Introduction: Endoscopic sinus surgery (ESS) plays an integral role in the treatment of chronic rhinosinusitis (CRS), with well-documented benefits in both symptoms and quality of life. However, synechiae formation, polypoid change, and mucosal edema can compromise long-term surgical outcomes. Corticosteroids have been found to be effective in managing such postsurgical inflammation, but current delivery methods are limited by poor sinonasal distribution and potential systemic side effects. Sinus implantation offers a novel vehicle for topical drug delivery in CRS, enabling sustained, controlled corticosteroid application directly to sinonasal mucosa.

Areas covered: The bioengineering, mechanism of drug delivery, degradation and resorption of sinus implantation will be delineated. Research findings from animal and clinical studies will be assessed as well as alternative devices. Future directions for this technology in the management of CRS will also be discussed.

Expert opinion: The sinus implant is a revolutionary mode of localized drug delivery in CRS. Its utilization enhances wound healing, with diminished need for secondary postoperative medical and surgical interventions. Such novel technology has far-reaching implications, with future indications likely extending beyond the operating room into the clinic setting, to treat CRS patients, with inflammatory exacerbations or recurrent polypoid disease, who would otherwise require additional surgery.

Keywords: bioabsorbable, chronic rhinosinusitis, corticosteroid, drug-eluting, endoscopic sinus surgery, implant, inflammation, mometasone furoate, polyactide-co-glycolide

Expert Opin. Drug Deliv. [Early Online]

1. Overview of the market

Chronic rhinosinusitis (CRS) represents one of the most common healthcare problems in the United States, with 1 in 7 adults affected and 31 million individuals newly diagnosed each year [1-3]. The precise etiology of CRS remains unclear, but mucosal inflammation is understood to be one of the main underlying causes for its pathogenesis [4-8]. It has been established that even minimal inflammation in a localized but critical location (i.e., ostiomeatal complex) can lead to significant pathology in surrounding areas and incite widespread sinonasal disease [9]. Nasal obstruction/congestion, facial pain/pressure, mucopurulent drainage and diminished olfaction are common symptoms of CRS [10,11]. Significant adverse effects on quality of life have been well-documented, with CRS patients reporting greater bodily pain and impaired social functioning than other chronic diseases (i.e., congestive heart failure, chronic obstructive pulmonary disease) [3,12-14].

Medical management of CRS encompasses a broad spectrum of therapeutic modalities including antibiotics, corticosteroids, saline irrigations, immunomodulators, etc. [4,15-17]. Patients with persistent symptoms despite optimal medical therapy
will require surgical intervention for symptom improvement. Introduced into the United States in 1985, endoscopic sinus surgery (ESS) has been found to represent an effective method of surgical treatment for CRS, with success rates of 76–98% 

[18-21]. ESS involves restoration of functional paranasal sinuses through identification of sites of inflammation, focused removal of diseased tissue and judicious widening of natural drainage pathways. These maneuvers serve to relieve sinonasal obstruction, re-establish ventilation and facilitate mucociliary flow. Multiple studies have demonstrated the efficacy of this procedure, with significant improvements in individual symptoms, general health status and overall quality of life [22-28].

However, the success of ESS is contingent upon optimization of the wound healing environment during the postoperative period [29]. There is strong evidence to indicate that postsurgical endoscopic debridement of the sinonasal cavity prognosticates disease recidivism and potential need for revision ESS [18]. Consequently, meticulous postoperative care following ESS, as opposed to other surgical intervention for the sinuses, has been recognized to be just as critical as the surgery itself in ensuring long-term positive surgical outcomes [10,18,30,31]. Local complications such as synechiae formation, middle turbinate (MT) lateralization and stenosis of surgically enlarged ostia can lead to recurrent sinonasal obstruction and eventual surgical failure. Residual inflammation can also impede mucosal recovery and incite polypoid disease, further compromising surgical results [18,32-35]. Numerous postoperative strategies, both mechanical and pharmaceutical, have been developed to mitigate such issues including saline rinses, stents/spacers, steroids and medicated irrigations [36-39].

ESS is considered to be adjunctive treatment to overall medical management. As it does not address the underlying causes of CRS, sinus surgery must be integrated with ongoing pharmacotherapy to address mucosal inflammation [4,9]. Oral and topical corticosteroid therapy has emerged as an integral component in the maintenance of successful postsurgical outcomes. Topical steroids enhance postsurgical mucosalization by decreasing edema, granulation tissue and fibrin deposition. [40,41]. A short course of systemic steroids given after ESS (30 milligrams (mg) prednisone, 9 days) leads to significant short- (2–4 weeks) and medium-term (3–6 months) endoscopic improvement of the dissected sinonasal cavity [42]. However, adverse effects associated with systemic administration (i.e., adrenal insufficiency, decreased bone density, cataract formation, etc.) restrict prolonged use [43]. On the other hand, topical intranasal steroids (sprays, drops, irrigations) have been shown to be of symptomatic and objective benefit in CRS, without increased risk of systemic toxicities even with long-term treatment [44-50]. Consequently, standard intranasal steroid sprays are recommended as part of routine postoperative practice, and nonstandard topical steroid solutions have also been recognized as potential options in postsurgical management [50]. However, pattern of deposition for intranasal steroid preparations has shown minimal sinus penetration [51-53]. The actual amount of steroid reaching target sinonasal tissue from nasal sprays is unknown, as a large proportion has been found to be expelled through the nostrils [36]. However, pattern of deposition for intranasal steroid preparations has shown minimal sinus penetration [51-53]. 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2. How the technology works

The Propel sinus implant device was developed by Intersect ENT (Palo Alto, California) and is currently the only Food and Drug Administration (FDA)-approved product (August 2011) that offers targeted steroid delivery directly to sinus mucosa with simultaneous stenting of the sinonasal cavity (Figure 1A) [56]. The implant is comprised of a biodegradable polylactide-co-glycolide (PLG) polymer matrix which is infused with 370 micrograms (µg) of mometasone furoate (MF).

The PLG polymer is a biomedical substance that is commonly used in suture material (i.e., vicryl sutures). When incorporated into sutures, the individual polymer fibers are braided together to form a multifilament structure which increases its tensile strength. Processing compounds are then utilized to bind the filaments, with the addition of coloring and lubrication to facilitate suturing of tissues. However, in the Propel implant, the polymer is processed as a monofilament with no lubricants, colorants, nor other finishing materials applied. It is also constructed in an open-lattice configuration, which gives the implant its unique expansile properties. These characteristics have made the implant biologically inert, with no inflammatory nor foreign body reaction elicited in response to the implant’s presence or degradation [57,58]. This is in stark contrast to vicryl PLG sutures, which are characterized by macrophage and multinucleated giant cell infiltration.

The PLG forms the backbone of the implant, which is covered by a drug-releasing layer comprised of PLG, polyethylene glycol (PEG) and MF. PEG serves as an anti-inflammatory, protein-resistant barrier that influences water retention and promotes tissue biocompatibility. It also assists in controlling the rate of elution of MF from the implant, which, in turn, is dictated by a diffusion mechanism that is regulated by drug concentration, chemical composition, substrate type, polymer morphology and coating layer thickness [58]. All of these factors allow the steroid to be gradually eluted into surrounding tissue in a measured fashion over a 30-day period as the implant dissolves. Peak concentrations are attained at 7 – 13 days post implant, with > 90% of the steroid released by 13 days [58]. MF is a potent corticosteroid which acts to reduce inflammation, fibrin deposition and granulation tissue [55]. Its effectiveness in the treatment of NP is well-documented, and it remains the only intranasal steroid in which CRS with NP is specifically designated as an indication for its use [59-64]. Because of its high potency, established safety, and low bioavailability (< 0.1%), MF serves as an ideal candidate for topical drug delivery [55].

Analysis of implant resorption has demonstrated the dissolution process to occur in a predictable fashion, with 15% of the stent remaining at 30 days and 0.2% at 60 days post implantation [56]. The PLG is gradually degraded and bioabsorbed via hydrolysis, with no cellular nor enzymatic involvement [65,66]. As the implant absorbs water from the adjacent environment, a decrease in molecular weight and mass loss leads to structural breakdown and softening of the implant scaffold [67]. This induces a reduction of radial force 2 – 3 weeks after implant placement. Degradation by-products (glycolic acid, lactic acid) are metabolized by the tricarboxylic acid cycle into carbon dioxide and water, which are removed from the implant site by vasculature from the surrounding tissues [65-68].

The spring-like design of the implant enables its function as a spacer. The sinus implant acts to physically separate healing sinonasal tissues when it expands into the dissected sinus cavity. This expansile capability prevents MT lateralization and synechiae formation. When compressed, the implant has a diameter of 5.2 millimeters (mm). A single-handed delivery device is used to deploy the implant, which once released,
Figure 2. Single-use delivery systems for deployment of the Propel (A) and Propel mini (B) into the ethmoid cavity. The curved tip facilitates placement of the Propel mini in patients with narrower sinus anatomy or less extensive ethmoid surgery.

widens to a diameter of 23 mm (Figure 2A). It is inserted intraoperatively under endoscopic visualization during ESS into the ethmoid sinus; allowing direct, sustained application of MF to the diseased sinonasal mucosa following surgery (Figures 3A, 3B, 4) [56]. Since the original Propel implant prototype, a smaller version has been created for use in patients undergoing less extensive sinus surgery or possessing narrower sinonasal anatomy (Figure 1B). Known as the Propel mini, this implant has a compressed diameter of 4.0 mm (versus 5.2 mm), which enlarges to 16 mm (versus 23 mm) upon maximal expansion. Constructed with the identical biomaterials, open-lattice design and MF dosage (370 µg), the Propel mini is likely to provide the same clinical benefits as the standard Propel. It was approved by the FDA in November 2012 for deployment into the ethmoid sinuses, but the Propel mini could be potentially used in the frontal and maxillary sinuses given its smaller profile. The delivery system for the mini has a more curved tip than that used for the Propel (Figure 2B).

While the Propel and Propel mini were designed for use in conjunction with sinus surgery to enhance postoperative outcomes, a third steroid-releasing sinus implant is currently being investigated for application in the clinic setting. Comprised of the same bioabsorbable polymers, the in-office implant has similar steroid-eluting and self-expandable properties as the Propel, which enable it to conform to a previously dissected ethmoid cavity. However, it has a unique design features and increased radial strength, which allow it to mechanically dilate a reobstructed sinus and secure the implant in place for a longer period of time. A single-use delivery system is used to insert the implant into the ethmoid cavity by depressing a plunger. Once deployed, the eight-pronged implant expands radially to physically expand the obstructed sinus while concomitantly releasing MF onto sinonasal mucosa over the course of 3 months. This procedure can be performed during a routine physician office visit under endoscopic visualization by using the same topical anesthesia as nasal endoscopy. Such in-office implantation may prove beneficial in managing NP and potentially obviate the need for oral steroid therapy or revision ESS in the future.

3. Clinical profile and post-marketing findings

The Propel steroid-releasing sinus implant is currently the only product with level 1A evidence to support its utilization in sinus surgery [69-71]. Published findings from animal and clinical studies for sinus implantation are summarized in Table 1. The performance, safety and tolerance of this technology were first explored using a rabbit model [58]. Smaller versions of the implants (1.5 centimeters (cm) in diameter, 0.6 cm in height) were coated with MF (100 µg) and placed into the maxillary sinuses (MSs) of 31 rabbits. Therapeutic doses of steroid (range, 175 – 28,189 nanograms/gram (ng/gm)) were attained within MS and nasal tissues in a time-dependent manner, with peak levels at days 7 – 13 and a gradual decline thereafter. Greater than 90% of the steroid was released by 13 days, with drug concentrations higher in MS versus nasal mucosa. Plasma MF levels were below the lower limit of quantification (15 picograms/milliliter (pg/ml)), indicating negligible systemic absorption. Pathologic analysis of mucosal specimens showed mild epithelial ulceration and no inflammation, fibrosis or bony reaction. By 6 weeks, the implant had completely resorbed into the sinus wall through overgrowth of adjacent stromal tissue at points of contact. At 18 weeks, histologically normal epithelium was observed with complete reconstitution of mucosal integrity. Sites that had incorporated the implant were indistinguishable from the rest of the mucosa. This preclinical study successfully illustrated the effectiveness of this mode of drug delivery as well as its biocompatibility with sinonasal tissue [58].

The safety and efficacy of mometasone-coated, bioabsorbable implants were first clinically tested in a pilot study conducted by Murr et al. [56]. A multicenter (4 sites), DB-RCT was performed on 43 adult CRS patients (minimum Lund McKay (LM) score of 6) undergoing ESS; 28% had concurrent NP, and 37% had a history of previous sinus surgery. Using an intrapatient control design, 38 patients received the steroid-eluting sinus implant on one side and the identical, non-steroid-eluting implant on the contralateral side. The remaining five patients had bilateral steroid-releasing implants placed to assess for systemic safety. Preoperatively, oral steroids were not permitted 14 days prior to sinus surgery. However, topical intranasal steroid sprays were allowed up to the day of surgery, and weight-adjusted intravenous decadron (4 – 20 mg) was administered at the time of ESS. Postoperatively, oral and topical intranasal steroids were disallowed for the first 30 days after surgery. Efficacy endpoints were determined by endoscopic grading from on-site clinical investigators at the various study centers [56]. At 60 days follow-up, drug-eluting implants showed significant reduction in polyph formation (p = 0.0391), adhesions (p = 0.0313) and inflammation (p < 0.0003, days 21 – 45).
MT lateralization was also decreased, but not statistically significant. A strong correlation between the presence of polyps and oral steroid prescription was also observed by day 30, suggesting that improvement in the former could potentially result in diminution of the latter. In terms of safety; no local adverse events were reported, and no MF could be detected systemically (< 30 pg/ml) at all time points tested. In addition, there was no evidence of hypothalamic-pituitary-adrenal axis suppression, as mean serum cortisol concentrations remained normal both at baseline and day 30. This initial clinical trial demonstrated the efficacy of the sinus implant in improving postsurgical wound healing without incurring systemic steroid-related complications.

Murr’s pilot study was followed by the ADVANCE trial; a single-cohort, multisite (7 centers) prospective clinical evaluation [69]. The ADVANCE study was designed to further assess the performance and safety of the MF-eluting implants through analysis of ocular toxicity and effects on patient symptoms and quality of life. Ocular safety was evaluated via measurements of intraocular pressure (IOP) at baseline and day 30, as well as dilated slit-lamp examination for lens opacities. Sinusitis symptoms were determined using validated disease-specific instruments (22-item SinoNasal Outcome Test or SNOT-22, Rhinosinusitis Disability Index or RSDI). Postoperative inflammation, polypoid change, adhesion formation and MT position were again examined using the same endoscopic grading scale as the pilot study [69].

Fifty adult CRS patients undergoing ESS were enrolled, with 90 sinus implants placed; 66% had concurrent NP, and 16% had a history of prior sinus surgery. Patients had a minimum LM score of 6, and a mean LM score of 11. ESS.
Table 1. Literature summary of safety and efficacy studies of MF-eluting sinus implants.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study type</th>
<th>No. of subjects (sinuses)</th>
<th>Study groups</th>
<th>Treatment protocol</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li [57] (2009)</td>
<td>In vivo animal</td>
<td>31</td>
<td>Rabbit MS</td>
<td>MF-coated and uncoated implants placed in MS BL</td>
<td>MF levels in MS, NM, plasma; histological analysis</td>
<td>MF levels within MS&gt;NM (175 – 28,189 ng/g); Plasma MF &lt; 15 pg/ml; same tissue reaction between 2 groups</td>
<td>MF-coated implants provide local steroid delivery with no systemic absorption</td>
</tr>
<tr>
<td>Murr [55] (2011)</td>
<td>Pilot; MC DB-RCT</td>
<td>43 (86)</td>
<td>Adult CRS patients undergoing ESS</td>
<td>38: MF-eluting &amp; non-MF-eluting implants placed in IL &amp; CL ES; 5: MF-eluting implants in BL ES</td>
<td>Adhesions, MT position, NP, inflammation; plasma MF, serum cortisol levels</td>
<td>SS RR in adhesions (p = 0.0313, d30), NP (p = 0.0391, d30), inflammation (p &lt; .0003, d21 - 45). MT lat dec but not SS; No plasma MF levels; serum cortisol WNL</td>
<td>MF-eluting implants improve post-op wound healing without systemic steroid exposure</td>
</tr>
<tr>
<td>Fortwith [69] (2011)</td>
<td>ADVANCE; MC prospective uncontrolled cohort</td>
<td>50 (90)</td>
<td>Adult CRS patients undergoing ESS</td>
<td>MF-eluting implants placed into ES (10UL, 40BL)</td>
<td>SNOT-22, RSDI, adhesions, MT position, NP inflammation; IOP, slit-lamp</td>
<td>D30: SS RR NP (10-15%), LOA (44.9%, p = 0.002), post-op interventions (44%, p = 0.002). Dec in OCS (29%, p = 0.08) but not SS; No d90 change in IOP or cataracts</td>
<td>MF-eluting implants reduce need for post-op interventions with no risk to ocular safety</td>
</tr>
<tr>
<td>Marple [70] (2012)</td>
<td>ADVANCE II; MC DB-RCT</td>
<td>105 (210)</td>
<td>Adult CRS patients undergoing ESS</td>
<td>MF-eluting implant placed in IL ES, non-MF-eluting implant in CL ES</td>
<td>NP, OCS, LOA, overall post-op interventions; IOP, slit-lamp</td>
<td>D30: SS RR NP (44.9%, p = 0.002), LOA (52%, p = 0.005), post-op interventions (29%, p = 0.028). Dec in OCS (29%, p = 0.08) but not SS; No d90 change in IOP or cataracts</td>
<td>MF-eluting implants reduce need for post-op interventions with no risk to ocular safety</td>
</tr>
<tr>
<td>Han [71] (2012)</td>
<td>Meta-analysis</td>
<td>143 (286)</td>
<td>Adult CRS patients undergoing ESS</td>
<td>MF-eluting &amp; non-MF-eluting implants placed into IL &amp; CL ES</td>
<td>NP, OCS, LOA, overall post-op interventions</td>
<td>D30: SS RR in NP (46%, p &lt; .0001), OCS (40%, p = 0.0023), LOA (51%, p = 0.0016), &amp; post-op interventions (35%, p = 0.0008)</td>
<td>MF-eluting implants reduce need for OCS &amp; post-op surgical interventions</td>
</tr>
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</table>

BL, Bilateral; CL, Contralateral; CRS, Chronic rhinosinusitis; d, Day; DB-RCT: Double-blinded randomized controlled trial; dec, Decreased; ES, Ethmoid sinus; ESS, Endoscopic sinus surgery; gm, Grams; il, Ipsilateral; IOP, Intraocular pressure; lat, lateralization; LOA, lysis of adhesions; MC, multicenter; MS, Maxillary sinus; MF, Mometasone furoate; ml, milliliter; MT, Middle turbinate; No, number; NP, Nasal polyposis; ng, Nanograms; UL, unilateral; NM, Nasal mucosa; OCS, Oral corticosteroids; post-op, Postoperative; pg, picograms; RR, Relative reduction; RSDI, Rhinosinusitis disability index; SS, Statistically significant; SNOT-22, 22-item sinonasal outcome test questionnaire; VAS, Visual analogue scale; WNL, Within normal limits.
involved complete unilateral or bilateral ethmoidectomy, with concurrent septoplasty and surgical treatment of the other paranasal sinuses permitted if deemed necessary by the operating surgeon. Similar preoperative and perioperative steroid protocols were used as the pilot study. Postoperatively, no topical or oral steroids were administered for 60 days following surgery. At 1 month follow-up, polypoid tissue, significant adhesions, and MT lateralization were reported in 10, 11, and 4.4% patients, respectively. Minimal ethmoid inflammation was observed at all time points studied. In addition, significant improvement (p = 0.0001) in patient-reported outcomes (SNOT-22, RSI) were described at 30 days, 60 days and 6 months compared to baseline data. Only one local adverse event was reported – headache and sinus irritation that was exacerbated by crusting adherent to the implant. The incident occurred on day 21 and resolved upon removal. Otherwise, neither significant changes in lens opacities nor IOP were noted 30 days post surgery in all patients. Thus, the ADVANCE trial further elucidated the clinical utility of steroid-eluting implants in minimizing inflammation, adhesions and polypoid tissue formation without deleterious ocular sequelae (69).

The ADVANCE II study published by Marple et al. investigated whether the endoscopic improvements in wound healing observed in the earlier 2 clinical trials translated into direct patient benefit, with decreased need for secondary postoperative medical (oral steroid administration) and surgical (lysis of adhesions or LOA) interventions (70). A multicenter (11 sites) DB-RCT was conducted on 105 adult CRS patients (minimum LM score of 6, mean LM score of 13) undergoing ESS; 59% had concurrent NP and 29.5% had a history of previous sinus surgery. The same intrapatient control design as the pilot study was employed, with 210 ethmoid sinuses successfully implanted. NP, synchieae formation and MT lateralization were again evaluated. In addition, a new composite efficacy outcome measure was introduced to assess all postoperative interventions performed, which was defined as either the need for surgical intervention to lyse an adhesion, or oral steroid prescription to treat inflammation. Primary efficacy endpoints were graded not only by on-site clinical investigators in real-time but also by an independent panel of 3 sinus surgeons, who were tasked with reviewing postoperative day 30 video-endoscopy recordings. Panel members were blinded to treatment assignment, patient information and video origin. Safety evaluation was again conducted through IOP measurements and dilated slit-lamp lens examinations at days 0 and 90 (70).

At 1 month post implantation, 44.9% (treatment 16/85 – 18.8%, control 29/85 – 34.1%, p = 0.002), 61.6% (treatment 5/104 – 4.8%, control 13/104 – 12.5%, p = 0.039) and 29% (treatment 32/96 – 33.3%, control 45/96 – 46.9%, p = 0.028) relative reductions in NP, adhesions and postsurgical interventions, respectively, were observed by panel judgment compared to controls. The need for oral steroids also decreased by 29% (p = 0.08), but this finding was not statistically significant. Similarly, clinical investigator assessments demonstrated a relative reduction of 50.6% (p = 0.344), 43% (p = 0.033), 30.3% (p = 0.068) and 25% (p = 0.388) in NP, LOA, overall postoperative interventions and oral steroid prescription, respectively. There was also a trend towards diminished MT lateralization, but this did not reach statistical significance (p = 0.125). In addition, like the ADVANCE study, neither IOP elevations nor cataracts were observed through day 90. Only two local adverse events were reported. One patient developed granulation tissue and scarring of the MT that required implant removal and LOA on day 14. Another was found to have mucopurulence on the contralateral side following removal of the control stent. This also occurred on day 14 and was successfully treated with prednisone and antibiotics. Thus, the ADVANCE II demonstrated the effectiveness of MF-releasing sinus implantation in maintaining ethmoid patency and reducing the need for postsurgical therapeutic interventions without ocular toxicities (70).

Subsequently, Han et al. performed a meta-analysis of the aggregate data, pooled from the pilot and ADVANCE II trials (71). Collectively, 143 adult CRS with (91) and without (52) NP patients were enrolled, in which 286 implants were inserted. Combined independent panel results revealed statistically significant, relative reductions of 46% (p < 0.0001), 40% (p = 0.0023), 51% (p = 0.0016) and 35% (p = 0.0008) in NP, oral steroid administration, LOA and postsurgical interventions, respectively (Figure 5A). Clinical investigator assessments also showed a 70% relative reduction in adhesions (p = 0.0013) and 75% decrease in MT lateralization (p = 0.0225) (Figure 5B). No differences between CRS patients with and without NP were observed, with the former showing a 36% relative reduction in postoperative interventions versus 35% in the latter. This landmark study signified the first level 1A evidence demonstrating the clinical benefits of localized steroid delivery via sinus implantation during the postoperative period (71).

Although yet to be published, a pilot study of the in-office steroid-releasing implant was conducted in the United States from 2011 to 2012. This multicenter, single-arm clinical trial examined the safety and efficacy of the device in 12 postsurgical CRS patients through assessments of symptom reduction and endoscopic polyp volume over time. As preliminary data from this initial study was strong, a larger, single-blinded, multicenter RCT (RESOLVE study) of 100 CRS patients was launched in January 2013. All subjects for the Resolve study are patients with refractory CRS who had undergone ESS; but still suffered persistent symptoms secondary to recurrent sinonasal obstruction from NP. Patients are randomized into a treatment arm (n = 50), in which in-office sinus implantation was performed, or a control arm (n = 50) in which an in-office procedure was feigned but no actual implant placed. Like the ADVANCE trials, objective grading of recorded endoscopic examinations, patient-reported outcomes, and ocular safety will be assessed.
up to 6 months following sinus implantation. Enrollment and follow-up for the RESOLVE study is expected to be completed by early next year.

4. Alternative technologies

Drug-eluting devices have been recognized as potential therapeutic options to enhance wound healing and optimize post-surgical outcomes following ESS [36]. Countless nasal dressings comprised of a vast array of biomaterials (hyaluronic acid, chitosan, silastic, etc.) and designs (sponges, sheets, gels) have been devised, in an attempt to counteract adherence between healing sinonasal tissues in the postoperative setting [41,72-86]. However, their clinical utility remains controversial, with incidence of synechiae formation anywhere from 7 – 55%, depending on the product used [72-74]. More recently introduced resorbable nasal dressings (i.e., carboxymethylcellulose, polyurethane foam, etc.) have been associated with lower adhesion rates (7 – 10%) than earlier formulations [80,82,83]. Nevertheless, none have been FDA-approved for concurrent drug delivery to address mucosal inflammation.

Infusion of steroids into both absorbable and nonabsorbable spacers, stents and various packing materials have been reported as an off-label alternative, in an effort to provide targeted release of anti-inflammatory agents close to the pacemaker, sinonasal sinuses [41,72,77,87-90]. The only other level 1 clinical study besides the ADVANCE studies thus far was conducted by Cote et al. who described significant improvement in postoperative healing following sinus surgery with the use of triamcinolone-impregnated bioresorbable nasal dressings [87]. The latter was comprised of biodegradable synthetic polyurethane foam which rapidly fragments upon exposure to water, with > 90% dissolution after 5 days [82]. 19 CRS patients with NP undergoing ESS were enrolled in a DB-RCT and received a triamcinolone-filled (triamcinolone acetonide solution 40 mg/ml, 2 ml), absorbable nasal dressing (Nasopore; Stryker, Ontario, Canada) in one nasal cavity and the identical saline-soaked (normal saline, 2 ml) packing in the contralateral side. Statistically significant superior nasal endoscopy scores (Lund-Kennedy, Perioperative Sinus Endoscopy) were evident in the treatment group 3 and 6 months after surgery versus controls. However, an acknowledged limitation of this study was the variability in consistency and duration of drug delivery to sinonasal tissue [87].

The Relieva Stratus MicroFlow spacer (Acclarent, Menlo Park, California) is a nonabsorbable stent with drug-eluting capabilities [88-90]. It is comprised of a membrane, balloon-like reservoir that contains several hundred micropores which enable gradual seepage of therapeutic agents into surrounding tissues over a prolonged period of time. The device can be instilled with any liquid compound, including steroids (Kenalog-40, triamcinolone acetonide solution 40 mg/ml, 0.32 ml). However, only saline has been FDA-approved for use with this device. All other applications are considered to be off-label. A catheter shaft is present with a one-way valve within the reservoir to prevent backflow, and nitinol retention wings are attached to secure the stent in proper position. The microporous spacer can be deployed into the ethmoid or frontal sinuses using a catheter guide-based system, and left in place for 14 – 28 days at which time it can be removed in the office. In a single-cohort, prospective study; 23 CRS patients treated with 40 triamcinolone-loaded ethmoid stents showed significant improvement in SNOT-20 and LM scores 6 months after placement [89]. No complications were reported. However, like the steroid-infused Nasopore dressing, precise dosing and duration of corticosteroid delivery were unknown. The Relieva Stratus MicroFlow spacer has since been withdrawn from the US market, but is still available internationally.

No randomized, multicenter, controlled clinical trials have been performed investigating the safety and efficacy of the aforementioned devices to support their use in the

Figure 5. Meta-analysis efficacy endpoints at day 30 of treatment group as determined by independent panel review of endoscopic video recordings (A) and real-time on-site clinical investigators (B) Tx: treatment.

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**Table:**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Post-operative</th>
<th>Surgical</th>
<th>Oral steroid</th>
<th>Frank polyposis</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>60%</td>
<td>40%</td>
<td>51%</td>
<td>-51%</td>
</tr>
<tr>
<td>Treatment</td>
<td>35%</td>
<td>51%</td>
<td>40%</td>
<td>-46%</td>
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</tbody>
</table>

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<table>
<thead>
<tr>
<th>Percent of sinuses</th>
<th>p = 0.00008</th>
<th>p = 0.0016</th>
<th>p = 0.0023</th>
<th>p &lt; 0.0001</th>
</tr>
</thead>
</table>

A. Percent of sinuses:

- Post-operative interventions
- Surgical interventions
- Oral steroid interventions
- Frank polyposis

B. Meta-analysis real-time grading:

- Middle turbinate lateralization
  - Control: 75%
  - Treatment: 70%

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**Figure 5:** Meta-analysis efficacy endpoints at day 30 of treatment group as determined by independent panel review of endoscopic video recordings (A) and real-time on-site clinical investigators (B) Tx: treatment.
postsurgical environment. In addition, specific pharmacodynamics of steroid release with these methods of topical drug delivery have yet to be determined. At present, the MF-eluting sinus implant remains the only product FDA-approved for delivery of corticosteroids directly to sinonasal tissues following ESS.

5. Conclusion

The advent of steroid-releasing sinus implantation marks a revolutionary mode of topical drug delivery in the postoperative management of CRS. Not only do the implants provide sustained, controlled application of MF directly to sinonasal mucosa, but they also serve as self-expanding, bioabsorbable stents, mechanically opening the dissected surgical cavity to preserve ostial patency. This dual functionality has led to significantly enhanced wound healing following ESS, with reduced adhesions, MT lateralization, polypoid change and ethmoid inflammation, as demonstrated by 3 clinical trials and a meta-analysis of the aggregate data. Endoscopic improvements have translated into direct patient benefits, with diminished need for secondary postoperative medical and surgical interventions. Such novel technology has far-reaching implications, with potential applicability beyond the operating room into the clinic setting, to treat CRS patients with inflammatory exacerbations or recurrent disease that may otherwise require additional surgery. Thus, further investigation is still needed to determine the long-term clinical efficacy as well as future applications of sinus implantation.

6. Expert opinion

As early postoperative healing has been known to be a harbinger of long-term surgical success, therapeutic modalities that enhance tissue recovery following sinus surgery can contribute to improved patient outcomes. The introduction of steroid-eluting sinus implants signifies a novel approach to localized drug delivery in the treatment of CRS, as the implants are able to physically dilate and simultaneously deliver topical anti-inflammatory medications directly to sinonasal mucosa. CRS patients often harbor mucosal inflammation in the immediate postoperative period that can serve as a nidus for recurrent disease and require revision ESS if left untreated. Consequently, continuous, targeted corticosteroid therapy to inflamed sinus tissue is extremely advantageous, as it facilitates normalization of the postoperative sinus cavity which is pivotal in optimizing surgical results. Such focused steroid application also minimizes the need for oral steroids, avoiding potential complications. The self-expanding feature of the implant ameliorates apposition of healing mucosal tissues, decreasing scar formation between the MT and lateral nasal wall. The latter helps maintain ethmoid sinus patency which, in turn, enhances access of saline irrigations and other topical therapies. Thus, by addressing the underlying inflammation and maintaining sinus patency, the Propel sinus implants are able to promote postoperative wound healing and significantly improve surgical outcomes.

The safety and effectiveness of this bioabsorbable implant technology has been demonstrated by 3 comprehensive, well-executed, multicenter clinical trials and a meta-analysis of the aggregate data, which encompassed over 200 CRS patients. Evaluation of these studies revealed rigorous scientific protocols with well-delineated efficacy endpoints; uniform, standardized grading instruments across multiple sites; and the unique incorporation of an independent panel of rhinologists to review randomized endoscopic video recordings for complete blinded assessment. Pooled analysis of efficacy data from the pilot and ADVANCE II trials illustrated the direct patient benefit derived from the steroid-eluting sinus implants; with reductions in inflammation, polyps, adhesions and MT lateralization leading to diminished need for subsequent medical and procedural interventions. Such results are particularly compelling given that steroid therapy was withheld during the postoperative period, and that these outcomes were achieved in a patient population in which a significant proportion presented with NP, a history of prior sinus surgery and extensive disease (mean LM of 13) upon study entry.

In terms of product safety; only 3 adverse effects have been reported thus far with sinus implantation, all of which were minor and local in nature. These included crusting, scarring, infection and granulation tissue, that resolved either with implant removal and/or antibiotics. Some of these adverse effects could have resulted from the CRS disease process itself or even due to the natural healing process after ESS. Neither adverse systemic effects nor ocular toxicities have been documented in association with implant use. The maximal daily dose of MF released by the implant is significantly less than the daily dose of intranasal MF spray deemed safe and effective in the treatment of allergic rhinitis. Estimated at 200 µg per side, a 1-month course of MF intranasal spray would be equivalent to 12 mg, much greater than the 370 µg delivered by the implant. An inhaled bronchial dose of 1600 µg/day of MF has been found to be necessary to detect any adverse systemic effects, including reduction in plasma cortisol. Accordingly, MF plasma levels have remained below the quantifiable threshold with implantation, and serum cortisol concentrations have also been within normal limits. Ophthalmologic tests of ocular safety conducted in the ADVANCE (day 30) and ADVANCE II (day 90) trials also revealed no clinically significant changes in IOP nor lens opacities compared to baseline. However, cost issues rather than safety or clinical efficacy may prove most prohibitive in the widespread adaptation of sinus implantation in rhinology practice. The current listed price for the Propel and Propel mini is 695 dollars per implant. Further studies are necessary to elucidate what the cost-effectiveness of the sinus implant will ultimately be.
Such an investment may prove worthwhile if the device reduces the need for postoperative interventions and revision ESS is averted.

Future indications for sinus implantation will likely extend beyond the operating room into the clinic setting, to encompass treatment of CRS patients who develop recurrent inflammatory disease despite previous surgical intervention [94,95]. The in-office steroid-eluting implant, currently undergoing active clinical trials, can be placed into a previously operated but reobstructed ethmoid cavity, gradually releasing corticosteroids to target tissue over the course of 3 months. Such localized drug delivery technology holds significant promise as a potential treatment alternative for CRS patients who experience periodic inflammatory exacerbations or NP relapse following previous ESS. The in-office sinus implant may also obviate the need for oral steroid therapy as well as revision ESS, avoiding potential morbidities associated with either therapeutic modality. Preliminary data from the pilot study have shown the in-office steroid-releasing implant to represent a promising treatment option for such refractory CRS patients, who would otherwise require additional surgery or systemic steroids to manage recurrent polypoid disease.

Balloon dilation technology has been introduced as a surgical device [96-100]. These devices can dilate sinus ostiums and also be utilized in conjunction with sinus procedures such as an ethmoidectomy. Balloon sinus dilatation has received significant attention in recent years as a potential option in the management of CRS, but has had a somewhat limited role in long-term therapy as it does not address the underlying inflammatory process. However with sinus implantation into the dilated ostium in conjunction with balloon sinus dilatation, the surgical opening can be accompanied by corticosteroid elution to diminish adjacent inflammation that may compromise ostial patency. The combination of balloon ostial dilation with sinus implantation may emerge as an effective, minimally invasive, in-office alternative to ESS for a certain subset of CRS patients.

Looking forward, MF-releasing sinus implants likely represent just the beginning of an entire new spectrum of devices that will assuredly be launched in the future, which will exhibit both drug-eluting and mechanical stenting capabilities. Although the Propel implants were initially designed and FDA-approved for use in the postsurgical ethmoid cavity only, other implants may be engineered using a similar platform to conform specifically to the maxillary, sphenoid and frontal sinuses. Accordingly, implants could be envisioned that would be customized to fit into each of the respective sinuses, which would serve as vehicles for topical steroid delivery in the management of peripheral sinus disease. In addition, it is conceivable that the implant polymer matrix could be loaded with medications other than MF, including high-dose antibiotics, other anti-inflammatory agents or various combinations of drugs. This opens the door to a vast array of topical pharmaceutical therapies that could be administered to each of the sinuses in this manner; for purposes of accelerating postoperative wound healing, treating recurrent infection or managing residual inflammation. Thus, the steroid-eluting sinus implants have ushered an exciting, new era of localized drug delivery technology in the therapeutic management of CRS, which will undoubtedly witness continued growth and innovation in the years to come.

Acknowledgment

The authors acknowledge Intersect ENT for providing additional information regarding the bioengineering of the implant, data on upcoming clinical studies and the illustrations in Figures 1, 2, 4 and 5B.

Declaration of interest

J Han is a consultant for Intersect.
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