RESOLVE: a randomized, controlled, blinded study of bioabsorbable steroid-eluting sinus implants for in-office treatment of recurrent sinonasal polyposis

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Background: **Patients with recurrent sinonasal polyposis after endoscopic sinus surgery (ESS) have limited treatment options. This study evaluated the safety and efficacy of a bioabsorbable steroid-eluting implant with 1350 μg of mometasone furoate for its ability to dilate obstructed ethmoid sinuses, reduce polyposis, and reestablish sinus patency.**

Methods: **This was a randomized, controlled, blinded study including 100 patients chronic rhinosinusitis with nasal polyposis (CRSwNP) refractory to medical therapy and considered candidates for revision ESS. Follow-up included endoscopic grading by investigators and patient-reported outcomes.**

Results: **Treated patients (n = 53; age as mean ± standard deviation [SD] 47.8 ± 12.6 years; 55% male) underwent in-office bilateral placement. Control patients (n = 47; age 51.6 ± 13.1 years; 66% male) underwent a sham procedure. At 3 months, treated patients experienced a significant reduction in bilateral polyp grade ($p = 0.0269$) and ethmoid sinus obstruction ($p = 0.0001$) compared to controls. Treated patients also experienced a 2-fold improvement in the mean nasal obstruction/congestion score (−1.33 ± 1.47 vs −0.67 ± 1.45; $p = 0.1365$). This improvement reached statistical significance ($p = 0.025$) in patients with greater polyp burden (grade ≥2 bilaterally; n = 74). At 3 months, 53% of treated patients compared to only 23% of controls were no longer indicated for repeat ESS. There was no serious adverse event or clinically significant increases in intraocular pressure or cataract formation.**

Conclusion: **The symptomatic improvement and statistically significant reduction in polyp grade and ethmoid sinus obstruction supported the efficacy of the steroid-eluting implant for in-office treatment of CRS patient with recurrent polyposis after ESS. The study results demonstrated that the steroid-eluting implant represents a safe and effective alternative to current management for this patient population.**

Key Words:
corticosteroid; mometasone furoate; CRSwNP; drug-eluting; safety; efficacy; sinusitis; endoscopic sinus surgery; nasal polyps; refractory

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Chronic rhinosinusitis (CRS), especially CRS with nasal polyposis (CRSwNP), significantly impacts quality of life.[1,2] Despite maximal medical therapy and endoscopic sinus surgery (ESS) to remove nasal polyps, recurrence is common due to the inflammatory nature of the sinonasal mucosa in CRSwNP.[3,4] Postoperative medical management with topical steroids has been used to prevent the recurrence of NP, but this form of therapy is often unsuccessful and other interventions become necessary.[3,5] Currently, the options for patients with recurrence of NP after ESS are limited to systemic steroids or repeat ESS with polypectomy.[5–9]

Mometasone furoate is the only topical nasal steroid approved by the U.S. Food and Drug Administration (FDA) for the treatment of nasal polyposis.[10,11] In previous studies, a mometasone furoate–eluting sinus implant was inserted in the operating room setting to improve postoperative results after ESS through localized, controlled delivery of 370 μg of the steroid over 1 month.[12–15] Recently, the technical feasibility of in-office insertion of a higher-dose mometasone furoate eluting implant and its initial safety and efficacy were demonstrated by Lavigne et al.[16] in a pilot study with 12 patients. The sinus implant used in this study was designed to dilate sinuses reobstructed by polyps and provide localized, controlled delivery of 1350 μg of mometasone furoate for 3 months to reduce inflammation and reestablish sinus patency.

The objective of this multicenter, randomized, parallel group, controlled, blinded clinical study was to assess the safety and efficacy of the steroid-eluting sinus implant inserted in the office setting in post–sinus surgery patients who present with recurrent ethmoid obstruction due to NP.

Patients and methods

Implant description

The steroid-eluting sinus implant used in this study was supplied by Intersect ENT (Menlo Park, CA) for investigational use. The implant is composed of a bioabsorbable polymer and has a self-expanding, non-obstructive design (Fig. 1), which allows it to adjust to fit in a previously-operated ethmoid sinus cavity. The implant has an arched design, which gives it sufficient radial strength to dilate an obstructed ethmoid sinus cavity and to be self-retaining in the cavity as polypoid tissue recedes. The polymer matrix contains 1350 μg of mometasone furoate and controls the gradual release of the drug over 3 months. The implant provides for an immediate onset of action by creating and maintaining an opening in the obstructed middle meatus and ethmoid sinus, thus restoring ventilation and drainage and reducing the sensation of nasal blockage and congestion, which is the hallmark symptom of CRSwNP.[6,7]

Study design

A prospective, randomized, controlled, parallel group, blinded clinical trial was conducted in 100 patients at 18 clinical centers across the United States. Patients had confirmed diagnosis of CRS[17] and were candidates for revision ESS due to recurrent symptoms and bilateral polyposis (minimum grade 2 on 1 side). The participating clinical sites obtained institutional review board approval for the protocol and written informed consent from all patients prior to study entry. The study was registered on ClinicalTrials.gov under identifier NCT01732536.

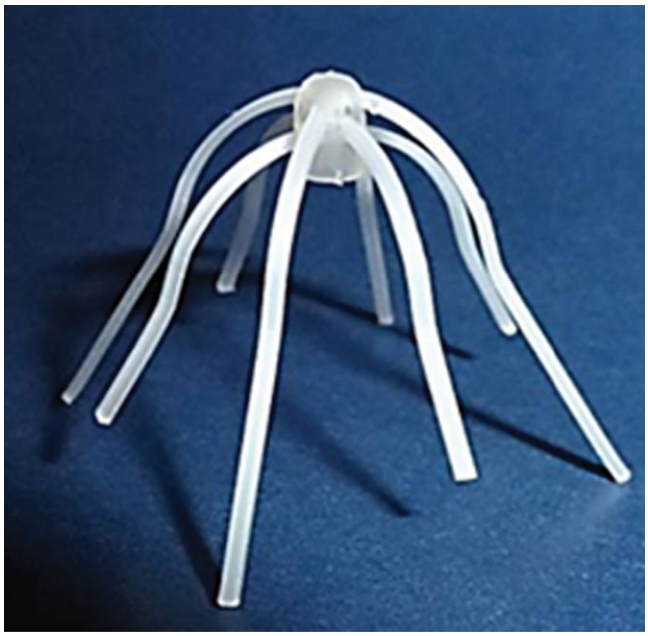

FIGURE 1. Steroid-eluting sinus implant with controlled release of 1350 μg of mometasone furoate over 90 days for in-office treatment of recurrent ethmoid sinus obstruction after ESS. ESS = endoscopic sinus surgery.

Prospective study candidates entered a screening phase consisting of medical history, 2-week medical washout/run-in period, endoscopic examination, symptom scoring, and ocular examination. Adult patients were included if they were at least 18 years old, had been diagnosed with CRS,[17] and had undergone prior bilateral total ethmoidectomy more than 3 months earlier.

Patients were required to have endoscopically-confirmed recurrent bilateral ethmoid sinus obstruction due to polyposis that was refractory to medical therapy. Patients were required to have symptom burden consisting of 2 or more of the prominent symptoms of CRS despite repeated aggressive corticosteroid therapy; this therapy was defined as ongoing topical intranasal steroid irrigation or spray for recurrent sinusitis, together with repeated courses of treatment with steroid therapy, of which at least 1 course was with a high-dose form of steroids (eg, oral, parenteral, injection into polyps), and/or sinus steroid irrigations within 6 months prior to enrollment.

Patients were required to be candidates for revision sinus surgery. Surgical candidacy was determined on a decision made between clinician and patient, based on clinical judgment, patient medical history, symptom burden, disease stage, objective findings using endoscopy or imaging, and outcomes of medical management. Because there is no 1 set of standards for determining candidacy for revision

surgery,[18] we applied criteria that were recommended based on thorough discussion with a number of rhinologists. Consensus was reached that if a patient had a prior sinus surgery followed by continued medical therapy, had a history of repeat courses of systemic steroid therapy—with 1 of those courses being within 6 months–is continuing to take a topical intranasal steroid spray, and yet still presents with bilateral polyposis and CRS symptoms, then such a patient could reasonably be considered for revision surgery.

Patients were excluded if they had known history of intolerance to corticosteroids, an oral steroid-dependent condition, history of immune deficiency, insulin dependent diabetes, clinical evidence of either acute bacterial sinusitis or invasive fungal sinusitis, or had previously undergone ESS and experienced a cerebrospinal fluid (CSF) leak or ocular complication. Patients were excluded if there was presence of physical obstruction that would preclude access to either ethmoid sinus for delivery of the study implants (eg, scar formation, septal deviation, septal spur) or if they had grade 4 polyposis on either side. Patients were also excluded if they had a known history or diagnosis of glaucoma or ocular hypertension, posterior subcapsular cataract, or at least grade 3 nuclear sclerotic or cortical cataract.

Continuous use of a topical steroid spray during the screening phase leading up to randomization at the baseline procedure was required for all patients. During the 2 week washout period immediately prior to randomization, the use of oral steroids or topical steroid irrigations was not permitted in order to ensure, as much as possible, that all patients entered the randomized phase of the study on a uniform medical regimen. Randomization was performed using an electronic data capture system at the time of the baseline procedure after confirming that all eligibility criteria had been met. Patients were randomly assigned to 1 of 2 groups: a treatment group in which the implants were placed bilaterally, or an active control group in which a sham procedure was performed. The randomization scheme used permuted blocks of varying sizes and was stratified by study site.

At the baseline procedure, which occurred in the office setting, patients were masked to treatment assignment by being both blindfolded and "earmuffed" using eye masks and noise-cancelling audio headphones, respectively. All patients were then anesthetized using a standardized protocol consisting of spraying the nasal cavity with 4% lidocaine (or equivalent) and oxymetazoline nasal decongestant, followed by middle meatal placement of cottonoids or pledgets soaked in 4% lidocaine and decongestant solution. Local injection into the sinus tissue and nasal septum was permitted as necessary to ensure patient comfort. Patients in the treatment group had the study implants inserted and deployed bilaterally in the ethmoid sinuses using the supplied delivery system. Patients in the control group underwent a sham procedure, which consisted of insertion of the implants into the ethmoid sinus, but without deployment. The implant and delivery system were withdrawn without deployment of the implant into the ethmoid sinus cavity. The eye mask and headphones were removed after the procedure was completed and all device packaging was removed from the room.

After the procedure and throughout the study follow-up period, all patients were required to take mometasone furoate nasal spray (Nasonex®; 100 μg/nostril once daily) and were encouraged to use saline sprays or irrigations as needed. This was required to ensure that the control patients continued to receive a clinically-proven topical steroid therapy for their sinonasal polyposis and the treatment patients remained blinded to treatment assignment (patients could not guess their treatment assignment based upon use and taste of the nasal steroid spray). Topical steroid irrigations were restricted for the first 90 days, but patients were permitted to continue stable regimens of orally-inhaled steroids and sinus-related medical therapy such as immunotherapy or leukotriene antagonists throughout the 90-day follow-up interval. Use of antibiotics was allowed at any time if sinus infection was suspected.

Follow-up visits up to 90 days involved endoscopic examination and grading, monitoring for adverse events, and patient-scoring of nasal congestion/blockage, the hallmark symptom of sinonasal polyposis. To maintain patient blinding throughout all study visits, the symptom questionnaire was administered by a member of the research staff who was unaware of the patient's treatment assignment, and patients were again blindfolded and "earmuffed" during the endoscopic examinations. To avoid any chance of unblinding of the treatment patients before day 90 assessment, the implants were removed at the day 60 visit to eliminate the risk of spontaneous dislodgement of the implants with their gradual softening and reabsorption.

Endoscopic assessments

Objective outcomes were determined by endoscopic examination. The evaluations were instantaneous on the day of each study visit, meaning study investigators were not permitted to review grading from prior visits, and all endoscopic examinations were recorded (Fig. 2). Prior to participation, study investigators attended a training session on endoscopic grading that included photographic examples. A standardized case report form containing endoscopic parameters with definitions, which was used in a previous study,[16] was used for the endoscopic grading. Adhesion/scarring was graded as: 0 = none; 1 = small, non-obstructing (no separation required); 2 = obstructing, easily separated; 3 = dense obstructing, separation difficult; or 4 = severe, complete adhesion middle turbinate to lateral nasal wall. Polyposis was graded using a 5-point scale according to the guidance for clinical trials with CRSwNP by Meltzer et al.[19] as: 0 = no visible nasal polyps; 1 = small amount of nasal polyposis confined within the middle meatus; 2 = expanded amount of polyps confined in the middle meatus; 3 = polyps extending beyond the middle meatus, within the sphenoethmoid recess but not totally obstructing, or both; or 4 = polyps completely obstructing

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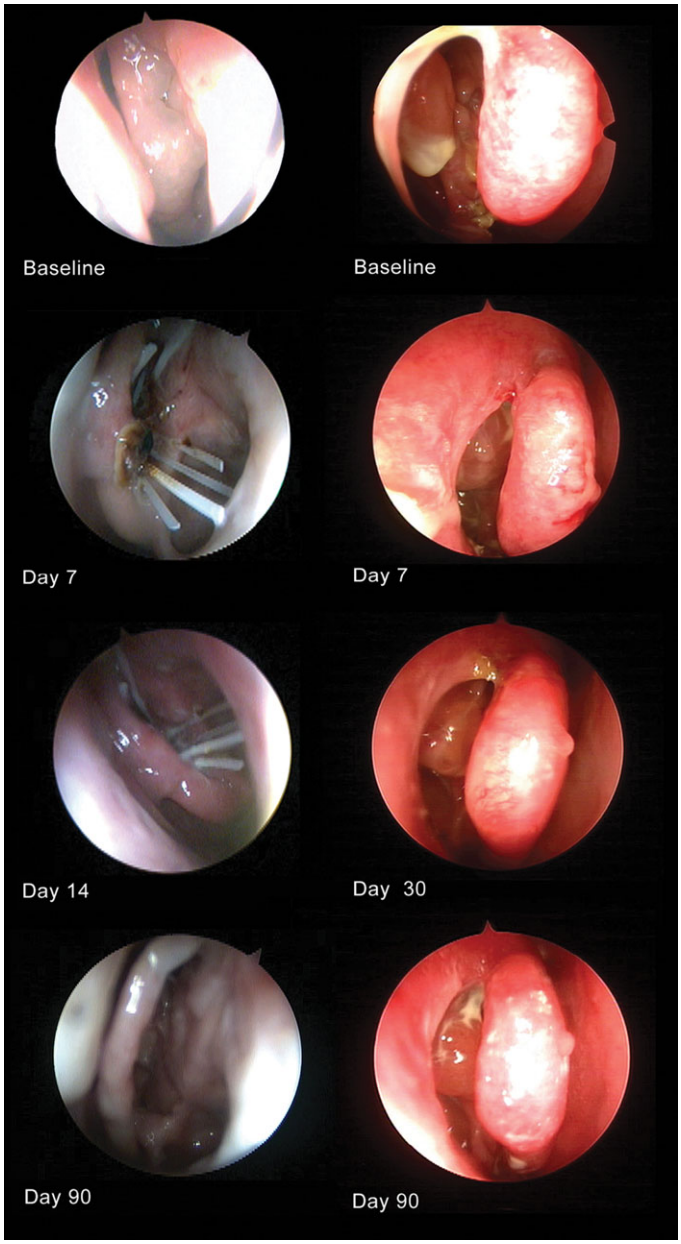

FIGURE 2. Endoscopic images of ethmoid sinus from 2 study patients from the treatment group (left) and control group (right) before and through 90 days after placement of a steroid-eluting implant or sham procedure, respectively.

the nasal cavity. Percent ethmoid sinus obstruction was graded on a 100-mm visual analogue scale (VAS) anchored at 0 = the absence of obstruction by scarring, polyps or edema, and 100 = complete obstruction of the cavity by scarring, polyps, or edema. The participating clinical centers were also provided with a scoring guide that included photographic examples of the various polyp stages with definitions to enhance rating consistency across all study sites.

Patient-reported outcome measures

Patients were asked to assess their sensation of nasal obstruction/congestion over 1 week preceding the visit on a 5-point scale as: 0 = none; 1 = very mild problem; 2 = mild or slight problem; 3 = moderate problem; 4 = severe problem; and 5 = problem as bad as it can be.

Safety measures

Safety was assessed by monitoring for device-related adverse events. Ocular safety was characterized by measurement of intraocular pressure (IOP) at baseline and days 14, 30, 45, and 90. Dilated slit-lamp examination of the crystalline lens was performed at baseline and day 90. IOP measurements were obtained by Goldman applanation or Tonopen tonometry. Lens opacities were classified on a 5-point scale. The Lens Opacities Classification System, Version III (LOCS III) was modified for the purposes of the study to grade cataracts in a consistent manner across the study centers.[20] The participating clinical centers were provided with a classification guide that included photographic examples of the various cataract stages to enhance rating consistency across all study sites.

Medical and surgical interventions

If infection was suspected, treatment with antibiotics was permitted at any time during the study. Oral steroids were allowed during the study follow-up period as a medical intervention if a clinically significant increase or persistence in ethmoid sinus polyposis occurred, coupled with patient complaint of sinusitis symptoms that caused the patient to request intervention. ESS was allowed during study follow-up if it was deemed clinically necessary because of a significant increase or persistence in ethmoid sinus polyposis coupled with complaint of sinusitis symptoms that caused the patient to request sinus surgery. At 90 days, clinical investigators reassessed whether their patients were still indicated for revision surgery using the same methodology as that used at the study entry.

Statistical analyses

A total sample size of 48 patients per treatment group was determined to provide 80.5% combined power at a 2-sided alpha level of 0.05 to detect a standardized effect size between groups of at least 0.6 point in the change from baseline to day 90 in bilateral polyp grade and a standardized effect size between groups of at least 1.0 points in the change from baseline to day 90 in nasal obstruction/congestion score. To allow for potential missing data, enrollment of 4 additional patients was planned, bringing the total planned enrollment to 100.

All data were entered into a validated electronic data capture system, 100% monitored, and analyzed by an independent biostatistician group. Summaries of data were based on all randomized patients, using the principle of intention-to-treat. Descriptive statistics and graphical summaries were used to summarize the data, with continuous variables presented as means ± standard deviations (SDs) and categorical variables presented as counts and percentages.

In cases where medical or surgical intervention was performed during follow-up, the patient's most recent post-baseline endoscopic and symptom scores prior to intervention were used for the primary analysis method. An analysis of covariance (ANCOVA) was used to analyze responses for the efficacy endpoints, with study center as stratification variable and baseline score as a covariate. Comparisons between treatment groups were based on differences in mean estimates from the ANCOVA models. All tests were carried out at the 2-sided significance level of 0.05.

Results

A total of 183 patients were consented for screening between January and November 2013, of whom 100 met eligibility criteria and were randomized to either the treatment (n = 53) or the control (n = 47) group (Fig. 3). No statistical differences in demographic and baseline characteristics between the treatment and control groups were observed (Table 1). All patients underwent at least 1 prior ESS for medically refractory CRSwNP, and the majority of patients in each group had more than 1 prior ESS (58% treatment, 66% control). All patients were considered to be candidates for revision ESS per study criteria; 87% of them were previously offered revision ESS but 69% declined, 16% were undecided, and only 2% were considering it. The study required bilateral polyposis with a minimum grade 2 on 1 side. Among 25 patients with grade 1 polyp on 1 side (8 treatment, 17 control), all patients had at least grade 2 on the other side, and the majority of them (68%) reported persistent nasal obstruction/congestion symptoms of grade 3 and higher. The study criteria for revision ESS required at least 1 course of oral steroids in the preceding 6 months; 98% of patients received at least 1 course of oral steroids (2 patients refused it due to side effects), 70% received at least 2 courses, and 45% had received at least 3 courses of oral steroids since recurrence of symptoms. Doses ranged from 10 to 30 mg daily of prednisone (or equivalent) for 1 to 2 weeks followed by a variety of tapers for 2 to 12 weeks. None of the patients received parenteral injection of corticosteroids. The study criteria for revision ESS also required that patients had been using topical intranasal steroid irrigation or spray daily prior to enrollment. There were 99% of patients who used topical intranasal steroid irrigation or spray daily: 30% for 1 month; 8% for 1 to 6 months; 12% for 6 to 12 months; and 49% for more than 1 year. Doses ranged from 0.5 to 2 mg daily of budesonide for 3 to 113 weeks, 200 to 400 μg daily of mometasone for a mean duration of 82 weeks, 1 mg daily of dexamethasone for 10 weeks, or 200 to 400 μg daily of fluticasone for a mean duration of 195 weeks (note that most patients were on ongoing therapy that started on average within 1 year from randomization and finished within 6 months from randomization). There were 94% of patients who had

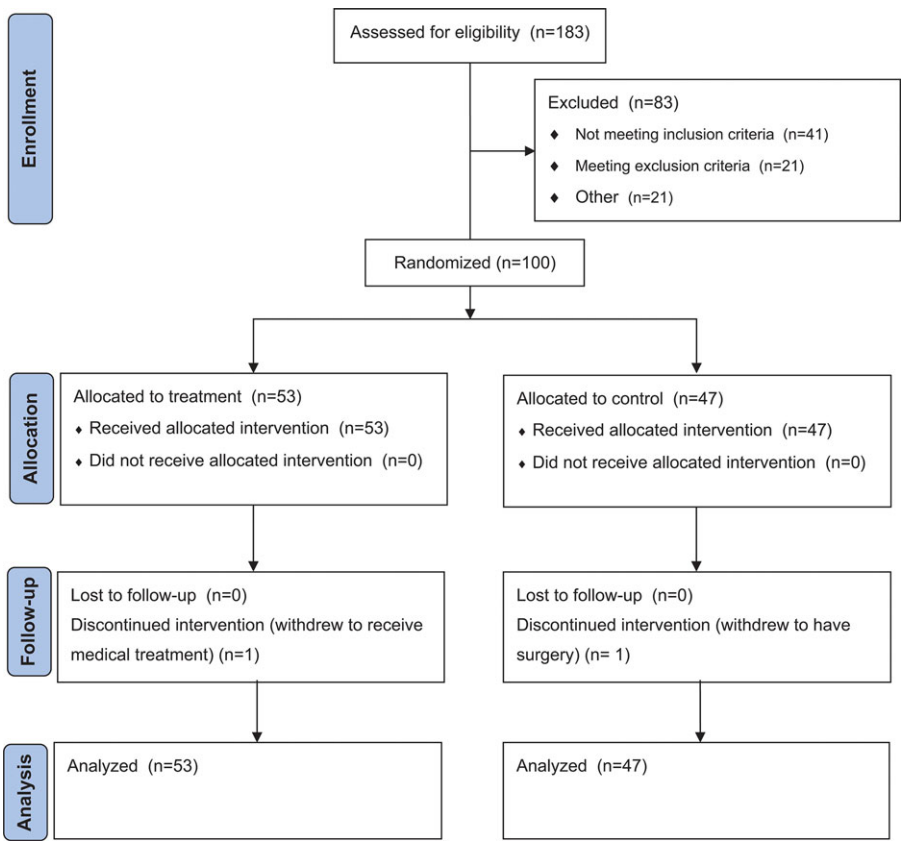

FIGURE 3. Disposition of study patients (CONSORT diagram).

TABLE 1. Baseline demographics and clinical characteristics

	Treatment (n = 53)	Control (n = 47)	*p*
Age (year), mean (range)	47.8 (19–74)	51.6 (30–80)	0.142
Male, n (%)	29 (54.7)	31 (66.0)	0.255
Medical history, n (%)			
Aspirin intolerance/allergy	15 (28.3)	11 (23.4)	0.579
Asthma	33 (62.3)	31 (66.0)	0.702
Samter's triad	11 (20.8)	9 (19.1)	0.842
Most common symptoms, n (%)			
Nasal obstruction/congestion	48 (90.6)	40 (85.1)	
Postnasal drainage	48 (90.6)	44 (93.6)	
Thick nasal discharge	50 (94.3)	41 (87.2)	
Facial pain, pressure, fullness	42 (79.2)	32 (68.1)	
Anosmia	36 (67.9)	30 (63.8)	
Ear pain, pressure, fullness	25 (47.2)	20 (42.6)	
Fatigue	29 (54.7)	27 (57.4)	
Cough	25 (47.2)	22 (46.8)	
Hyposmia	20 (37.7)	20 (42.6)	
Headache	21 (39.6)	16 (34.0)	
Nasal obstruction/congestion score, mean ± SD	3.6 ± 1.2	3.3 ± 1.2	
Number of prior ESSs, n (%)			0.865
1	22 (41.5)	16 (34.0)	
2	12 (22.6)	15 (31.9)	
3	9 (17.0)	8 (17.0)	
≥4	10 (18.9)	8 (17.0)	
Prior in-office sinus procedures, n (%)			
Polypectomy	11 (20.8)	15 (31.9)	
Sinuplasty	10 (18.9)	9 (19.1)	
Bilateral polyp grade, mean ± SD	4.9 ± 0.9	4.4 ± 1.4	
Percent ethmoid sinus obstruction, mean ± SD	69.2 ± 19.5	61.2 ± 25.6	
Middle turbinate position, n (%)			0.952
Medialized, normal or partially lateralized	105 (99.1)	91 (96.8)	
Lateralized	1 (0.9)	2 (2.1)	
Adhesions severity scores, n (%)			0.543
Small, non-obstructing or obstructing	22 (20.8)	21 (22.3)	
Dense obstructing/complete adhesion	0	1 (1.1)	
Intraocular pressure (mmHg), mean ± SD	15.2 ± 2.8	14.9 ± 2.7	

ESS = functional endoscopic sinus surgery; SD = standard deviation.

sinus infection requiring treatment with antibiotics within 2 years prior to enrollment: 7% had 1 episode; 15% had 2 episodes; 41% had 3 to 4 episodes; and 31% had more than 4 episodes.

Implant placement and performance

The sinus implant was successfully placed at the target location in 106 (100%) sinuses in the treatment arm. Investigators provided a visual estimate by endoscopy of the percentage of implant remaining at each time point. The percentage of implant remaining over time was a reflection of both bioabsorption and removal of the implant. The mean percentage remaining at days 30, 45, and 60 was 92.5, 86.5, and 56.7, respectively. Clinical investigators removed the remaining implant remnants at the day 60 visit.

Safety assessments

No serious adverse events were reported during the study. There were no study drug–related and only 2 implant-related adverse events (1 nasal discomfort and 1 nasal odor, both mild), which resolved without sequelae. The overall incidence of adverse events, the majority of which were considered related to sinusitis, was similar between the groups. There were 34 (64%) patients in the treatment group and 35 (75%) in the control group who experienced an adverse event of any type. Of these, sinusitis was reported in 17 (32%) and 21 (45%) of treatment and control patients, respectively. Other adverse events that occurred were infrequent, were balanced between the groups and included (in order of decreasing frequency) nasopharyngitis, asthma, epistaxis, headache, upper respiratory infection, presyncope, and nasal congestion.

The mean intraocular pressure at day 90 was reduced by -0.1 ± 2.6; range, -9 to 8) in the treatment group and by -0.6 ± 2.7; range, -10 to 7) compared to baseline. None of the patients experienced a clinically significant increase in intraocular pressure or any type of cataract (nuclear sclerotic, cortical, or posterior subcapsular).

Efficacy endpoints

Endoscopic measures

At day 90 the treatment group experienced a significantly greater reduction in bilateral polyp grade ($p = 0.016$, Fig. 4) and percent ethmoid obstruction on 100-mm VAS ($p = 0.001$, Fig. 5) compared to the control group. The significant reduction in both measures was sustained from day 7 through the entire 90-day study period. A clinically significant 1-grade reduction in bilateral polyp burden was experienced by 60% of treatment patients compared to 33% of controls. A 2-grade reduction was experienced by 42% of the treatment patients compared to 9% of the control patients.

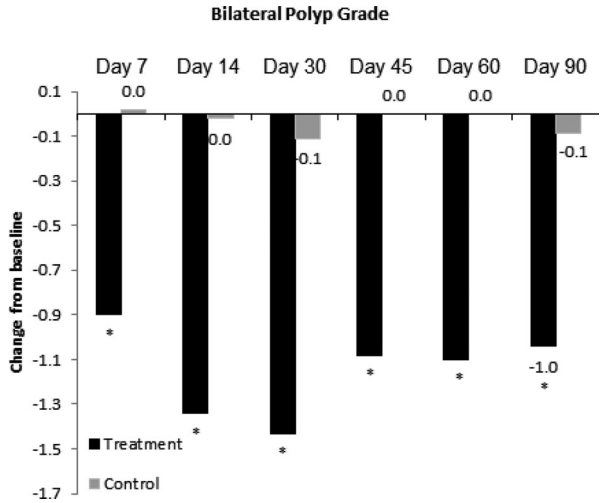

FIGURE 4. Change from baseline in mean bilateral polyp grade during 90 days following sinus implant placement (treatment) or sham procedure (control) showing significant treatment effect at all time points. Means and *p* values obtained from analysis of variance with baseline values as covariate and the site and treatment group as fixed effects. The symbol * denotes $p < 0.05$ vs control.

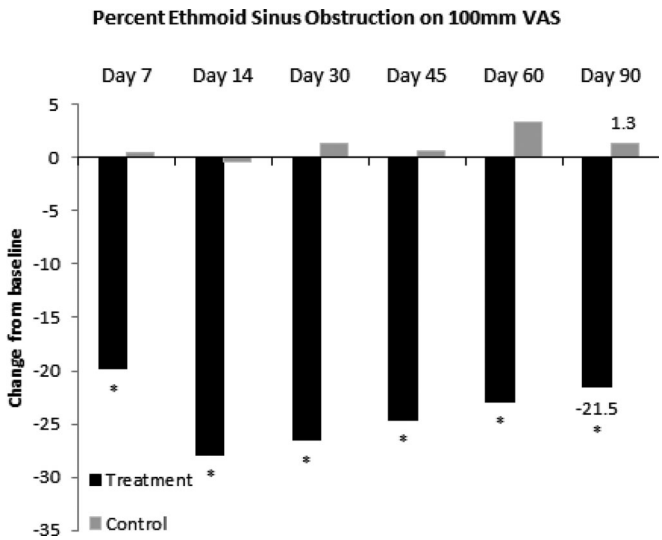

FIGURE 5. Change from baseline in ethmoid sinus obstruction evaluated using 100-mm visual analogue scale during 90 days following sinus implant placement (treatment) or sham procedure (control) showing significant treatment effect at all time points. Means and *p* values obtained from analysis of variance with baseline values as covariate and the site and treatment group as fixed effects. The symbol * denotes $p < 0.01$ vs control.

Patient-reported outcomes

The treatment group improved symptomatically over 90 days. Compared to control, the treatment group experienced a 2-fold reduction in nasal obstruction and congestion score at day 90. The change from baseline in the treatment group was -1.33 ± 1.5 on the 5-point scale compared to -0.67 ± 1.5 in the control ($p = 0.137$). A subset analysis was performed to assess this outcome measure in patients with at least grade 2 polyposis on each side at the time of study entry. The improvement at day 90 in nasal obstruction and congestion score was statistically significant

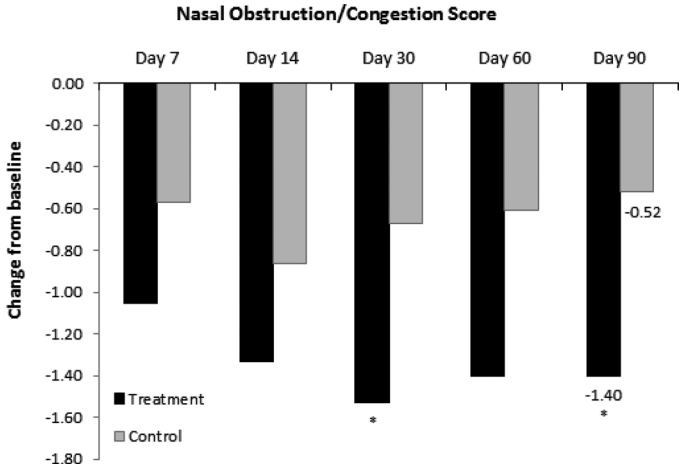

FIGURE 6. Change from baseline in nasal obstruction/congestion score in a subset of 74 patients with minimum polyp grade 2 on each side at baseline, demonstrating a significantly greater reduction in the treatment group at day 90 ($p = 0.025$). The symbol * denotes $p < 0.05$ vs control.

($p = 0.025$) in the subset of 74 patients with polyp grade 2 at baseline on each side. The change from baseline in the treatment group was -1.4 ± 1.5 (n = 43) compared to -0.52 ± 1.4 (n = 31) in the control group (Fig. 6).

Postoperative intervention

Compared to control, fewer treatment patients required oral steroids for ethmoid obstruction (11% vs 26%) and fewer treatment patients remained indicated for sinus surgery at 3 months based on the established criteria (47% vs 77%). Two patients in the treatment group and 1 in the control group underwent revision surgery during the 3-month follow-up. The 2 treatment patients requested to have surgery shortly before their day 90 visit to take advantage of the end-of-year insurance coverage and deductible. The control patient withdrew from the study at day 30 to have sinus surgery.

Discussion

This study was the first multicenter, randomized, controlled, blinded clinical trial that assessed the safety and efficacy of an office-based insertion of a steroid-eluting sinus implant in CRSwNP patients. The long-term, localized, controlled delivery of 1350 μg of mometasone furoate from the implant was shown to be effective in reducing polyposis over a clinically meaningful period. With only 2 mild implant-related adverse events (nasal discomfort and nasal odor) and the absence of ocular changes, the study supports the safety of the steroid-eluting sinus implant. The implant placement success rate was 100% and replicates the technical feasibility of the in-office placement.[16]

Current treatment options for CRSwNP include topical nasal steroid sprays, off-label use of topical steroid irrigations or drops, steroid injection into polyps, systemic oral steroids, and ESS to remove polyps and diseased mucosa. Regardless of the treatment, polyps have a strong tendency to recur and, therefore, repeated courses of these medications and/or repeat ESS are often needed. Repeated use of systemic steroid and ESS presents various concerns for patients and their managing otolaryngologists.[21,22] Given that all patients enrolled in the study were considered to be candidates for revision surgery, the study results are quite promising. Nearly 53% of patients in the treatment group were no longer considered to be surgical candidates by the end of the study compared to 23% in the active control group. The observed level of improvement among some of the control patients was not surprising given that they were maintained on mometasone furoate nasal spray at daily dose of 200 μg, which has been shown effective in reducing polyposis and also in preventing polyp relapse in revision ESS patients.[10,11,23]

The efficacy of the steroid-eluting implant is supported by the significant reductions in bilateral polyp grade and percent ethmoid sinus obstruction as measured by endoscopic evaluation. In addition, a 2-fold reduction in nasal obstruction/congestion was reported, which reached statistical significance in patients with higher polyp burden. These improvements in our study appear to compare favorably to other medical and surgical treatment modalities reported in the literature. Change from baseline in bilateral polyp grade in 2 studies evaluating the use of topical mometasone furoate for nasal polyps was −0.78 with twice daily dosing, and change from baseline in nasal congestion/obstruction was −0.6.[10,11] Hissaria et al.[24] reported on a randomized, double-blind, controlled trial in nasal polyp patients comparing 2 weeks of oral prednisolone (50 mg once daily) to placebo. Significant reductions in polyp grade and patient-reported outcomes were observed at 2 weeks. No further follow-up was described and the authors commented that the efficacy of systemic steroids for this indication is variable, ranging from 1 to 6 months.[14]

Because CRSwNP is a heterogeneous disease with no common pathophysiology, there is not a single universal medical treatment for these patients,[4] and despite the medical and surgical advances, a significant number of patients eventually require a revision ESS procedure. [18] A limitation of our study was that there was not a defined medical treatment prior to enrollment (eg, a 3-week course of a broad spectrum of antibiotics and 3-week trial of topical steroids as was used in prior studies[25,26]). To ensure generazability of our findings, we relied on real-life prior medical treatment decided by the treating otolaryngologists at each enrollment site based on clinical judgment and patient preferences. In fact, our patients received more intensive medical therapy than the above-mentioned medical treatment prior to study enrollment. Also, it was beyond the scope of our study to control the extent of prior medical therapy, patient compliance, and to control for the time elapsed from oral steroid treatment to screening. We were also not able to control for the possible impact that these various sources of prior treatment variability may have had on objectively determining surgical candidacy or study outcomes. Another

limitation was that the clinical investigators performing endoscopic grading were not blinded to the treatment assignment. We attempted to minimize the potential for bias in these assessments by requiring instantaneous grading at each study visit, where investigators referred to the standardized grading scales and were not permitted to review their grading from prior visits. In addition, the control group also received treatment because the use of mometasone furoate intranasal spray once daily was required by the study protocol to avoid confounding study results by unmasking patients to their treatment assignment. Patient noncompliance with topical steroid use is well known, and so it is possible that the improvements observed in the control group were due to better dosing compliance while on the study protocol. Finally, the study entry criteria required patients to be surgical revision candidates while concurrently allowing for 1 sinus side to have only grade 1 polyposis. This may represent a debatable discrepancy in defining surgical candidates, and may have resulted in enrollment of some patients with less opportunity for improvement from baseline. The subset analysis in patients with at least a grade 2 polyposis in each nasal cavity suggests that the implant treatment effect may be greater in more diseased CRSwNP patients, and whose revision candidacy is less contentious.

Conclusion

The symptomatic improvement and statistically significant reduction in both polyp grade and ethmoid sinus obstruction supported the efficacy of the steroid-eluting implant for in-office treatment of CRS patients with recurrent polyposis after ESS. The study results demonstrated that the steroid-eluting implant represents a safe and clinically meaningful alternative to current treatment approaches for this patient population.

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References

1. Banerji A, Piccirillo JF, Thawley SE, et al. Chronic rhinosinusitis patients with polyps or polypoid mucosa have a greater burden of illness. *Am J Rhinol*. 2007;21:19–26.
2. Fokkens WJ, Lund VJ, Mullol J, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinol Suppl*. 2012;(23):3 p preceding table of contents, 1–298.
3. Chaaban MR, Walsh EM, Woodworth BA. Epidemiology and differential diagnosis of nasal polyps. *Am J Rhinol Allergy*. 2013;27:473–478.
4. Han JK. Subclassification of chronic rhinosinusitis. *Laryngoscope*. 2013;123:S15-S27.
5. Fandino M, Macdonald KI, Lee J, Witterick IJ. The use of postoperative topical corticosteroids in chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis. *Am J Rhinol Allergy*. 2013;27:e146-e157.
6. Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. *Mayo Clin Proc*. 2011;86:427–443.
7. Schlosser RJ, Soler ZM. Evidence-based treatment of chronic rhinosinusitis with nasal polyps. *Am J Rhinol Allergy*. 2013;27:461–466.
8. Soler ZM, Rudmik L, Hwang PH, Mace JC, Schlosser RJ, Smith TL. Patient-centered decision making in the treatment of chronic rhinosinusitis. *Laryngoscope*. 2013;123:2341–2346.
9. Doellman MS, Dion GR, Weitzel EK, Reyes EG. Immunotherapy in allergic fungal sinusitis: the controversy continues. A recent review of literature. *Allergy Rhinol*. 2013;4:e32-e35.
10. Small CB, Hernandez J, Reyes A, et al. Efficacy and safety of mometasone furoate nasal spray in nasal polyposis. *J Allergy ClinImmunol*. 2005;116:1275–1281.
11. Stjarne P, Mösges R, Jorissen M, et al. A randomized controlled trial of mometasone furoate nasal spray for the treatment of nasal polyposis. *Arch Otolaryngol Head Neck Surg*. 2006;132:179–185.
12. Forwith KD, Chandra RK, Yun PT, Miller SK, Jampel HD. ADVANCE: a multisite trial of bioabsorbable steroid-eluting sinus implants. *Laryngoscope*. 2011;121:2473–2480.
13. Han JK, Marple BF, Smith TL, et al. Effect of steroid-releasing sinus implants on postoperative medical and surgical interventions: an efficacy meta-analysis. *Int Forum Allergy Rhinol*. 2012;2:271–279.
14. Marple BF, Smith TL, Han JK, et al. ADVANCE II: a prospective, randomized study assessing safety and efficacy of bioabsorbable steroid-releasing sinus implants. *Otolaryngol Head Neck Surg*. 2012;146:1004–1011.
15. Murr AH, Smith TL, Hwang PH, et al. Safety and efficacy of a novel bioabsorbable, steroid-eluting sinus stent. *Int Forum Allergy Rhinol*. 2011;1:23–32.
16. Lavigne F, Miller SK, Gould AR, Lanier BJ, Romett JL. Steroid-eluting sinus implant for in-office treatment of recurrent nasal polyposis: a prospective, multi-center study. *Int Forum Allergy Rhinol*. 2014;4:381–389.
17. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology*. 2012;50:1–12.
18. Bhattacharyya N. Clinical outcomes after revision endoscopic sinus surgery. *Arch Otolaryngol Head Neck Surg*. 2004;130:975–978.
19. Meltzer EO, Hamilos DL, Hadley JA, et al.; Rhinosinusitis Initiative. Rhinosinusitis: developing guidance for clinical trials. *J Allergy ClinImmunol*. 2006;118(5 Suppl):S17-S61.
20. Bencić G, Zorić-Geber M, Sarić D, Corak M, Mandić Z. Clinical Importance of the lens opacities classification system III (LOCS III) in phaecoemulsification. *CollAntropol*. 2005;29:91–94.
21. Patiar S, Reece P. Oral steroids for nasal polyps. *Cochrane Database Syst Rev*. 2007:CD005232.
22. Vaidyanathan S, Barnes M, Williamson P, et al. Treatment of chronic rhinosinusitis with nasal polyposis with oral steroid followed by topical steroids. *Ann Intern Med*. 2011;154:293–302.
23. Stjarne P, Olsson P, Alenius M. Use of mometasone furoate to prevent polyp relapse after endoscopic sinus surgery. *Arch Otolaryngol Head Neck Surg*. 2009;135:296–302.

24. Hissaria P, Smith W, Wormald PJ, et al. Short course of systemic corticosteroids in sinonasal polyposis: a double-blind, randomized, placebo-controlled trial with evaluation of outcome measures. *J Allergy Clin Immunol*. 2006;118:128–133.

25. Smith TL, Kern R, Palmer JN, et al. Medical therapy vs surgery for chronic rhinosinusitis: a prospective, multi-institutional study with 1-year follow-up. *Int Forum Allergy Rhinol*. 2013;3:4–9.

26. Smith TL, Kern RC, Palmer JN, et al. Medical therapy vs surgery for chronic rhinosinusitis: a prospective, multi-institutional study. *Int Forum Allergy Rhinol*. 2011;1:235–241.

UPCOMING MEETING ANNOUNCEMENT 2014

The 33rd ISIAN meeting (International Society of Inflammation and Allergy of the Nose), in combination with the IRS (International Rhinologic Society) will be held in **Dubai, November 20th to 24th 2014**, under the leadership of Reda Kamel, M.D. This major international meeting promises to bring together rhinologic leaders from around the globe. For more information, please go to http://isian-irs-pars2014.org/about-dubai.php