

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Sinus Implant
Device Trade Name:	Propel™
Applicant's Name and Address:	Intersect ENT 1049 Elwell Court Palo Alto, CA 94303
Premarket Approval Application (PMA) Number:	P100044
Date of Panel Recommendation:	None
Date of Notice of Approval:	August 11, 2011
Expedited:	Not applicable

II. INDICATIONS FOR USE

The Propel™ is intended for use in patients ≥ 18 years of age following ethmoid sinus surgery to maintain patency, thereby reducing the need for post-operative intervention such as surgical adhesion lysis and/or use of oral steroids. The Propel™ separates mucosal tissues, provides stabilization of the middle turbinate, prevents obstruction by adhesions, and reduces edema.

III. CONTRAINDICATIONS

The use of the Propel™ is contraindicated in the following patients:

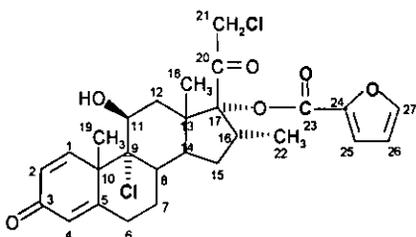
- Patients with suspected or confirmed intolerance to mometasone furoate.
- Patients with a known hypersensitivity to lactide, glycolide or caprolactone copolymers.

IV. WARNINGS AND PRECAUTIONS

Please refer to the labeling.

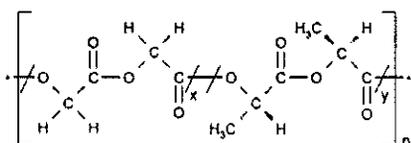
V. DEVICE DESCRIPTION

The Propel™ is a bioabsorbable implant designed to maintain patency of the sinus cavity. The Propel™ is manufactured from a synthetic bioabsorbable copolymer, poly (L-lactide-co-glycolide) (PLG). The implant contains mometasone furoate (active ingredient), a synthetic corticosteroid with anti-inflammatory activity. Mometasone furoate is a white to off-white powder. The chemical name is 9 α ,21-dichloro-11 β ,17 α -dihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17-(2-furoate), with the empirical formula C₂₇H₃₀Cl₂O₆, and a molecular weight of 521.43 g/mol. Mometasone furoate is a hydrophobic drug that is practically insoluble in water. Mometasone furoate is stable under aqueous, acidic and oxidative conditions. MF can degrade under extreme basic, thermal and photolytic conditions. The chemical structure is shown. The drug is embedded in a bioabsorbable polymer matrix containing poly-(DL-lactide-co-glycolide) and polyethylene glycol (inactive ingredients) which provides for gradual release of the drug.



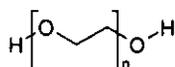
Chemical structure of mometasone furoate

The inactive ingredients on the sinus implant are poly-(DL-lactide-co-glycolide) and polyethylene glycol. Poly-(DL-lactide-co-glycolide) is an amorphous biodegradable polymer. The chemical structure is shown below.



Chemical structure of poly-(DL-lactide-co-glycolide)

Polyethylene glycol is a hydrophilic polyether compound that is highly flexible. It is non-toxic and non-immunogenic. The chemical structure is shown below.



Chemical structure of polyethylene glycol

The implant is designed to accommodate the size and variability of the post-surgical ethmoid sinus anatomy. The Propel™ is designed to be inserted by a physician under endoscopic visualization and once inserted, the implant is designed to be self-retaining against the mucosa of the surgically enlarged sinus. A delivery system is provided to access the ethmoid sinus and insert the implant.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

A variety of adjunctive devices are available and commonly placed or applied following functional endoscopic sinus surgery (FESS). These devices are referred to as either packing, structured stents or injectable space-filling gels/stents.

VII. MARKETING HISTORY

The Propel™ has not been marketed in or outside of the United States.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Observed Adverse Events: Adverse events were reported in three prospective clinical trials conducted in the United States, including 205 patients and a total of 400 sinus implants. Of these 400 implants, 250 were the Propel™ and 150 were non-drug-eluting controls. The overall incidence rate of device-related adverse events on a by-patient count was 1.5% (3/205 patients). One event was a headache with nasal burning and two were recurrent sinusitis. All three events resolved without sequelae. No patients withdrew due to an adverse event and no deaths occurred during any of the three trials. Adverse events (regardless of relationship to implant) reported in $\geq 2\%$ of patients across all three trials are displayed in **Table 1**.

Table 1: Adverse Events Occurring in $\geq 2\%$ of Patients

Adverse Event Type	Percent of Patients Reporting
Sinusitis	32.2
Headache	5.4
Epistaxis	2.0
Bronchitis	2.0

Note: Events were tabulated through day 90 from the pivotal study and through 60 days in the supportive studies.

Potential Adverse Effects: Potential adverse effects associated with the Propel™ are anticipated to be similar to those associated with other sinus stents, gels or packing.

Potential adverse effects associated with the Propel™ include, but may not be limited to:

- Premature displacement of implant or small implant fragments out the nares
- Swallowing implant or implant fragments
- Adherence of crusting to implant, resulting in, or contributing to sensations of pain/pressure/headache
- Aspiration of small implant fragments (not observed in clinical trials)
- Foreign body response, including formation of granulation tissue

Potential risks or side effects associated with intranasal mometasone furoate include:

- nasal irritation
- hypersensitivity reaction
- intranasal bleeding
- localized infection (bacterial, fungal or viral) in the nose or pharynx

- nasal burning
- nasal dryness
- susceptibility to secondary infections due to bacteria, fungi or viruses
- glaucoma/elevation of intraocular pressure
- cataracts/change in lens opacities
- headache
- pharyngitis

Potential risks or general side effects associated with steroids:

- alteration of the HPA axis including growth suppression
- immunosuppression
- hypersensitivity reactions
- headache
- epistaxis
- coughing
- vomiting
- candidiasis
- glaucoma/elevation in intraocular pressure
- cataracts/changes in lens opacities
- arthralgia
- myalgia

IX. SUMMARY OF PRECLINICAL STUDIES

The following section provides a summary of the non-clinical studies conducted to support the Propel™.

A. Laboratory Studies

Biocompatibility

Biocompatibility testing was conducted in accordance with ISO 10993, Biological Evaluation of Medical Devices — Part 1: Evaluation and Testing. The testing was conducted in accordance to the FDA Good Laboratory Practice (GLP) regulations (21 CFR, Part 58). Biocompatibility testing was performed on finished, sterilized devices to ensure the raw materials, manufacturing processes and sterilization processes result in a biocompatible product.

The results of the biocompatibility studies indicate that the Propel™ is biocompatible.

Table 2 provides a summary of the biocompatibility testing conducted on the Propel™ implant.

Table 2: Summary of Propel™ Biocompatibility Testing

Test	Requirement	Test Article	Result
Cytotoxicity MEM Elution (ISO 10993-5)	Samples are extracted. The sample extract is placed in contact with monolayer of L-929 cells and incubated for 72 hours. Cells are scored for cytopathic effect. Reactivity grades of ≤ 2 are considered non-cytotoxic. This test is designed to evaluate cytotoxicity of the extract materials	Implant and Delivery System	PASS (non-cytotoxic)
Sensitization ISO Guinea Pig Maximization Sensitization (ISO 10993-10)	Sensitization tests for adverse reactions in animals by exposing skin to extracts from the device and injecting and/or topically applying them to the animal. Sensitization reactions are noted by observing redness and swelling as it interacts with the body's immune system. Sensitization scores of less than 1 are considered non-sensitizing.	Implant and Delivery System	PASS (non-sensitizing)
Subchronic Toxicity Subchronic (30 day) Intravenous Toxicity – Mouse (ISO 10993-11)	Test substance or extract is administered to the animal for 14 days. The animal is observed each day for signs of toxicity: weight change, appetite, signs of disease or abnormal behavior. The effects are then evaluated and a histopathology is conducted on all animals.	Implant	PASS (non-toxic)
Irritation ISO Intracutaneous Reactivity (ISO 10993-10)	Irritation tests the reaction to a single, repeated or continual exposure from device materials that may produce skin, mucosal, or eye irritation—a local tissue response characterization by the usual signs of inflammation—redness and swelling, and could be accompanied by heat and pain. The test sample is considered a non-irritant if the difference between mean score of the test and the control is less than or equal to 1.	Implant and Delivery System	PASS (non-irritant)
Genotoxicity Reverse Mutation Assay (Ames test) (ISO 10993-3)	These tests use cell cultures to determine gene mutations, change in chromosome structure and number, and other gene toxicities caused by medical devices, material, or their extracts. These tests are used to determine the potential mutagenic activity of a slide test sample extract. The assay is based on exposing a large number of the test organisms to the test sample extract in agar plates. The agar plates are monitored for growth of revertants which are counted and used to estimate the mutagenic potential of the test article. For the AMES test the tested strains achieved appropriate response for genotype verification. For chromosomal aberration the critical value for chi-square test ≤ 3.841 . For the mouse lymphoma testing, the cultures have a mutant frequency < 1.8 fold higher than that of the concurrent negative control groups.	Implant	PASS (non-mutagenic)
Genotoxicity Chromosomal Aberration (ISO 10993-3)		Implant	PASS (non-clastogenic)
Genotoxicity Mouse Lymphoma (ISO 10993-3)		Implant	PASS (non-mutagenic)

In vitro Testing

The Propel™ was tested to evaluate mechanical performance after sterilization, extreme conditioning and simulated transportation to verify the Propel™ performs as intended and that the packaging performs as intended by preventing damage to the device and the sterile barrier during sterilization and transportation.

Table 3 summarizes the bench tests performed and results for the Propel™. Results of the tests demonstrate that the Propel™ performs as intended and meets the product specifications.

Table 3: Summary of Bench Testing

Test	Requirement	Results
Implant Testing		
Dimensional Inspection	The implant is inspected and measured to verify that it contains 18 crowns and that the strut length is between 24-26mm.	Pass
Post Deployment Diameter	The implant is deployed (simulating clinical use). The diameter is measured post deployment and verified to be at least 4cm.	Pass
Implant Integrity Inspection	The implant is inspected to verify the structural integrity is maintained after multiple crimp and deploy cycles	Pass
Implant Bond Joint Tensile Strength	The force required to break the bond joint is measured and verified. The strength of the bond joint must be sufficient to withstand clinical use.	Pass
Integrity Inspection (Visual)	The implant surface is inspected and the integrity of the coating is verified.	Pass
Integrity Inspection (Analytical)	Total mometasone furoate content is determined and verified to be within 10% of label claim.	Pass
Implant Radial Strength	The radial strength of the implant is measured and verified. The testing is conducted to verify the force exerted by the implant will be adequate to stabilize the middle turbinate and maintain patency of the sinus cavity.	Pass
Ethmoid Sinus Model	The implant is placed in an ethmoid sinus model. The implant must be able to stabilize the middle turbinate and maintain patency of the sinus over time.	Pass
Inherent Viscosity	The entire implant is dissolved and the viscosity is measured. The inherent viscosity is calculated and verified to ensure the strength of the polymer, and thus the mechanical performance of the implant, is maintained.	Pass
Delivery System Testing		
Delivery System Functional Testing	The delivery system is tested to verify proper function. The delivery system must function as intended in the clinical setting.	Pass
Applicator Tensile Strength	The tensile strength of the applicator is measured and verified. The applicator bond joint must have sufficient strength to withstand implant delivery and deployment in the clinical setting.	Pass
Delivery Handle Tensile Strength	The tensile strength of the delivery system bond joints is measured and the strength verified. The delivery handle bond joints must have sufficient strength to withstand implant delivery and deployment in the clinical setting.	Pass
Complete Device/Packaging Inspection		
Visual Inspection	The package is inspected to verify all components have been included, that they are free from damage and that the labels are legible and contain the correct information.	Pass

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B. Animal Studies

Intersect ENT conducted a series of animal studies evaluating various mometasone furoate-eluting formulations (e.g. drug dosages) and polymer control implants. These studies were conducted in the maxillary sinuses of New Zealand white rabbits. Implants were scaled to fit the rabbit anatomy. One hundred and thirty-six implants were evaluated in 68 rabbits. Evaluations conducted at various time points throughout the studies included: biological response to the implant, bioabsorption, mechanical effects and drug release characteristics. In addition, drug levels in plasma and tissue were quantified over time. Data from these studies provided an assessment of the safety of the product over a range of time points. The results of these tests support the safety and biocompatibility of the Propel™.

C. Additional Studies

Chemistry, Manufacturing and Controls (CMC) Testing

Testing routinely performed on the Propel™ is summarized in **Table 4**.

Table 4: CMC Release Testing

Test	Requirement
Appearance	Implants are visually inspected and verified to meet the acceptance criteria. The implant must contain the appropriate number of loops and cross joints. The implant must be free from damage, deformation, and contamination. Implant coating must have the appropriate texture and appearance.
Drug Identity	Assays are conducted to verify the identity of the drug substance, mometasone furoate, on the implant. The MF peak retention time and maximum wavelength must agree with the reference standard.
Drug Content	Assays are conducted to quantitatively determine the total amount of mometasone furoate on the implant and to verify the drug content meets the specification. The average value of the samples tested must lie within 10% of label.
Content Uniformity	Ten units are tested to verify the content uniformity meets the specification. The Content Uniformity is calculated per USP 31 <905> as a Case 5 (solids in single unit containers with multiple components).
Degradation Products/Impurities	Assays are conducted to quantitatively determine the amount of impurities and degradation product on the implant and to confirm the acceptance criteria is satisfied. Individual Impurities ≤ 1% Total Impurities ≤ 2%
Release Rate	The <i>in-vitro</i> release is measured by quantifying the amount of drug released at multiple time points. The release rate must be within the specified range at each time point following USP 31 <724>.
Residual Solvent	Assays are conducted to verify that residual levels of solvents used in the manufacturing process are below the acceptable levels established for finished goods release.

Stability/Shelf-Life

Stability and aging studies were conducted to establish the shelf-life/expiration date for the Propel™. Stability testing was conducted per ICH Q1A(R2), *Stability Testing of New Drug Substances and Products*. Appropriate mechanical, functional and packaging integrity tests were also performed on aged product and compared to baseline to ensure that the Propel™ performed within specification throughout the stated shelf-life of the product.

Expiration dating for this device has been established and approved at 12 months.

Sterilization

Sterilization validation has been conducted to demonstrate the sterilization cycle of the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6} .

X. SUMMARY OF PRIMARY CLINICAL STUDY

The principal safety and effectiveness evidence for the Propel™ comes from the pivotal clinical study, ADVANCE II and is supported by the ADVANCE and CONSENSUS II clinical studies. These studies evaluated the safety, effectiveness and performance of the Propel™ when used in patients with chronic sinusitis following Functional Endoscopic Sinus Surgery (FESS). Subjects in all studies provided written informed consent. Major study characteristics are summarized in **Table 5**.

Table 5: Major Characteristics of the Clinical Studies

Clinical Study	Study Design	Objective	Number of Sites	Number of Subjects
ADVANCE II (pivotal)	Prospective, randomized, double-blind, concurrently controlled, multi-center Intra-patient control	Assess the safety and effectiveness of the Propel™ Sinus Implant when used following Functional Endoscopic Sinus Surgery (FESS) in patients with chronic sinusitis. Characterize Ocular Safety	11	105
ADVANCE	Prospective, single arm, multi-center	Generate additional performance, and safety data, for the Propel™ Sinus Implant when used following FESS in patients with chronic sinusitis. Characterize Ocular Safety	7	50
CONSENSUS II (pilot)	Prospective, randomized, double-blind, concurrently controlled, multi-center Intra-patient control	Assess the safety, effectiveness, and performance of the Propel™ Sinus Implant when used following Functional Endoscopic Sinus Surgery (FESS) in patients with chronic rhinosinusitis.	4	50

A. Study Design – Advance II

The ADVANCE II clinical study was a prospective, randomized, double-blind, concurrently controlled, multi-center study that enrolled 105 subjects at 11 US sites. The objective of the study was to assess the safety and effectiveness of the Propel™ when used following Functional Endoscopic Sinus Surgery (FESS) in patients with chronic sinusitis (CS). The study utilized an intra-patient control design to assess the safety and effectiveness of the Propel™ compared to a non-drug-eluting control that is identical in appearance. Patients returned for periodic follow-up exams over a total of 90 days.

The non-drug-eluting implant was selected as the control to ensure blinding of both physician and patient to sinus treatment assignment. The drug-eluting and control versions are identical in appearance, as is the delivery system and packaging.

Use of an intra-patient control was selected as this study design minimizes variability that would be inherent in a parallel patient group design – most notably, variability introduced by concomitant medication usage. To eliminate any potential for bias introduced from the treating physician, a panel of 3 blinded sinus surgeons independently graded the 30-day endoscopic videos. The videos were blinded to treatment effect and randomized (not provided in pairs).

The primary effectiveness endpoint of reduction in post-operative interventions was selected to provide evidence of a clinically meaningful patient benefit to clearly demonstrate the contribution of the addition of mometasone furoate to the implant.

Success/failure criteria:

The Primary Safety Endpoint was Ocular Safety defined as absence of clinically significant sustained elevation (≥ 10 mm Hg) in intraocular pressure through Day 90. Ocular examinations also included assessment of changes in or development of lens opacities.

The Primary Efficacy Endpoint was the reduction in need for Post-Operative Interventions at Day 30, as determined from video-endoscopies reviewed by a panel of three independent blinded sinus surgeons. Post-Operative Intervention was a composite endpoint that included:

- Surgical Intervention required to separate an adhesion and/or
- Oral Steroid Intervention warranted to resolve recurrent ethmoid sinus inflammation, edema and/or polyp recurrence.

Pre-Specified Statistical Analysis Plan: The primary effectiveness hypothesis was that the Propel™ would reduce the need for Post-Operative Interventions at Day 30 compared to the control. The planned analysis was McNemar's test for correlated proportions.

The study sample size for the effectiveness endpoint was calculated based on the following assumptions:

- Target power: $\geq 90\%$
- Type I error rate: $\alpha = 0.05$, 2-sided
- Treatment effected based on results observed in pilot study, CONSENSUS II.
- A sample size of 105 was calculated to achieve power of at least 90%

The Primary Safety Hypothesis was that the Propel™ is safe, as evidenced by the proportion of patients experiencing a clinically significant elevation in IOP being demonstrably less than 10%.

Sample size for the safety endpoint was calculated based on the following assumptions:

- Target power: $\geq 90\%$
- Type I error rate: $\alpha = 0.025$, 1-sided
- The true rate of occurrence (p_A) of a clinically significant elevation in IOP is below 2.5%. This was based on the opinion of medical advisors, and the observed rates in the ADVANCE study, where there were 0 clinically significant elevations in IOP observed in the 89 eyes evaluated.

A sample size of 100 yielded power of 0.894. If $p_A = 0.02$ or 0.01 , the power would be 0.949 or 0.997, respectively.

1. Clinical Inclusion and Exclusion Criteria

The study population included adult patients with chronic sinusitis (CS), with or without nasal/sinus polyps, scheduled to undergo Functional Endoscopic Sinus Surgery (FESS; primary or revision), and in whom placement of the Propel™ was both feasible and medically appropriate. Enrollment in the ADVANCE II study was limited to patients who met the selection criteria in

Table 6.

Table 6: ADVANCE II Patient Selection Criteria

Inclusion Criteria	Exclusion Criteria
General Inclusion Criteria	General Exclusion Criteria
Written informed consent obtained, informed consent approved by an IRB.	Known history of immune deficiency (IGG subclass deficiency or IGA deficiency).
Age ≥ 18.	Oral-Steroid dependent condition.
Compliance with protocol requirements.	Known history of allergy or intolerance to corticosteroids.
Diagnosis of CS defined as inflammation of the mucosa of the paranasal sinuses of at least 8 consecutive weeks' duration.	Clinical evidence of acute bacterial sinusitis (e.g. acute increase in purulent discharge, fever, facial pain, etc.).
Consented for FESS.	Ocular: History or diagnosis of glaucoma or ocular hypertension.
Ability to tolerate general anesthesia and the FESS procedure.	Ocular: Closed angle (with or without the presence of peripheral anterior synechiae on gonioscopy).
Treatment with the sinus implant is technically feasible and clinically indicated.	Ocular: Presence (in either eye) of posterior subcapsular cataract, nuclear sclerosis of grade +3 or higher, or cortical cataract of grade +3 or higher.
FESS successfully completed without significant complication.	Ocular: subject has an artificial eye.
Female patients of child-bearing potential must not be pregnant and must agree to not become pregnant during the course of the study.	Clinical evidence or suspicion of invasive fungal sinusitis (e.g. bone erosion on CT scan, necrotic sinus tissue, etc.).
CT Imaging Inclusion Criteria	Evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments during the 90-day follow-up period.
CS diagnosis confirmed by CT scan within 6 months of the FESS procedure.	Current or recent participation in another clinical trial.
Minimum total Lund-Mackay CT score of 6.	History of insulin dependent diabetes.
CT scan confirms bilateral disease in the ethmoid sinuses.	Previous FESS with a known complication of CSF leak or compromised vision.
Surgical Inclusion Criteria	Prior complete MT resection.
Planned bilateral total ethmoidectomy.	Intra-Operative (FESS) Exclusion Criteria
	Significant complication/s during procedure.
	FESS is aborted for any reason.
	Complete MT resection required.
	MT steroid injection required.

2. Follow-up Schedule

Baseline evaluations included a routine history and physical exam, ENT-HNS evaluation and CT scan to confirm CS diagnosis and candidacy for sinus surgery, and an ocular examination (IOP measurement, cataracts grading). Follow-up assessments occurred prior to hospital discharge or clinic release and at post-operative days 14, 30, 60 and 90 post procedure. Ocular examinations included intraocular pressure (IOP) measurements at all visits. The baseline and day 90 ocular exams included dilated slit-lamp examination for cataracts, visual acuity and estimation of vertical cup / disc ratio.

3. Clinical Endpoints:

The Primary Effectiveness Endpoint was the reduction in need for Post-Operative Interventions at Day 30, as determined from video-endoscopies reviewed by a panel of three independent blinded sinus surgeons. Post-Operative Intervention was a composite endpoint that included:

- Surgical Intervention required to separate an adhesion and/or
- Oral Steroid Intervention warranted to resolve recurrent ethmoid sinus inflammation, edema and/or polyp recurrence.

The Primary Safety Endpoint was Ocular Safety defined as absence of clinically significant elevation in intraocular pressure through Day 90.

B. Accountability of PMA Cohort

A total of 105 patients were enrolled in the study. One hundred two (102) of the 105 patients completed the ENT follow-up visits through 90 days, representing a follow-up rate of 97.1%. One hundred three (103) of the 105 patients completed the ocular follow-up visits through 90 days, representing a follow-up rate of 98.0%. No patient required termination from the study due to an adverse event.

C. Study Population Demographics and Baseline Parameters

The study population consisted of 57.1% males and the mean age was 46.5 years. The five most frequently reported symptoms reported by patients prior to the sinus surgery were, in order: nasal obstruction/congestion (90.5%), headache (64.8%), facial pain/pressure (61.0%), discolored nasal drainage (54.3%) and hyposmia/anosmia (50.5%). These findings are consistent with the typical set of persisting symptoms reported by chronic sinusitis patients. Thirty-one study patients (29.5%) had undergone one or more prior sinus procedures and this was predominantly FESS and septoplasty (77.4% and 48.4%, respectively). The mean total Lund-Mackay CT stage was 12.8. Right and left sides were well balanced with respect to mean CT stage (6.5 right vs. 6.4 left). Fifty-nine percent of study patients presented with polyps at baseline. All patients underwent bilateral ethmoidectomy at the time of sinus surgery for this study.

D. Safety and Effectiveness Results

Table 7 provides an overview of the primary and secondary endpoints and their outcomes.

Table 7: ADVANCE II Primary and Secondary Endpoint Results

		Treatment	Control	Difference / p-value ^a (Ctrl - Tx)
Number of patients in ITT population	N	105	105	
PRIMARY EFFECTIVENESS RESULTS[§]	Evaluable ^a	N (%)	N (%)	
Post-Operative Intervention	96	32 (33.3%)	45 (46.9%)	13 (13.5%) / 0.0280
PRIMARY SAFETY RESULTS				
Clinically Significant Elevation in IOP**	105	0 (0.0%)	0 (0.0%)	p < 0.0001
	95% CI***	0.0000, 0.0352	0.0000, 0.0352	
SECONDARY EFFECTIVENESS RESULTS[§]	Evaluable ^a	N (%)	N (%)	
Frank Polyposis (Grades 2 and 3) [§]	85	16 (18.8%)	29 (34.1%)	13 (15.3%) / 0.0023
SECONDARY EFFECTIVENESS RESULTS[‡]	Evaluable ^a	N (%)	N (%)	
Frank Polyposis (Grades 2 and 3)	104	4 (3.8%)	8 (7.7%)	4 (3.9%) / 0.3437
Middle Turbinate Lateralization	105	2 (1.9%)	7 (6.7%)	5 (4.8%) / 0.1250
Significant Adhesions	104	5 (4.8%)	13 (12.5%)	8 (7.7%) / 0.0386

^aAll patients returned for the Day 30 visit and had their endoscopy recorded for grading by independent panel; however, data were considered missing if the panel could not grade a video due to sub-optimal video quality or inadequate imaging of the relevant anatomy. Inadequate imaging of the relevant anatomy can occur when presence of significant edema or an adhesion prevents access into the ethmoid sinus. Since the planned statistical test (McNemar's test of correlated proportions) requires subjects with an observed pair of outcomes, 9 subjects could not be included in the test. Evaluable subjects were those with gradable sinuses on both sides.

**Intraocular pressure

***Exact 2-sided confidence intervals are calculated by the method of Clopper and Pearson.

[§]By independent panel at Day 30

[‡]By on site clinical investigators at Day 30

^aMcNemar's test was employed to obtain the 2-sided p-value at alpha level of 0.05 for all effectiveness endpoints; an exact version was used for endpoints with <20 discordant pairs; an exact binomial test was employed to obtain the 1-sided p-value at alpha level of 0.025 for the primary safety endpoint.

1. Safety Results

The primary safety endpoint was met (reference

Table 8). There were no clinically significant elevations in intraocular pressure through Day 90.

Table 8: ADVANCE II Primary Safety Results

		Treatment	Control	Difference / p-value (Ctrl - Tx)
Number of patients in ITT population	N	103	103	
SAFETY RESULTS	N (%)	0 (0.0%)	0 (0.0%)	
Clinically Significant IOP Elevation	95% CI*	0.0000, 0.0352	0.0000, 0.0352	p<0.0001**

Intent to Treat (ITT) population consists of all subjects enrolled that received the study device.

* Exact 2-sided confidence intervals were calculated by the method of Clopper and Pearson.

** An exact binomial test was employed to obtain the 1-sided p-value

There were no clinically significant changes in lens opacities observed in the clinical study.

Adverse Events that occurred in the PMA clinical study

Table 9 provides a tabulation of the adverse events observed. Recurrent sinusitis was the most frequently reported adverse event type, reported in 34 of the 105 patients (32.4%). Sinusitis was the only event type localized by sinus side; this was possible in 14 of the events. Six occurred on treatment sides and 8 occurred on the control sides. Two of the adverse events (sinusitis) were determined to be related to the study device. Both resolved without sequelae. There were no serious adverse events reported in the study.

Table 9: ADVANCE II Adverse Events Observed through Day 90

MedDRA Preferred Term	All Events N (%)
Number of Subject in ITT Population	105
Subjects With At Least One Adverse Event	57 (54.3)
Sinusitis	34 (32.4)
Headache	5 (4.8%)
Epistaxis	3 (2.9%)
Bronchitis	3 (2.9%)
Adverse drug (medication) reaction	2 (1.9%)
Pharyngitis streptococcal	2 (1.9%)
Eye swelling	1 (1.0%)
Otitis media acute	1 (1.0%)
Vulvovaginal mycotic infection	1 (1.0%)
Eye pain	1 (1.0%)
Eyelid irritation	1 (1.0%)
Foreign body sensation in eyes	1 (1.0%)
Retinal artery embolism	1 (1.0%)
Uveitis	1 (1.0%)
Gastroenteritis viral	1 (1.0%)
Nasopharyngitis	1 (1.0%)
Musculoskeletal stiffness	1 (1.0%)
Pain in extremity	1 (1.0%)
Temporomandibular joint syndrome	1 (1.0%)
Thyroid neoplasm	1 (1.0%)
Anosmia	1 (1.0%)
Sleep apnea syndrome	1 (1.0%)
Urticaria	1 (1.0%)
Debridement	1 (1.0%)
Emergency care	1 (1.0%)
Sinusitis fungal	1 (1.0%)
Intraocular pressure increased	1 (1.0%)
Presyncope	1 (1.0%)
Lymphadenopathy	1 (1.0%)

2. Effectiveness Results

The primary effectiveness endpoint was met. The rate of Post-Operative Intervention was 46.9% on the control sides compared to 33.3% on the treatment sides. This difference was statistically significant ($p=0.0280$) and represents a 29% relative reduction in Post-Operative Interventions. The primary effectiveness results are provided in

Table 10. The rate of post-operative interventions was driven largely by the reduction in surgical interventions required for adhesions.

Table 10: ADVANCE II Primary Effectiveness Endpoint

		Treatment	Control	Difference / p-value (Ctrl - Tx)
Number of patients in ITT population	N	105	105	
EFFECTIVENESS RESULTS	Evaluable*	N (%)	N (%)	
Post-Operative Intervention	96	32 (33.3%)	45 (46.9%)	13 (13.5%) / 0.0280

*All patients returned for the Day 30 visit and had their endoscopy recorded for grading by independent panel; however, data were considered missing if the panel could not grade a video due to sub-optimal video quality or inadequate imaging of the relevant anatomy. Inadequate imaging of the relevant anatomy can occur when presence of significant edema or an adhesion prevents access into the ethmoid sinus. Since the planned statistical test (McNemar's test of correlated proportions) requires subjects with an observed pair of outcomes, 9 subjects could not be included in the test. Evaluable subjects were those with gradable sinuses on both sides.

All secondary effectiveness endpoints (polypoid tissue formation, middle turbinate lateralizations and significant adhesions) demonstrated reductions in favor of the Propel™ compared to the control.

The device delivery success rate was 100%.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A. Study Design – ADVANCE

The ADVANCE study was a prospective, single-arm, multi-center, open label trial which enrolled 50 patients at 7 sites in the United States. As a consecutive case series, the study provided additional evidence of the clinical utility of the Propel™ in standard clinical practice through the Day 60 time point. The study generated additional performance and safety data, including characterization of ocular safety, for the Propel™ implant. A 6-month time point provided data on the longer-term impact of sinus surgery itself on patient symptoms and outcomes. The study enrolled a single cohort with either unilateral or bilateral ethmoid sinus disease who met eligibility criteria.

Success/Failure Criteria: The study was considered successful if Device Success, defined as successful access and deployment of a Propel™ to the target site, was accomplished in $\geq 90\%$ of deployments.

The study was considered a success if the frequency of Serious Adverse Local Tissue (SALT) response through 30 days post-procedure was $\leq 15\%$.

1. Clinical Inclusion and Exclusion Criteria

The ADVANCE study utilized similar inclusion and exclusion criteria as the pivotal study, ADVANCE II, but allowed unilateral ethmoidectomy.

2. Follow-up Schedule

Baseline evaluations included a routine history and physical exam, ENT-HNS evaluation and CT scan to confirm CS diagnosis and candidacy for sinus surgery and an ocular examination (IOP and cataracts). Follow-up assessments occurred prior to hospital discharge or clinic release and at Day 7, 14, 21, 30 and 60 post procedure. Follow-up examinations included endoscopic examination and scoring, patient symptom

questionnaires, review of concomitant medications and review for adverse events. Patients underwent an end-of-treatment ocular examination at Day 30, consisting of IOP measurement and dilated slit-lamp examination for cataracts. At month 6, the last study visit, patients were asked to complete symptom questionnaires.

Sinus-related safety endpoints were assessed by direct endoscopic examination performed by the sinus surgeon at follow-up visits. Sinus-related adverse events were determined by a combination of objective endoscopic observation and patient symptoms. The SALT endpoint (primary safety endpoint) was determined by endoscopic examination and per the definition, required removal of the implant(s) to resolve.

Ocular safety assessment included baseline and end-of-treatment (Day 30) measurement of IOP and dilated slit-lamp examination of lens opacities (cataracts).

Patients' symptoms were assessed over time using accepted disease-specific scoring instruments. The Rhinosinusitis Disability Index (RSDI), the Sinonasal Outcomes Tests – 22 (SNOT-22) and Total Nasal Symptom Scoring (TNSS).

3. Clinical Endpoints

The Primary Performance Objective was Device Success, defined as the ability to successfully deliver and deploy the sinus implant to the target site.

The Primary Safety Objective was the rate of Serious Adverse Local Tissue (SALT) response through 30 days post-procedure.

B. Accountability of Subjects

A total of 50 subjects were enrolled at seven investigational centers. Forty-nine of the 50 subjects completed the study through 60 days, representing a follow-up rate of 98%. Forty-five subjects (90%) completed follow-up through 6 months. Of the 50 patients enrolled, 10 had unilateral implant placement, and 40 had bilateral implant placement, resulting in a total of 90 treated sinuses. One of the patients with bilateral implant placement had an artificial eye, resulting in a total of 89 eyes for evaluation of ocular safety. One subject withdrew from the study after Day 30 due to scheduling difficulties.

C. Study Population Demographics and Baseline Parameters

In the overall study population, the proportion of male subjects was 52.0% and the mean age was 44.2 years. The most frequently reported symptoms reported by subjects prior to the sinus surgery were, in order: nasal obstruction/congestion (94.0%), headache (82.0%), fatigue (74.0%) and facial pain/pressure (68.0%). These findings are consistent with the typical set of persisting symptoms reported by chronic sinusitis patients. Mean baseline Lund-Mackay CT stage was 11.2, 28% had undergone a prior sinus procedure and 66% presented with nasal/sinus polyps.

D. Safety and Effectiveness Results

The primary performance endpoint (device success > 90%) was met. The device success rate was 100%.

The Propel™ implant was substantially reabsorbed from the sinus cavity within 4 to 6 weeks during routine follow-up patient care after sinus surgery.

1. Safety Results

The primary safety endpoint was met. The analysis of safety was based on the rate of SALT measured for each sinus implanted with the Propel™ at the 30-day time point. SALT was observed in six sinuses (3 patients) during the study, giving a rate of 6.7% through 30 Days. Thus, the primary safety endpoint (observed SALT rate ≤15% through Day 30) was achieved. There was no SALT observed after 30 days. There were no clinically significant changes from baseline in IOP or lens opacities.

Adverse Events

A total of 54 adverse events occurred in 32 of the 50 patients through 60 days (**Table 11**). There was one device-related adverse event reported (headache and nasal burning) that resolved without sequelae.

Table 11: ADVANCE Adverse Events through Day 60

Adverse Event	N (%)
Number of Subject in PTE Population	50
Subjects with an Adverse Event	33
Infection: Sinus, bilateral	14 (28%)
Infection: Sinus, unilateral	4 (8%)
Sinus: Headache	5 (10%)
Defect in lamina papyracea	1 (2%)
Sinus: Other*	8 (16%)
Infection: Other**	8 (16%)
Other ***	13 (26%)

*Sinus: Other, includes nasal congestion due to allergies, worsening allergic rhinitis, middle turbinate effusion, intranasal bleeding with packing removal, eye pain and difficulty focusing eyes, teeth pain, pain and pressure around eyes (2).

**Infection: Other, includes otitis media, URI (3), vaginal candidiasis (2), infected hair follicle, UTI

***Other, includes ruptured diverticulitis, elevated intraocular pressure (unilateral), elevated blood sugar, fluid in ear(2), nausea (2),

tinnitus, gout, decreased sexual pleasure, sore throat, facial paresthesia, tension headache

2. Effectiveness Results

Mean scores for ethmoid sinus inflammation were similar to the treatment arm of CONSENSUS II and were minimal at all time points. The observed rate of polypoid tissue formation of any grade at 30 days was 10.0%; adhesions 1.1%; and middle turbinate lateralization 4.4%.

Patient reported outcomes were included in the ADVANCE study to assess the impact of sinus surgery itself on patient symptoms. The mean changes from baseline to Day 60 and 6 months in total RSDI score were -36.2 and -29.7, respectively (p<0.0001). For the

SNOT 22, the changes were -1.9 and -1.7, respectively ($p < 0.0001$). All changes from baseline in RSDI, SNOT-22 and TNSS were statistically significant ($p \leq 0.0002$).

A. Study Design - CONSENSUS II

The CONSENSUS II study was the first clinical trial to evaluate the safety and effectiveness of the Propel™. CONSENSUS II was a randomized, double-blind, multi-center clinical study in which 50 patients were enrolled at 4 clinical sites in the United States and included follow-up through 60 days. The objective of the study was to assess the safety, effectiveness, and performance of the Propel™ when used following Functional Endoscopic Sinus Surgery (FESS) in patients with chronic rhinosinusitis. Patients were enrolled in two groups. One group (Cohort A) used an intra-patient control design to assess performance of the Propel™ compared to the control (non-drug-eluting implant). The other group of patients (Cohort B) received bilateral Propel™ implants and served as a pharmacokinetics (PK) study group. A Continuation Cohort was added to expand the size of the clinical trial. All patients in the Continuation Cohort used an intra-patient control. Patients were enrolled chronologically into the following three study cohorts:

Cohort A (Pilot Phase; Randomized; Double-Blind; Intra-Patient Control): 20 patients received the Propel™ in one ethmoid sinus and a control in the opposite ethmoid sinus. The side receiving the Propel™ was randomized. This cohort served as an intra-patient control in order to assess the performance and ability of the Propel™ to minimize post-surgical inflammation. Drug-eluting implants were placed unilaterally and compared to the control (non-drug-eluting implant) over time. The first 7 patients enrolled received a shorter length version of the Propel™. The study device was then changed to the current 23mm version. The remaining 13 patients received the 23 mm version of the Propel™.

Cohort B (Non-Randomized): Five patients received the Propel™ (23 mm version) bilaterally (in both ethmoid sinuses) for a total of 2 drug-eluting implants per patient. This patient cohort was included to evaluate whether any systemic exposure was detectable when 2 drug-eluting implants were used. Patients from Cohort B were included in a pharmacokinetic evaluation, requiring serial blood sampling to assess plasma mometasone furoate and cortisol concentrations. Intraocular pressure was also measured at baseline and end of treatment (Day 30) in these subjects.

Continuation Cohort (Randomized; Double-Blind; Intra-Patient Control): At completion of enrollment of the initial 25 patients in Cohort A and Cohort B, an additional 25 patients were enrolled into the randomized Cohort A group. All patients received the 23mm length Propel™.

Success/Failure Criteria: The three primary objectives (performance, safety, effectiveness) needed to be satisfied in order for the study to be considered successful. The study was considered a success if: 1) the device placement success rate was at least 75%, 2) ethmoid sinus inflammation at Day 21 was reduced (by at least half a standard deviation) in the treatment arm when compared to the control and 3) the rate of Serious Adverse Local Tissue response through 30 days post-procedure was less than 20%.

1. Clinical Inclusion and Exclusion Criteria

The inclusion and exclusion criteria of the CONSENSUS II study were similar to those used in the pivotal study, ADVANCE II.

2. Follow-up Schedule

Baseline evaluations included a routine history and physical exam, ENT-HNS evaluation and CT scan to confirm CRS diagnosis and candidacy for sinus surgery. Follow-up assessments occurred prior to hospital discharge or clinic release and at Day 7, 14, 21, 30, 45 and 60 post procedure. Follow-up examinations included endoscopic examination and scoring, review of concomitant medications and review for adverse events. Patients in Cohort B underwent weekly blood draws through Day 30 and an IOP measurement at baseline and Day 30.

3. Clinical Endpoints

The Primary Performance Objective was Device Success, defined as the ability to successfully deliver and deploy the implant to the target site.

The Primary Effectiveness Objective was a reduction in ethmoid sinus inflammation at Day 21, as measured by the physician's score using a 100 mm Visual Analog Scale (VAS) during endoscopic examination.

The Primary Safety Objective was the rate of Serious Adverse Local Tissue response (SALT) through 30 days post-procedure.

B. Accountability of Subjects

A total of 50 patients were enrolled in the study at four investigational centers. Forty-nine (49) of the 50 subjects completed all follow-up visits through 60 days, representing a follow-up rate of 98%.

C. Study Population Demographics and Baseline Parameters

In the overall study population, the proportion of male subjects was 56.0% and the mean age was 47.1 years. The most frequently reported symptoms reported by subjects prior to the sinus surgery were, in order: nasal obstruction/congestion (80.0%), facial pain/pressure (40.0%), headache (34.0%), and anosmia (30.0%). These findings are consistent with the typical set of persisting symptoms reported by chronic rhinosinusitis patients. Mean baseline Lund-Mackay CT stage was 13.6, 42% had undergone a prior sinus procedure and 76% presented with nasal/sinus polyps.

D. Safety and Effectiveness Results

The primary performance endpoint (device success > 75%) was met. The device success rate was 100% in the overall study population, and therefore, in each study cohort as well.

The device was substantially reabsorbed from the sinus cavity within 4 to 6 weeks as seen during routine follow-up patient care after sinus surgery.

1. Safety Results

The primary safety endpoint was met: SALT was not observed in any sinus during the study. The analysis of safety was based on the rate of SALT measured for each sinus implanted with the Propel™ through the 30-day time point. There was no instance where the implant (either treatment or control) required removal due to SALT.

Systemic Safety: Plasma MF concentrations were not quantifiable at any time point. The mean cortisol concentration at baseline was within normal limits at 6.16 µg/dL. Mean cortisol concentrations at follow-up time points were also within normal limits and indicate no evidence of adrenal suppression.

Ocular Safety: There were no clinically significant changes in intraocular pressure (IOP) observed.

Adverse Events

There were no device-related adverse events. A total of 47 adverse events occurred in 25 of the 50 patients. **Table 12** summarizes adverse events that occurred during the study.

Table 12: CONSENSUS II Adverse Events

Adverse Event	Number* (n=50 patients)	Number** Localized to a Sinus Side		
		Treatment	Control	Not localized to one side
Recurrent Sinusitis / Infection	17 / 16 (32%)	5 (9%)	5 (11.1%)	7
Recurrent Polyps	6 / 6 (12%)	0 (0%)	2 (4.4%)	4
Epistaxis	1 / 1 (2.5%)	NA	NA	1
Dysosmia	1 / 1 (2.5%)	NA	NA	1
Septal Perforation	1 / 1 (2.5%)	NA	NA	1
Other***	21 / 13 (26%)	NA	NA	NA
Total AEs	47 / 25 (50%)	NA	NA	NA

*Number is presented as Number of AEs / Number of Patients (% of patients)

**Denominator for AEs localized to a sinus side is number of sinuses with that treatment (n=55 for treatment, n=45 for control)

***Other includes stomach cramps, tension headache, vasovagal episode during endoscopy (2), medication reaction, vaginal candidiasis, tinnitus, depression, UTI (2), gastroenteritis, bronchitis, conjunctivitis, viral cold, ocular swelling, eye viral infection, ear pain (2), anesthesia reaction, oxygen desaturation, pulmonary embolism

2. Effectiveness Results

The primary effectiveness endpoint was met. For Combined Cohort A (all 23 mm implants; n=38), mean differences in ethmoid sinus inflammation between sides was -12.0 mm (p= 0.0032) at day 21. A reduction in inflammation from Days 14 to 60 was demonstrated in favor of the Propel™, with statistically significant reductions also observed at days 30 and 45 (p≤0.0022). The drug-eluting implant reduced the frequency

of middle turbinate lateralization, significant adhesion occurrence, and polypoid tissue formation through day 30, compared to the control implant.

Summary of Overall Device Performance: In all three studies, implant placement occurred following ethmoidectomy. Implants were successfully placed in a total of 400 sinuses in the 205 patients. Of the 400 implants, 16 (4%) were removed and replaced immediately after deployment due to sub-optimal apposition, crossed struts or inadvertent removal, and 3 (0.8%) were damaged during preparation. In these 3 cases, a new implant was used successfully.

Outside US Clinical Experience: The Propel™ was used in 18 patients in Canada under the Special Access program. There were no reported adverse events.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the ENT Panel, an FDA advisory committee.

XIII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The ADVANCE II study demonstrated the safety of the Propel™. The primary safety endpoints were met. The study confirmed that the addition of the drug poses negligible safety risks.

B. Effectiveness Conclusions

The ADVANCE II study demonstrated the effectiveness of the Propel™. The primary effectiveness endpoints were met. The study confirmed the hypothesis that the addition of the corticosteroid to the implant would augment the device's ability to physically maintain sinus patency by reducing inflammation, adhesions and significant polyposis and that these endoscopic findings are translated into measurable clinical benefits. The ADVANCE II study generated evidence that the Propel™ offers meaningful clinical benefit to patients by reducing the need for post-operative interventions following endoscopic sinus surgery.

C. Overall Conclusions

The safety, efficacy and performance of the Propel™ have been demonstrated in three prospective, multi-center clinical studies in the United States. The primary safety, efficacy and performance endpoints in all three clinical studies were met. The clinical

data confirmed the hypothesis that the addition of the corticosteroid to the stent coating would augment the device's ability to physically maintain sinus patency by reducing inflammation, adhesions and polyposis and that these endoscopic findings could be translated into measurable clinical benefits. The study confirmed that the addition of the drug to the stent poses negligible safety risks. The data generated provides a high level of evidence that the Propel™ offers meaningful clinical benefit to patients. The data demonstrates that the Propel™ provides a reasonable assurance of safety and effectiveness when used in patients in accordance with the instructions for use.

XIV. CDRH DECISION

CDRH issued an approval order on August 11, 2011. The final conditions of approval cited in the approval order are described below.

1. Your proposed acceptance criteria for the drug release test at 0.5 hrs (20-44%) and 2 hrs (52-76%) are acceptable, but the proposed specification range of 73-97% for the 8 hrs time-point is not acceptable. We recommend setting the specification for the 8 hrs time-point to $\geq 80\%$. However, considering the absence of drug release-stability data supporting the 8 hours time-point, we will accept on an interim basis, a specification of $\geq 80\%$ for the 24 hours time-point, for which you have stability data. Please commit to collecting additional drug release profile data (i.e., 0.5, 2, 8, 10, 12, and 24 hours, n=12) from the three commitment stability batches. Please provide a revised drug release specifications proposal for the last sampling time-point based on these data in a Supplement as soon as this information becomes available.
2. Conduct an evaluation of the source of the drug loss observed during the e-beam sterilization process (~3 – 4%) and to report the results of your investigation to FDA annually in Annual Reports. Please acknowledge this commitment.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATION

Directions for use: See device labeling. (*See General hints*)

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.