 months, 78.0% (95% CI, 68.9% to 85.0%) at 6 months, 83.0% (95% CI, 73.8% to 89.4%) at 1 year, and 84.9% (95% CI, 75.0% to 91.4%) at 2 years. A baseline to follow-up change in NOSE score of 30 has been also been suggested as a clinically meaningful measure of surgical success for NAO patients based on a systematic review [20], but this value was based on group mean point differences across multiple studies rather the classical anchor-based approach to MCID derivation.

Subpopulation analyses

The pretreatment baseline prevalence of severe NAO in the trial population was 56/108 (51.9%) and 50/108 (46.3%) for extreme; 31/108 (28.7%) patients had prior nasal surgery (Supplemental Table 3). The prevalence of NAO anatomic contributors in the trial population at pretreatment baseline was 22/108 (20.4%) for septal deviation, 15/108 (13.9%) for septal swell body, and 16/108 (14.8%) for turbinate enlargement (Supplemental Table 3). A total of 16/108 (14.8%) patients exhibited both septal deviation and turbinate enlargement, although the contributors were considered individually to maintain a reasonable sample size. Univariate analyses of the patient subpopulations showed that they all had a similar mean baseline NOSE score, except for severe/extreme baseline NOSE Scale severity class subpopulations (Figure 3 and Supplemental Table 3). The adjusted mean changes in NOSE score reflected significant and sustained improvements in symptom burden for all subpopulations over time; p<0.001 at all follow-up timepoints compared to baseline for each subpopulation. For example, the baseline NOSE scores of patients with septal deviation/without septal deviation were 79.3 (95% CI, 73.3 to 85.4) and 75.6 (95% CI, 72.5 to 78.6), respectively; at 2 years, the NOSE scores were 32.9 (95% CI, 20.3 to 45.5) and 35.2 (95% CI, 28.8 to 41.6), respectively. Significant differences in mean NOSE scores were observed in the severe/extreme baseline NOSE Scale severity class subpopulations (main effect p=0.011), but the differences were not consistent across visits (across visits p=0.007); this result was likely driven by the difference in baseline score that defines these subpopulations. For the multivariable analysis based on achieving a NOSE score of ≤25 points at 2 years (i.e., a NOSE Scale severity class of mild or no problems), only the severe/extreme baseline NOSE Scale severity class reached significance with an OR 95% CIs including 1 (Table 2). This was, again, likely driven by the difference in baseline condition in the severe/extreme baseline NOSE Scale severity class subpopulations.

Table 3. Medication/nasal dilator class use at baseline and status from baseline at 2 years.

	Use at baseline, No. (%) [a]	Started, No. (%) [a,b]	Use at 2 years, No. (%) [c]
Antihistamines	37 (50.7)	-	-
Started	-	1 (1.4)	-
Stayed the same	-		15 (40.5)
Increased	-		1 (2.7)
Decreased	-		8 (21.6)
Stopped	-		13 (35.1)
Decongestants	22 (30.1)	-	-
Started	-	2 (2.7)	-
Stayed the same	-		8 (36.4)
Increased	-		0 (0.0)
Decreased	-		1 (4.5)
Stopped	-		13 (59.1)
Leukotriene inhibitors	9 (12.3)	-	-
Started	-	0 (0)	-
Stayed the same	-		6 (66.7)
Increased	-		0 (0.0)
Decreased	-		1 (11.1)
Stopped	-		2 (22.2)
Intranasal steroids	38 (52.1)	-	-
Started	-	0 (0.0)	-
Stayed the same	-		10 (27.3)
Increased	-		2 (5.3)
Decreased	-		3 (7.9)
Stopped	-		22 (57.9)
Anticholinergics	2 (2.7)	-	-
Started	-	0 (0.0)	-
Stayed the same	-		0 (0.0)
Increased	-		0 (0.0)
Decreased	-		0 (0.0)
Stopped	-		2 (100)
Immunotherapy	2 (2.7)	-	-
Started	-	0 (0.0)	-
Stayed the same	-		1 (50.0)
Increased	-		0 (0.0)
Decreased	-		1 (50.0)
Stopped	-		0 (0.0)
Nasal dilators [d]	20 (27.4)	-	-
Started	-	1 (1.4)	-
Stayed the same	-		1 (5.0)
Increased	-		0 (0.0)
Decreased	-		4 (20.0)
Stopped	-		15 (75.0)

[a] Total No. = 73, the number of patients analysed at 2 years postprocedure. [b] The number of patients who started a medication/nasal dilator during the 2 years and was still using at 2 year postprocedure. [c] The number of patients that had the designated status (stayed the same, increased, decreased, stopped) at 2 years with the percentage based on the number of patients taking the medication/nasal dilator class at baseline. For example, 37 patients were taking antihistamines at baseline: 15 of those (40.5%) had the same status at 2 years, 1 of those (2.7%) had increased use at 2 years, 8 (21.6%) had decreased use at 2 years, and 13 (35.1%) had stopped use at baseline. [d] Includes nasal strips and cones.

Epworth Sleepiness Scale results

The mean baseline Epworth Sleepiness Scale score was 10.3 (95% CI, 9.2 to 11.4). The score improved from baseline at all follow-up time points, and the adjusted mean change at 2 years was −4.9 (95% CI, −6.2 to −3.7), resulting in a mean score of 5.4 (95% CI, 4.5 to 6.4) (Supplemental Table 4), which is at the lower end of interval (6-10) defining higher normal daytime sleepiness with the scale [16]. In the 51 (47.2%) patients with baseline scores of 11 or higher, indicative of excessive daytime sleepiness [16], the improvement was larger; the mean score at baseline was 15.6 (95% CI, 14.8 to 16.4), and the adjusted mean change in score at 2 years was −8.0 (95% CI, −9.6 to −6.4) resulting in a mean score of 7.6 (95% CI, 6.3 to 8.9) (Supplemental Table 4), which is in the middle of the interval (6-10) defining higher normal daytime sleepiness with the scale [16].

Concomitant medication and nasal dilator analysis

The sustained decrease in symptom burden at 2 years was accompanied by an overall decrease in medication/nasal dilator use. Medication/nasal dilator use for the baseline population (N=108) is shown in Table 1. Baseline medication/nasal dilator use in the population with NOSE score data at both baseline and 2 years (n=73) is shown in Table 1 and Table 3. Comparing medication/nasal dilator use by class at baseline and 2 years, a substantial number of patients had stopped or decreased use at 2 years: 21/37 (56.8%) for antihistamines, 14/22 (63.6%) for decongestants, 3/9 (33.3%) for leukotriene inhibitors, 25/38 (65.8%) for corticosteroid sprays, 2/2 (100.0%) for anticholinergics, and 19/20 (95.0%) for nasal strips/cones (Table 2). There were some patients who started or increased use in a medication/nasal dilator class but the numbers were substantially smaller than those that decreased/stopped use (≤5.3%) (Table 2). When considering the overall medication/nasal dilator use for each patient, 57/73 (78.1%) patients were using ≥1 medication/nasal dilator class at baseline. At 2 years, 19/56 (33.3%) had stopped using all medications/nasal dilators, 26/56 (45.6%) had stopped/decreased use in ≥1 medication/nasal dilator class (without increase in another class) and 6/56 (10.5%) had same medication/nasal dilator class use as baseline. Furthermore, 5/56 (8.8%) had changes in >1 medication/nasal dilator class use but with no clear overall upward or downward trend, 1/56 (1.8%) started use in ≥1 medication class.

Safety

Adverse events have previously been reported through 1 year [11]. No new adverse events related to the TCRF device/procedure were reported through 2 years. There were no serious adverse events with a relationship to the trial device/procedure reported throughout the 2 years.

Discussion

In this long-term analysis of patients receiving TCRF device treatment of the internal nasal valve, the treatment effects observed at 3 months were sustained through 2 years. This 2-year NOSE score treatment effect (−40.9 [95% CI, −46.9 to −35.0]) was significantly larger than the effect observed in the sham procedure control arm at the 3-month trial endpoint (−16.8 [95% CI, −26.3 to −7.2]) [12]. The sustained treatment effect was accompanied by a substantial reduction in medication/nasal dilator use. Nasal dilators are generally regarded as uncomfortable and need to be applied daily; it is therefore notable that 75.0% of the patients using nasal strips and cones at baseline had stopped use at 2 years in this trial. The TCRF procedure is designed to cause tissue tightening effects within the submucosal layer of the lateral nasal wall and therefore mimic the effect of strip or cone, but in a sustainable manner. RF-induced heating has been shown to induce tissue tightening and contraction through immediate contraction of existing collagen proteins and through the induction of the production of new collagen over the long term [21,22].

In systematic reviews and meta-analyses of TCRF device treatment of NVD, the pooled treatment effect at 3 months was –46.1 (95% CI, –49.0 to –43.3) per Casale et al. [23] and −44.5 (95% CI, −49.2 to −39.8) per Kang et al. [24]. Kang et al. also reported a pooled 2-year treatment effect of −56.4 (95% CI, −62.4 to −50.3), although this pooled effect was calculated from different timepoints in the same study, which showed consistently greater treatment effects than the other studies included in the meta-analyses [24]. This pivotal study of TCRF device treatment of NVD reported a 4-year treatment effect of ~−55, although again, this is the study that showed consistently greater treatment effects than other studies [9].

Clark et al. reported the prevalence of NVD+septal deviation in patients with severe/extreme NAO at 14%, and NVC+turbinate hypertrophy at 7%, [10] which is comparable with the prevalence observed in this trial, especially considering the trial eligibility criteria selected for patients with NVD as the primary contributor to NAO. The exploratory analyses on outcomes in patients with or without septal deviation, septal swell body, or turbinate enlargement showed these comorbidities did not significantly affect the odds of exhibiting a NOSE score of ≤25 at 2 years. These observations are consistent with the notion that NVD is the primary contributor to NAO, and treating the internal nasal valve significantly improves the symptoms of NAO, even in the presence of other NAO contributors, such as septal deviations. Patients often undergo surgical functional rhinoplasty to treat NAO and septoplasty and turbinate reduction is often performed in conjunction with rhinoplasty. Meta-analyses on functional rhinoplasty for the treatment of NAO reported a 6-12-month treatment effect of –43.4 (95% CI, –51.0 to –35.8) [25] and, separately, a 12-month treatment effect of –43.1 (95% CI, –59.6 to –26.6) [26]. A meta-analysis focused on lateral nasal wall repair for the treatment of dynamic NVD reported an >6-month treatment effect of –49.0 (95% CI, –62.1 to –35.8) [27]. A systematic review also reported a treatment effect of −40 in NAO patients undergoing a mix of surgical procedures (including rhinoplasty, septoplasty, and/or turbinate treatments) [20]. Considering minimally-invasive TCRF device treatment of NVD has consistently demonstrated a sustained treatment effect comparable to functional rhinoplasty, and outcomes are independent of anatomical comorbidities, it should be considered as an important option for the treatment of NAO and should be included in discussions of treatment alternatives with patients, where appropriate when formulating a treatment plan for NAO as part of a shared decision-making process.

While this trial showed a significant and durable effect on NAO after treatment of the internal nasal valve, the VivAer® TCRF device is also indicated for treatment of soft tissues such as inferior turbinates and septal swell bodies [28], although these structures were not treated in this trial. Therefore, the results of this trial may not represent the total effect that that may be achievable using TCRF in a comprehensive NAO treatment protocol. Future studies that incorporate more liberal application of TCRF to address multiple NAO contributors are needed to evaluate the full potential of TCRF-based treatment of NAO.

Limitations

The long-term follow-up in this trial was a single group, but this trial was an RCT at inception with the primary endpoint at 3 months. Long-term blinded follow-up (1-2 years) of a control arm is not practical as it may not be in the best interests of patients and carries a high level of patient attrition. The subpopulation analyses were exploratory and future studies focusing on discreet subpopulations may be useful in determining optimal TCRF treatment protocols to address NAO in specific patient populations. While medication/nasal dilator use was not dictated by the protocol, which could be perceived as a limitation, the pragmatic approach means the results are likely reflective of clinical practice, with the decreases substantial enough to be unlikely due to chance. The NOSE score is a patient-reported outcome measure, which, while widely used, is considered subjective; including an objective measurement such as rhinomanometry or acoustic rhinometry would add value to future study results. Finally, the study population was predominantly White, which limited the analysis of outcomes in patient populations with different races and ethnicities, who may have meaningful differences in nasal anatomy.

Conclusions

The long-term follow-up on the cohort of patients receiving active TCRF device treatment of the nasal valve in this RCT showed that the treatment effect that was superior to a sham procedure control was sustained through 2 years. Patients reported a

significant and durable improvement in NAO symptoms. The reduction in symptom burden was accompanied by a substantial reduction in medication/nasal dilator use. The presence of septal deviation, septal swell body, or turbinate enlargement did not significantly affect the odds of exhibiting a NOSE score ≤25 at 2 years. Importantly, minimally-invasive TCRF device treatment of NVD resulted in significant and sustained improvements in many patients that had been suffering from NAO for more than 1 year prior to treatment and were using pharmacological management/nasal dilators without sufficient relief.

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Authorship contribution

All authors were trial investigators and acquired data during the trial and reviewed overall trial data during the trial. SLS and JKH participated in data analysis and directed the initial draft. All authors reviewed and commented on the draft before finalisation. All authors gave final approval for submission.

Conflict of interest

Dr Silvers is a research consultant for Aerin Medical, 3D matrix, and Lyra Therapeutics and on the medical advisory board for STS stent. Dr McDuffie has no relevant disclosures. Dr Yen has received research funding from Aerin Medical, and is a consultant and/or has received research funding for/from: 3-D Matrix, Astra Zeneca, AventaMed, Cyrano Therapeutics, Evidera, GlaxoSmith-Kline, Lyra Therapeutics, Medtronic, Neubio North America, Neurent Medical, OptiNose, Oyster Point Pharmaceutical, Pocket Naloxone, Regeneron, Sanofi Genzyme, Sound Health, Spirair, Stryker ENT; and has stock options in Cyrano Therapeutics, DiagNose Medical, and Sound Health. Dr Rosenthal has no relevant disclosures. Dr Davis is a research consultant for Spirair and has received compensation for physician training from Medtronic. Dr Han is a research consultant for Aerin Medical, Medtronic, Intersect ENT, Genentech, Sanofi Genzyme, Astra Zeneca, and GlaxoSmithKline.

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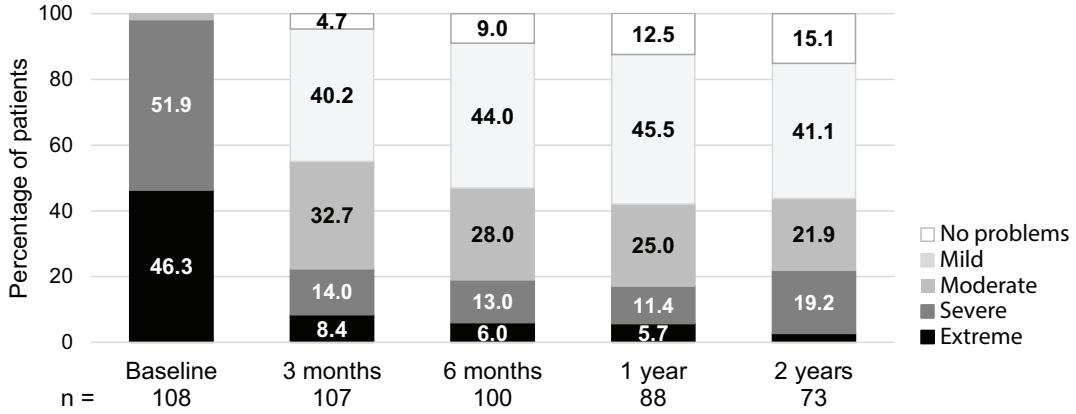

Supplemental Figure 1. The percentage of patients in each NOSE Scale severity class.

Supplemental Table 1. Prior nasal procedures.

Prior nasal surgery	No. (%) of total[a]
Cartilage removal following nasal trauma	1 (3.2)
Functional endoscopic sinus surgery	1 (3.2)
Inferior turbinate reduction/excision	2 (6.5)
Inferior turbinate reduction/excision, septoplasty	3 (9.7)
Inferior turbinate reduction/excision, septoplasty, radiofrequency of the tongue and palate [b]	1 (3.2)
Middle turbinate reduction/excision, septoplasty	1 (3.2)
Rhinoplasty	3 (9.7)
Septoplasty	8 (25.8)
Septoplasty, rhinoplasty	2 (6.5)
Septoplasty, rhinoplasty, sinuplasty	1 (3.2)
Septoplasty, sinuplasty	2 (6.5)
Septoplasty, sinuplasty, functional endoscopic sinus surgery	1 (3.2)
Septoplasty, uvulopalatopharyngoplasty [b]	1 (3.2)
Sinuplasty	4 (12.9)

[a] Total No. = 31, the number of patients with prior nasal procedures, as designated by the investigators. [b] Additional ENT procedure noted by the investigator.

Supplemental Table 2. Responder rate and NOSE score-based outcomes. [a]

Measure	Baseline	3 months	6 months	1 year	2 years
Responder rate, No. [b]	108	107	100	88	73
Responder rate	-	92 86.0% (78.2% to 91.3%)	91 91.0% (83.8% to 95.2%)	79 89.8% (81.7% to 94.5%)	66 90.4% (81.5% to 95.3%)
NOSE score, No. [b]	108	107	100	88	73
NOSE score	76.3 (73.6 to 79.1)	35.4 (30.8 to 40.1)	33.3 (28.5 to 38.1)	31.4 (26.3 to 36.5)	34.7 (29.0 to 40.3)
Change in NOSE score [c]	-	−40.9 (−46.9 to −35.0)	−43.0 (−49.5 to −36.6)	−45.0 (−51.7 to −38.2)	−41.7 (−48.8 to −34.6)
NOSE component score [d]					
Congestion	3.1 (2.9 to 3.2)	1.7 (1.5 to 1.9)	1.6 (1.4 to 1.9)	1.6 (1.3 to 1.8)	1.5 (1.3 to 1.8)
Blockage	3.1 (2.9 to 3.2)	1.4 (1.2 to 1.6)	1.4 (1.1 to 1.6)	1.3 (1.1 to 1.6)	1.3 (1.1 to 1.6)
Breathing	3.2 (3.0 to 3.3)	1.4 (1.2 to 1.6)	1.3 (1.1 to 1.5)	1.3 (1.0 to 1.5)	1.5 (1.2 to 1.8)
Sleeping	2.9 (2.7 to 3.1)	1.2 (1.0 to 1.4)	1.2 (1.0 to 1.4)	1.1 (0.8 to 1.3)	1.2 (0.9 to 1.5)
Air/exercise	3.1 (2.9 to 3.3)	1.4 (1.1 to 1.6)	1.2 (0.9 to 1.4)	1.0 (0.7 to 1.2)	1.3 (1.0 to 1.6)
Change in NOSE component score [c,d]					
Congestion	-	−1.4 (−1.6 to −1.1)	−1.4 (−1.7 to −1.1)	−1.5 (−1.8 to −1.2)	−1.5 (−1.9 to −1.2)
Blockage	-	−1.6 (−2.0 to −1.3)	−1.7 (−2.0 to −1.4)	−1.7 (−2.1 to −1.4)	−1.7 (−2.1 to −1.4)
Breathing	-	−1.8 (−2.0 to −1.5)	−1.9 (−2.2 to −1.6)	−1.9 (−2.2 to −1.6)	−1.7 (−2.0 to −1.3)
Sleeping	-	−1.7 (−2.0 to −1.4)	−1.7 (−2.0 to −1.4)	−1.8 (−2.2 to −1.4)	−1.7 (−2.0 to −1.3)
Air/exercise	-	−1.7 (−2.0 to −1.4)	−2.0 (−2.3 to 1.6)	−2.1 (−2.5 to −1.8)	−1.8 (−2.2 to −1.4)
NOSE Scale severity class, No. [b,e]	108	107	100	88	73
No problems (0)	0 (0.0%)	5 (4.7%)	9 (9.0%)	11 (12.5%)	11 (15.1%)
Mild (5-25)	0 (0.0%)	43 (40.2%)	44 (44.0%)	40 (45.5%)	30 (41.1%)
Moderate (30-50)	2 (1.9%)	35 (32.7%)	28 (28.0%)	22 (25.0%)	16 (21.9%)
Severe (55-75)	56 (51.9%)	15 (14.0%)	13 (13.0%)	10 (11.4%)	14 (19.2%)
Extreme (80-100)	50 (46.3%)	9 (8.4%)	6 (6.0%)	5 (5.7%)	2 (2.7%)

[a] Continuous data are presented as the adjusted (least squares) mean (95% confidence interval) and categorical data are presented as No. (%) (95% confidence interval) or No (%). [b] Number of patients with evaluable data. [c] Change from baseline. [d] Complete description of component scores: nasal congestion/stuffiness, nasal blockage/congestion, trouble breathing through the nose, trouble sleeping, and unable to get enough air through the nose during exercise or exertion. [e] NOSE score ranges included in each severity class are indicated in parentheses.

Supplemental Table 3. NOSE scores in patient subpopulations. [a]

Population	Baseline	3 months	6 months	1 year	2 years
All patients (for reference) No. 108, 107, 100, 88, 73	76.3 (73.6 to 79.1)	35.4 (30.8 to 40.1)	33.3 (28.5 to 38.1)	31.4 (26.3 to 36.5)	34.7 (29.0 to 40.3)
Severe class at baseline No. 56, 55, 52, 46, 38	66.2 (64.2 to 68.1)	31.0 (24.5 to 37.5)	30.5 (23.8 to 37.2)	30.2 (23.0 to 37.3)	33.3 (25.2 to 41.3)
Extreme class at baseline No. 50, 50, 47, 41, 34	89.1 (87.0 to 91.2)	40.4 (33.6 to 47.2)	37.1 (30.1 to 44.1)	33.3 (25.8 to 40.8)	37.4 (28.9 to 45.9)
Prior nasal surgery No. 31, 31, 28, 24, 22	77.6 (72.5 to 82.7)	40.8 (32.2 to 49.4)	35.4 (26.5 to 44.4)	37.0 (27.4 to 46.6)	40.7 (30.3 to 51.2)
No prior nasal surgery No. 77, 76, 72, 64, 51	75.8 (72.6 to 79.1)	33.2 (27.7 to 38.7)	32.4 (26.7 to 38.1)	29.2 (23.2 to 35.1)	32.0 (25.3 to 38.7)
Septal deviation No. 22, 21, 21, 20, 15	79.3 (73.3 to 85.4)	44.4 (34.1 to 54.8)	36.6 (26.0 to 47.3)	35.6 (24.6 to 46.6)	32.9 (20.3 to 45.5)
No deviation septal No. 86, 86, 79, 68, 58	75.6 (72.5 to 78.6)	33.2 (28.1 to 38.3)	32.6 (27.2 to 37.9)	30.4 (24.6 to 36.2)	35.2 (28.8 to 41.6)
Septal swell body No. 15, 15, 15, 15, 12	80.0 (72.7 to 87.3)	40.3 (27.9 to 52.8)	32.3 (19.7 to 44.9)	40.7 (28.1 to 53.2)	41.4 (27.0 to 55.8)
No septal swell body No. 93, 92, 85, 73, 61	75.8 (72.8 to 78.7)	34.6 (29.6 to 39.7)	33.5 (28.3 to 38.7)	29.5 (24.0 to 34.9)	33.3 (27.2 to 39.5)
Turbinate enlargement No. 16, 16, 16, 16, 14	80.3 (73.2 to 87.4)	40.0 (27.9 to 52.1)	33.4 (21.2 to 45.6)	28.1 (15.6 to 40.7)	31.9 (18.1 to 45.7)
No turbinate enlargement No. 92, 91, 84, 72, 59	75.7 (72.7 to 78.6)	34.6 (29.5 to 39.7)	33.3 (28.1 to 38.5)	32.3 (26.7 to 37.9)	35.5 (29.2 to 41.8)

[a] Data are presented as the adjusted (least squares) mean (95% confidence interval). The number of evaluable patients in each subpopulation at each timepoint are listed in the left-hand column.

Supplemental Table 4. Epworth Sleepiness Scale (ESS) scores. [a]

	Baseline	3 months	6 months	1 year	2 years
All patients, No. [b]	108	107	100	88	73
ESS score	10.3 (9.2 to 11.4)	6.5 (5.6 to 7.5)	6.2 (5.3 to 7.1)	5.5 (4.6 to 6.4)	5.4 (4.5 to 6.4)
Change in ESS score from baseline	-	−3.8 (−4.8 to −2.8)	−4.1 (−5.2 to −3.1)	−4.8 (−5.8 to −3.8)	−4.9 (−6.2 to −3.7)
Patients with abnormal baseline ESS (≥11), No. [b]	51	50	47	40	31
ESS score	15.6 (14.8 to 16.4)	9.5 (8.3 to 10.7)	9.0 (7.9 to 10.2)	8.2 (7.1 to 9.2)	7.6 (6.3 to 8.9)
Change in ESS score from baseline	-	−6.1 (−7.5 to −4.7)	−6.6 (−8.0 to −5.2)	−7.4 (−8.7 to −6.1)	−8.0 (−9.6 to −6.4)

[a] Data are presented as the adjusted (least squares) mean (95% confidence interval). [b] Number of patients with evaluable data. ESS score intervals: 0-5 = lower normal daytime sleepiness, 6-10 = higher normal daytime sleepiness, 11-12 = mild excessive daytime sleepiness, 13-15 = moderate excessive daytime sleepiness, 16-24 = severe excessive daytime sleepiness.