SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Drug-Eluting Sinus Stent
Device Trade Name:	PROPEL® Mini Sinus Implant
Device Procode:	OWO
Applicant's Name and Address:	Intersect ENT 1555 Adams Drive Menlo Park, CA 94025
Date(s) of Panel Recommendation:	Advisory Panel meeting not held
Premarket Approval Application (PMA) Number:	P100044/S018
Date of FDA Notice of Approval:	March 23, 2016

The original PMA (P100044) for the PROPEL Sinus Implant was approved on August 11, 2011 and has the following 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." The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the PROPEL Mini Sinus Implant (P100044/S001, approved on September 21, 2012) to include the frontal sinus opening.

II. INDICATIONS FOR USE

The PROPEL Mini sinus implant is intended for use in adult patients ≥ 18 years of age following ethmoid / frontal sinus surgery to maintain patency of the ethmoid sinus or frontal sinus opening. The PROPEL Mini sinus implant separates/dilates surrounding mucosal tissues, provides stabilization of the middle turbinate, prevents obstruction by adhesions, and reduces inflammation. The implant reduces the need for post-operative intervention such as surgical adhesion lysis and/or use of oral steroids.

III. CONTRAINDICATIONS

The use of the PROPEL Mini sinus implant 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

Warnings

- The PROPEL Mini sinus implant is designed for single patient use only. Do not reprocess or reuse.
- Do not use if the package is open or damaged.

Precautions

- Special care should be taken to avoid bending, twisting or damaging the implant.
- The implant is not designed to be modified by the physician.
- The implant is not intended to be compressed and loaded into the delivery system more than two times.
- The implant must be placed under endoscopic visualization.
- The implant exhibits no antimicrobial properties.
- Foreign body reaction may occur as is possible with most surgical adjuncts.
- In rare instances, the physiochemical condition associated with sinus surgery, both with and without sinus implants or packing, may present a risk of toxic shock syndrome (TSS).
- Pediatric Use: The safety and effectiveness of the implant in pediatric patients have not been established.
- Pregnancy and Nursing Females: The safety and effectiveness of the implant in pregnant or nursing females have not been established.

Drug Information

Mechanism Of Action: Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. The precise mechanism behind the anti-inflammatory properties of the eluted mometasone furoate is not known.

Pharmacokinetics: Following bilateral drug-eluting implant placement after sinus surgery for chronic sinusitis and subsequent weekly morning blood sampling for 4 weeks in 5 adult patients, plasma mometasone furoate concentrations were not quantifiable at any time point. Mean cortisol concentrations were within normal limits.

Drug Interactions

No drug-drug interaction studies have been conducted with the PROPEL Mini implant.

Carcinogenicity, Genotoxicity And Reproductive Toxicity

No long term studies in animals have been performed to evaluate the carcinogenic potential of the PROPEL Mini implant.

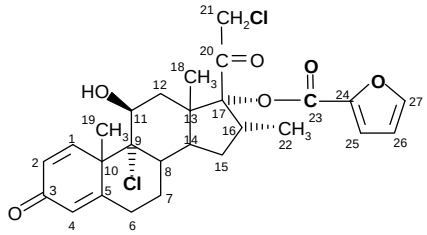
Pregnancy
There have been no controlled studies in pregnant women using the PROPEL Mini implant. The PROPEL Mini sinus implant should be used during pregnancy only if the potential benefits justify the potential risk.

Lactation
It is not known if mometasone furoate is excreted in human milk. Because other corticosteroids are excreted in human milk, the PROPEL Mini sinus implant should be used only if the potential benefits justify the potential risk.

Dosage And Administration
Each PROPEL Mini sinus implant contains 370µg of mometasone furoate which is gradually released over time.

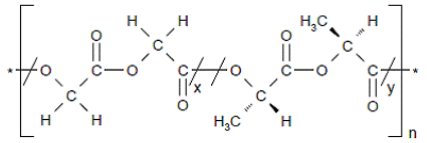
V. DEVICE DESCRIPTION

The PROPEL Mini sinus implant is a bioabsorbable implant designed to maintain patency of the sinus cavity. The PROPEL Mini implant 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 9α,21-dichloro-11β,17α-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione17-(2-furoate), with the empirical formula $C_{27}H_{30}Cl_2O_6$, 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. Mometasone furoate 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.



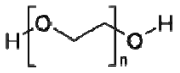
Chemical structure of mometasone furoate

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 or frontal sinus opening. The PROPEL Mini implant 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 or frontal sinus opening and insert the implant.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for maintaining patency of the ethmoid sinus or frontal sinus opening following functional endoscopic sinus surgery (FESS). These devices are referred to as either packing, structured stents or injectable space-filling gels/stents. They act as space-occupying materials, drainage tubes, or post-operative spacers to prevent obstruction by adhesions, allow ventilation and drainage of fluids, and maintain opening of the frontal sinus drainage pathway. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The PROPEL Mini sinus implant received FDA approval on September 21, 2012 for the ethmoid sinus stent indication and CE Mark approval on July 9, 2014 and is currently marketed in the United States and Germany.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

Potential adverse effects associated with the PROPEL Mini sinus implant 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

Observed Adverse Events:

Adverse events were reported in 3 prospective clinical trials (ADVANCE II, ADVANCE, and CONSENSUS II) conducted in the United States with 205 patients and a total of 400 treated ethmoid sinuses. Of these 400 sinuses, 250 received PROPEL sinus implants and 150 received non-drug-eluting control implants. The overall incidence rate of device-related adverse events on a by-patient count was 1.5% (3/205 patients). One patient experienced headache with nasal burning and 2 patients had recurrent sinusitis. All 3 events resolved without clinical 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 ≥2% of patients across all three trials are displayed in **Table 1**.

Table 1: Adverse Events Occurring in ≥ 2% of Patients*

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

** Events tabulated through day 90 from the pivotal study (ADVANCE II) and through 60 days in the supportive studies (ADVANCE, CONSENSUS II)*

Additional adverse events were reported in one other prospective clinical trial (PROGRESS Mini cohort) conducted in the United States with 80 patients. The study used an intra-patient design and each patient received 1 PROPEL Mini sinus implant in the frontal sinus opening on the treatment side. There were no device-related serious adverse events. Five adverse event types (headache, left upper eyelid swelling, epistaxis, recurrent chronic sinusitis and increased sinus pressure) were judged to be possibly unrelated to the device and all 5 events resolved without clinical sequelae. No patients withdrew due to an adverse event and there were no deaths that occurred in this clinical study. Adverse events (regardless of relationship to implant) reported in ≥2% of patients in the PROGRESS study are displayed in the **Table 2**.

Table 2: Adverse Events Occurring in ≥ 2% Patients *

Adverse Event Type	Percent of Patients Reporting
Acute Sinusitis	15.0
Chronic Sinusitis	11.3
Headache	11.3
Upper Respiratory Tract Infection	6.3
Epistaxis	5.0
Presyncope	5.0
Acute Otitis Media	3.8
Asthma	3.8
Nasal Congestion	3.8
Eyelid Edema	2.5
Influenza	2.5
Nasal Polyps	2.5
Nasopharyngitis	2.5
Nausea	2.5

** Events from the PROGRESS study with 80 patients tabulated through day 90*

For more information regarding the specific adverse events that occurred in the PROGRESS clinical study for the PROPEL Mini cohort, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

The following section provides a summary of the non-clinical studies conducted to support the PROPEL Mini sinus implant.

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 Mini implant is biocompatible. **Table 3** provides a summary of the biocompatibility testing conducted on the PROPEL implant.

Table 3: Summary of the PROPEL Sinus Implant 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	Implant and Delivery System	PASS (non-irritant)

Test	Requirement	Test Article	Result
	and the control is less than or equal to 1.		
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 Mini sinus implant was tested to evaluate mechanical performance after sterilization, extreme conditioning and simulated transportation to verify the PROPEL Mini implant 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 4** summarizes the bench tests performed and results for the PROPEL Mini implant. Results of the tests demonstrate that PROPEL Mini sinus implant performs as intended and meets the product specifications.

Table 4: 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 16.5-19.5 mm.	Pass
Post Deployment Diameter	The implant is deployed (simulating clinical use). The diameter is measured post deployment and verified to be at least 32 mm.	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

Test	Requirement	Results
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
Frontal Sinus Model	The implant is placed in a frontal 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 Inspection	The delivery system is inspected for shaft length and presence of a beveled tip.	Pass
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
Sinus Model Testing	The product must successfully execute all required performance aspects in a sinus model.	
Bubble Leak Testing	The foil pouch with product is tested for gross leaks. No gross leaks should be detected.	Pass
Pouch Peel Testing	Pouch seal strength must be $\geq$ 1.0 lb/in.	Pass

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 Mini sinus implant.

C. Additional Studies

Chemistry, Manufacturing and Controls (CMC) Testing

Testing routinely performed on the PROPEL Mini sinus implant is summarized in **Table 5**.

Table 5: 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 <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 *in-vitro* 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 <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 Mini implant. 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 Mini implant performed within specification throughout the stated shelf-life of the product.

Expiration dating for this device has been established and approved at 24 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 STUDIES

The applicant performed a clinical study (PROGRESS) to establish a reasonable assurance of safety and effectiveness of the use of the PROPEL Mini sinus implant (approved in P100044/S001) following Functional Endoscopic Sinus Surgery (FESS) to maintain patency of the frontal sinus opening in patients with chronic sinusitis in the US. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented in the following subsections.

Three other studies were previously conducted to assess the safety and effectiveness of the PROPEL sinus implant (approved in P100044) when used in the ethmoid sinus in patients with chronic sinusitis following FESS.

Subjects in all studies provided written informed consent. Major study characteristics are summarized in **Table 6**.

Table 6: 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 implant when used following Functional Endoscopic Sinus Surgery 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 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 implant when used following Functional Endoscopic Sinus Surgery in patients with chronic rhinosinusitis.	4	50
PROGRESS	Prospective,	Assess the safety and effectiveness	11	80

Clinical Study	Study Design	Objective	Number of Sites	Number of Subjects
Mini Cohort (pivotal – frontal indication)	randomized, double-blind, concurrently controlled, multi-center Intra-patient control	of the PROPEL Mini sinus implant in the frontal sinus opening when used following Functional Endoscopic Sinus Surgery in patients with chronic sinusitis.		

A. Study Design

Patients were treated between September 17, 2014 and September 9, 2015. The database for this (P100044/S018) reflected data collected through September 9, 2015 and included 80 patients. There were 11 investigational sites.

The PROGRESS clinical study (Mini Cohort) was a prospective, randomized, double-blind, concurrently controlled, multi-center study that enrolled 80 subjects at 11 US sites. The objective of the study was to assess the safety and effectiveness of the PROPEL Mini sinus implant in the frontal sinus opening when used following endoscopic sinus surgery in patients with chronic sinusitis. The study utilized an intra-patient control design to assess the safety and effectiveness of the PROPEL Mini sinus implant compared to endoscopic sinus surgery alone. Patients returned for periodic follow-up exams over a total of 90 days. Results from the PROGRESS Mini Cohort study are presented here.

The rationale for selection of endoscopic sinus surgery alone as the choice of control was to compare the outcomes of stenting to the current standard of care. The patient underwent bilateral endoscopic frontal sinus surgery following which only the treatment side received the PROPEL Mini sinus implant.

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 the potential for bias in endoscopic grading, protocol required implants be removed at Day 21 and a blinded sinus surgeon independently graded the Day 30 endoscopic videos.

The primary efficacy endpoint of reduction in need for post-operative interventions was selected to provide evidence of a clinically meaningful patient benefit to clearly demonstrate the contribution of a mometasone furoate coated implant in the frontal sinus opening.

Success/failure criteria:
The primary efficacy endpoint was the reduction in need for Post-Operative Interventions at Day 30, as determined from video-endoscopies reviewed by an independent blinded sinus surgeon. Post-Operative intervention was a composite endpoint that included:

- Surgical Intervention required to debride obstructive adhesions or scar tissue formation in the frontal sinus opening and/or

- Oral Steroid Intervention warranted to resolve recurrent inflammation or polypoid edema in the frontal recess/ frontal sinus opening.

The implant safety was determined by the assessment of adverse events throughout the study.

Pre-Specified Statistical Analysis Plan: The primary effectiveness hypothesis was that the PROPEL Mini sinus implant 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.

1. Clinical Inclusion and Exclusion Criteria

The study population included adult patients with chronic rhinosinusitis (CRS), scheduled to undergo frontal endoscopic sinus surgery (primary or revision), and in whom placement of the PROPEL Mini sinus implant was both feasible and medically appropriate. Enrollment in the PROGRESS Mini Cohort study was limited to patients who met the selection criteria in **Table 7**.

Table 7: PROGRESS 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 such as immunoglobin G or A subclass deficiency, or Human Immunodeficiency Virus (HIV).
Age ≥ 18.	Oral-Steroid dependent condition such as chronic obstructive pulmonary disease (COPD), asthma or other condition.
Compliance with protocol requirements.	Known history of allergy or intolerance to corticosteroids or mometasone furoate.
Diagnosis of CRS by CT scan defined as symptoms lasting longer than 12 consecutive weeks' duration, with inflammation of the mucosa of the nose and paranasal sinuses.	Clinical evidence of acute bacterial sinusitis (e.g. acute increase in purulent discharge, fever, facial pain, etc.).
Has a clinical indication and has consented for ESS including bilateral frontal sinus surgery.	Clinical evidence or suspicion of invasive fungal sinusitis (e.g. bone erosion on CT scan, necrotic sinus tissue, etc.).
Ability to tolerate general anesthesia.	Evidence of active viral illness (e.g., tuberculosis, ocular herpes simplex, chickenpox or measles).
Treatment with the PROPEL Mini sinus implant is technically feasible and clinically indicated in the frontal sinus opening.	Concurrent condition requiring active chemotherapy and/or immunotherapy management for the disease (e.g., cancer, HIV, etc.).
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 of disease or condition expected to compromise survival or ability to complete follow-up assessments during the 90-day follow-up period.

Inclusion Criteria	Exclusion Criteria
Female patients of child-bearing potential must agree to use consistent and acceptable method/s of birth control during the course of the study.	Current or recent participation in another clinical trial.
CT Imaging Inclusion Criteria	History of insulin dependent diabetes.
CRS diagnosis confirmed by CT scan within 6 months of the FESS procedure.	Previously undergone ESS and experienced a CSF leak or has compromised vision as a result of a complication in a prior ESS procedure.
Bilateral disease in both frontal sinuses confirmed by Lund-Mackay score of ≥1 on each side.	**Intra-Operative Exclusion Criteria**
Surgical Inclusion Criteria	Significant complication during the current ESS including frontal sinus surgery such as excessive blood loss, CSF leak or punctured lamina papyracea.
Planned ESS includes bilateral ethmoidectomy (if judged necessary) and frontal sinus surgery using Draf II (A or B) dissection and/or balloon dilation, with minimum of 5-mm diameter opening created.	Current ESS including frontal sinus surgery is aborted for any reason.
Technique used for frontal sinus surgery was the same on both sides (e.g. surgical dissection alone bilaterally, balloon dilation alone bilaterally, or both bilaterally).	At least one side is not amenable for implant placement.
Septoplasty for access to the ostio-meatal complex is permitted.	
ESS including bilateral frontal sinus surgery has been successfully completed without significant complication that, in the opinion of the investigator, would confound study results, and the patient's anatomy remains amenable to implant placement.	

2. Follow-up Schedule

Baseline evaluations included a routine history and physical exam, ENT-HNS evaluation and CT scan to confirm chronic rhinosinusitis diagnosis (if not performed within past 6 months) and candidacy for sinus surgery. Follow-up assessments occurred prior to hospital discharge or clinic release and at post-operative Days 7, 21, 30 and 90.

The follow-up assessments (**Table 8**) included endoscopic examinations and endoscopic video recording to DVD in addition to a CT scan conducted at the Day 90 visit only. At Day 21, the implant or its remnants were to be removed to allow for blinded review of video endoscopies at the Day 30 visit. Adverse events and serious adverse events were recorded and tabulated through day 30 and 90. Where possible and if applicable, adverse events were localized to a sinus location.

Table 8: PROGRESS Follow-Up Schedule

Assessments	Screening (within 30 days pre-placement)	Surgery/ Implant Placement Procedure	Day 7 Follow-up (+/-3 days)	Day 21 Follow-up (+/-3 days)	Day 30 Follow-up (+/-3 days)	Day 90 Follow-up (+/-7 days)
Medical history & physical, informed consent	X					
Endoscopic evaluation *(including video recording)*		X	X	X	X	X
CT Scan	X[1]					X
Pregnancy test [2] *(per institutional standard)*		X[2]				
Implant placement *(including video recording)*		X				
Implant removal *(including video recording)*				X		
Review of adverse events		X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Review of video-endoscopies by an independent blinded sinus surgeon					X	
CT scan review by independent blinded surgeon						X

[1] CT scan within 6 months prior surgery is permitted to confirm CRS diagnosis.
[2] Pregnancy test is required for females of child-bearing potential on the surgery day before implant placement.

3. Clinical Endpoints

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 debride obstructive adhesions or scar tissue formation in the frontal sinus opening and/or
- Oral Steroid Intervention warranted to resolve recurrent inflammation or polypoid edema in the frontal recess/ frontal sinus opening.

The safety endpoint was assessment of adverse events and serious adverse events through Day 90.

Secondary efficacy endpoints at Day 30 as determined from video-endoscopies reviewed by the independent blinded sinus surgeon included: frequency and severity of adhesion/scarring formation in the FSO, degree of inflammation in the frontal recess/FSO using a 100 mm Visual Analog Scale (VAS) and frequency and grade of polypoid edema in the frontal recess/FSO. Additional secondary efficacy endpoints assessed by on-site investigators at all time points through 30 days included:

frequency of post-operative interventions, endoscopic scores of inflammation using a 100 mm Visual Analog Scale (VAS), frequency and degree of adhesion/scarring formation in the FSO, frequency and grade of polypoid edema in the frontal recess/FSO and implant delivery success rate at device placement.

To be considered successful, the PROGRESS Study needed to pass the primary efficacy hypothesis. The hypothesis is that the drug-coated implant reduces the need for post-operative interventions at Day 30 compared to the control. The null and alternative hypotheses are

H_0: $P_T \geq P_C$ vs.
H_a: $P_T < P_C$,

where P_T and P_C represent the proportion of patients who warrant post-operative interventions on the treatment and control sides, respectively. These proportions can be expressed as $P_T = P_{11} + P_{10}$ and $P_C = P_{11}+P_{01}$, where P_{10} is the proportion of patients who warrant surgical intervention only on the treatment side, P_{01} is the corresponding proportion for the control side, and P_{11} is the proportion who warrant interventions for both sides. The above hypotheses are equivalent to a test of

H_0: $P_{10} \geq P_{01}$ vs
H_a: $P_{10} < P_{01}$.

Denoting $P^* = P_{01}/(P_{01}+P_{10})$, the hypotheses become H_0: $P^* \leq 0.5$ vs H_a: $P^* > 0.5$.

The planned analysis was McNemar's test for correlated proportions, arising from the intra-patient control design, where only discordant pairs of observations contribute to evidence of a treatment effect. A pair of observations is discordant when one sinus side requires intervention and the other does not.

B. Accountability of PMA Cohort

A total of 80 patients were enrolled in the study. Seventy nine (79) of the 80 patients completed the ENT follow-up visits through Day 30, representing a follow-up rate of 98.8%. No patient required termination from the study due to an adverse event through Day 30. The efficacy analyses were based on the intent-to-treat (ITT) population, which consists of all randomized patients who underwent implant placement.

C. Study Population Demographics and Baseline Parameters

The study population (**Table 9**) consisted of 57.5% males and the mean age was 49.9 years. At baseline, 76.3% patients had polypoid edema (grade 2), in the frontal recess/ frontal sinus opening; 37.5% patients had asthma; 7.5% patients had aspirin intolerance/allergy and 7.5% patients had Samter's Triad. The mean baseline total Lund-Mackay (L-M) score was 15.8; with 51.2% patients who had undergone at least one prior ESS. Control and treatment sides were well balanced with respect to mean

L-M CT stage (8.0 control vs. 7.8 treatment side). All patients underwent bilateral traditional frontal sinusotomy prior to implant placement on one randomized side.

Table 9: Demographic and Baseline Characteristics: Intent-to-Treat Population

Table 2: Demographic and Baseline Characteristics: Intent-to-Treat Population	
	All Patients (N=80)
Age, years [Mean (SD)]	49.9 (13.91)
Gender [1]	
Male	46 (57.5%)
Female	34 (42.5%)
Ethnicity [1]	
Not Hispanic or Latino	80 (100%)
Race [1]	
White	62 (77.5%)
Black or African American	12 (15.0%)
Asian	6 (7.5%)
Number of Prior ESS	
0	39 (48.8%)
1	20 (25.0%)
2	11 (13.8%)
3	5 (6.3%)
>=4	5 (6.3%)
History of Aspirin Intolerance or Allergy [1]	6 (7.5%)
History of Asthma Diagnosed by Physician	30 (37.5%)
History of Samter's Triad	6 (7.5%)
History of Smoking	28
Current	9 (11.3%)
Former	19 (23.8%)
Polypoid Edema in Frontal Recess/ FSO, Grade 2 [2]	61 (76.3%)
Lund Mackay Score, Total (Left + Right) [Mean (SD)]	15.8 (4.82)

[1] Percentage is calculated based on Intent-to-Treat Population.
[2] Patients with Grade 2 polypoid edema at either right sinus or left sinus sides.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the intent-to-treat population in the Mini cohort of 80 patients available for the 90 day evaluation.

Adverse effects that occurred in the PMA clinical study:

Table 10 provides a tabulation of the adverse events reported in ≥ 2% of patients in the PROGRESS trial through Day 90. Sinusitis (acute and chronic) and headache were the most frequently reported AEs, in 21 (26.3%) patients and 9 (11.3%), respectively. Five adverse event types (headache, left upper eyelid swelling, epistaxis, recurrent chronic sinusitis and increased sinus pressure) were

judged to be possibly unrelated to the device and all 5 events resolved without clinical sequelae. No patients withdrew due to an adverse event and no deaths occurred in this clinical study. There were no serious adverse events in the study that were related to the implant.

Table 70: PROGRESS Mini Adverse Events Observed through Day 90

System Organ Class Preferred Term	All Events (N=80)
Patients with Any Adverse Events	53 (66.3%)
Acute sinusitis	12 (15.0%)
Chronic sinusitis	9 (11.3%)
Headache	9 (11.3%)
Upper respiratory tract infection	5 (6.3%)
Presyncope	4 (5.0%)
Epistaxis	4 (5.0%)
Otitis media acute	3 (3.8%)
Asthma	3 (3.8%)
Nasal congestion	3 (3.8%)
Eyelid oedema	2 (2.5%)
Nausea	2 (2.5%)
Influenza	2 (2.5%)
Nasopharyngitis	2 (2.5%)
Nasal polyps	2 (2.5%)

2. Effectiveness Results

The analysis of effectiveness was based on the 67 evaluable patients at the 30 day time point.

Table 11 provides an overview of the primary and secondary endpoints and their outcomes.

Table 11: **PROGRESS Mini Cohort Primary and Secondary Efficacy Endpoint Results**

	Evaluable[§] N	Treatment (N=80)	Control (N=80)	p-value
PRIMARY EFFICACY RESULTS, [a,¥]				
Need for Post-Operative Interventions, N (%)	67	26 (38.8%)	42 (62.7%)	0.0070
SECONDARY EFFICACY RESULTS				
Need for Post-Operative interventions, N (%)[b]	79	13 (16.5%)	33 (41.8%)	<0.0001
Need for Oral Steroid Interventions, N (%)[b]	79	12 (15.2%)	27 (34.2%)	0.0015
Need for Surgical Interventions, N (%)[b]	75	3 (4.0%)	12 (16.0%)	0.0225
Inflammation(100-VAS, mm), Mean (SD)[b]	77	24.7 (27.02)	41.3 (29.34)	<0.0001
Occlusion/restenosis, n (%)[b]	76	16 (21.1%)	35 (46.1%)	0.0002
Implant delivery success	80	80 (100%)	-	

[¥] Seventy nine patients returned for the Day 30 visit and had their endoscopy recorded for grading by independent reviewer; however, data were considered missing if the independent reviewer 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 frontal sinus. Since the planned statistical test (McNemar's test of correlated proportions) requires patients with an observed pair of outcomes, 12 patients could not be included in the test. McNemar's exact test was employed to obtain the 2-sided p-value at alpha level of 0.05 for primary efficacy endpoint.
[a] *Determined at Day 30 by the independent reviewer based on video-endoscopy review*
[b] *Determined at Day 30 by clinical investigators*
[§] Number of patients with evaluable sinuses on both sides.
SD=Standard Deviation, VAS=Visual Analog Scale

The primary efficacy endpoint was met. The rate of Post-Operative Intervention was 62.7% on the control sides compared to 38.8% on the treatment sides. This difference was statistically significant (p=0.0070) and represented a 38% relative reduction in Post-Operative Interventions. The primary effectiveness results are provided in **Table 12**.

Table 12: PROGRESS Mini Cohort: Primary Efficacy Endpoint

	Evaluable[¥] N	Treatment (N = 80)	Control (N = 80)	p-value[a]
PRIMARY EFFECACY RESULTS				
Need for Post-Operative Intervention at Day 30, N (%)	67	26 (38.8%)	42 (62.7%)	0.0070

[¥] Seventy nine patients returned for the Day 30 visit and had their endoscopy recorded for grading by independent reviewer; however, data were considered missing if the reviewer 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 frontal sinus opening. Since the planned statistical test (McNemar's test of correlated proportions) requires subjects with an observed *pair* of outcomes, 12 patients could not be included in the test. Evaluable subjects were those with gradable sinuses on both sides.
[a]McNemar's exact test was employed to obtain the 2-sided p-value at alpha level of 0.05 for the primary efficacy endpoint.

Statistically significant reductions in the need for postoperative interventions, need for oral steroid intervention, need for surgical intervention, inflammation

scores and rate of occlusion/restenosis were observed at day 30 as determined by clinical investigators (see **Table 1**). The implant delivery success rate was 100%, as evaluated by clinical investigators.

The incidence of adverse events was consistent with those seen in prior studies for the PROPEL drug-coated sinus stents. The incidence of each individual AE type by side (control vs. drug-coated stent) was quite similar. Overall, review of the safety data reveals no significant concerns related to adverse events.

3. Subgroup Analyses
   The following preoperative characteristics were evaluated for potential association with outcomes: use of topical steroids and the use of the PROPEL or PROPEL Mini in the ethmoid sinus. There were no confounding effects on the primary efficacy endpoint.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 26 investigators of which none were full-time or part-time employees of the sponsor and 1 had disclosable financial interest/arrangement as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None
- Significant payment of other sorts: 1
- Proprietary interest in the product tested held by the investigator: None
- Significant equity interest held by investigator in sponsor of covered study: None

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Ear Nose and Throat Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The PROGRESS Mini Cohort study demonstrated the safety and efficacy of the PROPEL Mini sinus implant in the frontal sinus. The primary efficacy endpoint was met. Results from the Mini Cohort confirmed the hypothesis that the steroid-releasing implant reduces the need for post-operative interventions in patients with chronic rhinosinusitis. The study also demonstrated that, compared to surgery alone, placement of the PROPEL Mini sinus implant in the frontal sinus opening maintains sinus patency by reducing inflammation, scarring and polypoid edema and that these endoscopic findings could be translated into measurable clinical benefits.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. There were no deaths or serious adverse events attributed to the device. The incidence of non-serious adverse events was consistent in both the control and treatment group. Overall, the incidence and types of adverse events were similar to those reported in clinical studies for the similar drug-coated PROPEL sinus implant indicated for the ethmoid sinus. The PROGRESS Mini Cohort study data demonstrated the safety of the PROPEL Mini sinus implant. The primary safety endpoints were met. The study confirmed that the addition of the drug poses negligible safety risks.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The benefits of the device as an adjunctive therapy after functional endoscopic sinus surgery (FESS) for patients with chronic rhinosinusitis (CRS), are based on clinical data from a multi-center, randomized, within-subject controlled clinical trial. The results demonstrated that the device has a clinically meaningful benefit over standard surgery of the frontal sinus opening (FSO) region without use of the device. The study met its primary endpoint: the need for medical and surgical interventions was reduced postoperatively in the device-treated group. This result was robust when challenged with numerous sensitivity analyses. Likewise, the secondary effectiveness endpoint, i.e., the need for postoperative intervention FSOs over time on Days 21, 30, and 90 was significantly greater on control frontal sinus openings (FSO) than on device-treated FSOs. The use of this device is expected to benefit patients by reducing the need for post-operative interventions for CRS patients, thus reducing risks of side effects from using typically prescribed oral steroids or antibiotics, reducing the risk of infections, and to assist in the prevention of forming adhesions during healing.

In addition, the risks of the PROPEL Mini sinus implant are well-characterized and based on data collected from clinical studies of the similar PROPEL sinus implant device and are considered low in severity. In the clinical study for the PROPEL Mini sinus implant, there were no reported deaths and no serious adverse events related to the use of the device. Sinusitis and headache were the most frequently reported adverse events and were reported in 26.3% and 11.3% of patients, respectively. Additional adverse events reported included respiratory, thoracic and mediastinal disorders in 18.8% of patients. Adverse events related to acute otitis media, asthma, epistaxis, eye disorders (eyelid edema and swelling), influenza, nasal congestion, nasal polyps, nasopharyngitis, nausea, and presyncope, occurred in 2.5-5% of patients. The incidence of adverse events was consistent with those of the approved PROPEL sinus implant.

In conclusion, given the available information above, the data support that for use of the PROPEL Mini sinus implant in adults over 18 years of age following ehthmoid and/or frontal sinus surgery to maintain patency of the ethmoid sinus or frontal sinus opening, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The safety, efficacy and performance of the PROPEL Mini sinus implant has been demonstrated in nonclinical laboratory and animal testing, and a prospective, multi-center clinical study in the United States. The primary safety, efficacy and performance endpoints in the clinical study 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 frontal sinus opening patency by reducing inflammation, adhesions and polyposis and that these endoscopic findings could be translated into measurable clinical benefits. The studies 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 Mini sinus implant offers meaningful clinical benefits to patients in terms of reducing the incidence of post-operative interventions. The results demonstrate that the PROPEL Mini sinus implant provides a reasonable assurance of safety and effectiveness when used in the frontal sinus opening of chronic rhinosinusitis patients undergoing sinus surgery.

XIII. CDRH DECISION

CDRH issued an approval order on March 23, 2016.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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.