SUPPLEMENTARY APPENDIX 1

This appendix contains the clinical protocol and the statistical analysis plan and is provided by authors to give readers additional information about their work. It will be available only with the full text of the article at JAMAoto.org.

Supplement to: A. Luong, R. A. Ow, A. Singh, et al. Safety and Effectiveness of a Bioabsorbable Steroid-Releasing Implant for the Paranasal Sinus Ostia: A Randomized Clinical Trial

The PROGRESS Study

A Non-Significant Risk Trial

Safety and Efficacy of the Propel Mini and Propel Nova Steroid-Releasing Sinus Implants Following Surgical Opening of the Frontal Sinus for Chronic Sinusitis: A Randomized Blinded Controlled Study

Protocol #:	P500-0514
Doc. Control #:	28020
Version #:	5.0
Version Date:	April 29, 2015
Principal Investigator:	Timothy L. Smith, MD, MPH Otolaryngology-Head and Neck Surgery Oregon Health Science University 3181 SW Sam Jackson Park Road, PV-01 Portland, OR 97239 Tel: +1 503-494-7413
Study Sponsor:	Intersect ENT 1555 Adams Drive Menlo Park, CA 94025 Tel: +1 650-641-2100 Fax: +1 650-641-2053
Data Management:	Intersect ENT
Biostatistics and Data Analysis:	Advance Research Associates, Inc. 2107 Landings Drive Mountain View, CA 94043 Tel: +1 650-810-1190 Andrew Mugglin PhD Paradigm Biostatistics 1288 Benton Street Anoka, MN 55303 Tel: +1 763-515-7576
Study Monitoring:	Intersect ENT

TABLE OF CONTENTS

1.0 Protocol Summary

Study Title:	Safety and Efficacy of the Propel Mini and Propel Nova Steroid-Releasing Sinus Implants Following Surgical Opening of the Frontal Sinus for Chronic Sinusitis: A Randomized Blinded Controlled Study
Objective:	To assess the safety and efficacy of the Propel Mini and Propel Nova Sinus Implants when placed in the frontal sinus opening following frontal sinus surgery in patients with chronic sinusitis
Study Implants:	The **Propel Mini Sinus Implant** is currently approved for use following ethmoid sinus surgery to maintain patency. The implant is a self-expanding scaffold intended for placement in the ethmoid sinus or frontal sinus opening to stabilize the middle turbinate, separate mucosal surfaces, prevent synechiae and maintain sinus patency. The Propel Mini Sinus Implant has a strut length of 18 mm and a top-coating containing 370 μg of the corticosteroid mometasone furoate (active ingredient in Nasonex intranasal spray). The drug coating is intended to perform an ancillary function by helping to minimize inflammation and edema. The **Propel Nova Sinus Implant** is also a self-expanding scaffold intended for placement in the frontal sinus opening to separate mucosal surfaces, prevent synechiae and maintain sinus patency. The Propel Nova has a strut length of 16 mm and a top-coating containing 370 μg of the corticosteroid mometasone furoate. This study will evaluate the safety and efficacy of both implants when placed in the frontal sinus opening following frontal sinus surgery by traditional surgical technique or balloon dilation that includes enlargement of the frontal sinus opening (referred to as FSO henceforth).
Study Design:	A prospective, randomized, blinded, controlled, multicenter study utilizing an intra-patient control design to assess the safety and efficacy of the steroid-releasing implant when placed following surgery on one sinus side compared to surgery alone on the contralateral side.
Patient Enrollment:	The study will enroll two consecutive patient cohorts at up to 20 study centers: • **Mini Cohort**: A minimum of 50 and a maximum of 80 patients will be enrolled to achieve 20 discordant pairs of results (i.e., requiring intervention on only one side). A maximum of 15 patients may be randomized in this cohort at a single study center. • **Nova Cohort**: A minimum of 50 and a maximum of 80 patients will be enrolled to achieve 20 discordant pairs of results (i.e., requiring intervention on only one side). A maximum of 15 patients may be randomized in this cohort at a single study center. Enrollment in the Nova Cohort will commence once total enrollment is

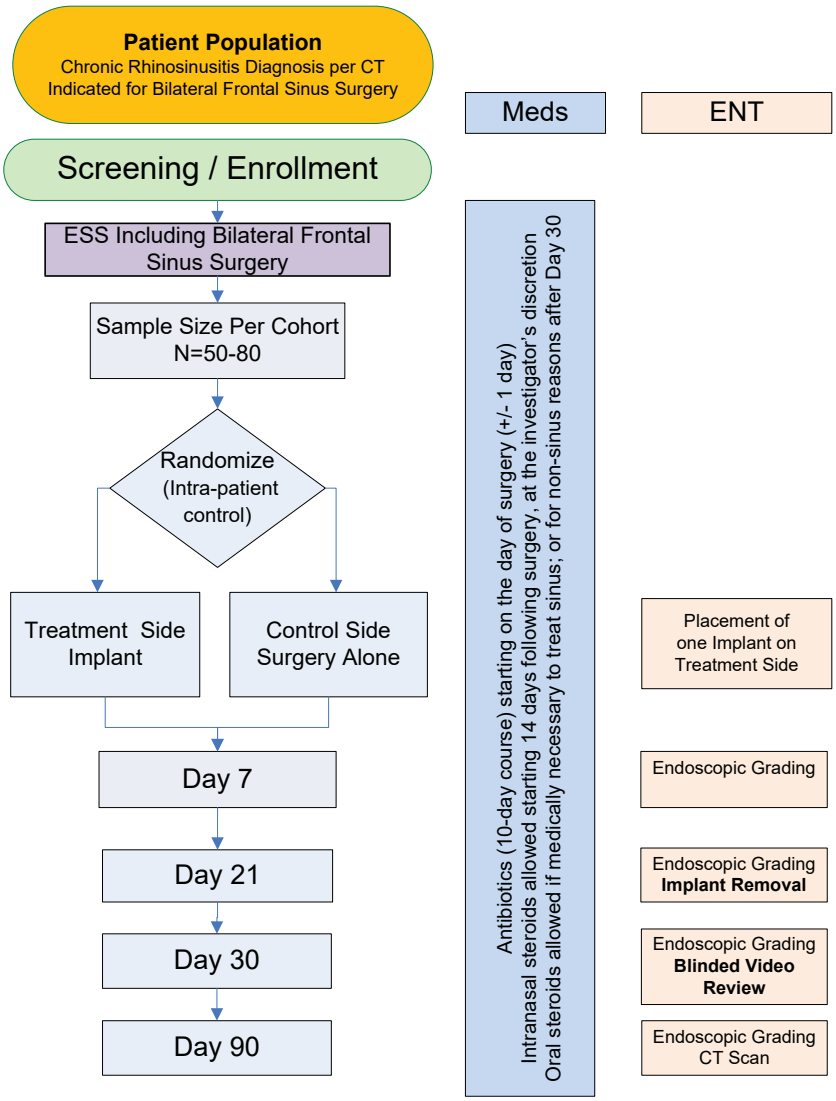
	completed in the Mini Cohort, or when one study center reaches the 15 patient enrollment maximum in the Mini Cohort.
Treatment Assignment:	Each patient will undergo placement of one implant. The side of placement will be randomly assigned.
Primary Efficacy Endpoint:	The primary efficacy endpoint will be the reduction in need for post-operative interventions at Day 30, as determined by an independent, blinded sinus surgeon based on video-endoscopy reviews. Post-operative intervention is a composite endpoint that includes: • Surgical intervention required to debride obstructive adhesions or scar tissue formation* in the FSO, and/or • Oral steroid intervention warranted to resolve recurrent inflammation or polypoid edema in the frontal recess/FSO. • *defined as grades 2 or 3 on the adhesion/scarring scale. **The primary efficacy endpoint will be evaluated for each study cohort separately.**
Secondary Efficacy Endpoints:	Secondary efficacy endpoints will include: Endoscopic outcomes assessed by an <u>independent blinded sinus surgeon</u> based on video-endoscopy review: • Frequency and severity of adhesion/scarring formation in the FSO at Day 30 • Degree of inflammation in the frontal recess/FSO at Day 30 using a 100-mm Visual Analog Scale (VAS) • Frequency and grade of polypoid edema in the frontal recess/FSO at Day 30 • A sensitivity analysis will be performed to assess the impact of actual interventions that occur prior to Day 30, upon the assessments made by the independent reviewer at Day 30. CT outcomes assessed by an <u>independent blinded sinus surgeon</u> based on CT scan review: • Patency of the FSO and Lund-Mackay score at Day 90 Endoscopic outcomes assessed by <u>on-site investigators</u>: • Need for post-operative intervention at all time-points through Day 90 • Degree of inflammation in the frontal recess/FSO at all time-points through Day 90 using the 100-mm VAS • Frequency and severity of adhesion/scarring formation in the FSO at all time-points through Day 90 • Frequency and grade of polypoid edema in the frontal recess/FSO at all time-points through Day 90 • Rate of frontal sinus patency at Day 90 determined endoscopically and radiologically (CT scan) • Implant delivery success rate

	Secondary efficacy endpoints will be evaluated for each study cohort separately.
Safety Measures:	Implant safety will be determined by assessment of adverse events. Adverse Events and Serious Adverse Events will be recorded and tabulated through Day 30 and Day 90. Where possible and if applicable, adverse events will be localized to a sinus location. **Safety measures will be determined for each study cohort separately.**
Study Duration:	The anticipated timeline for this study is as follows: Mini Cohort: • Initiation of enrollment: September 2014 • Completion of enrollment: May 2015 • Completion of Day 90 follow-up: August 2015 Nova Cohort: • Initiation of enrollment: June 2015 • Completion of enrollment: November 2015 • Completion of Day 90 follow-up: February 2016
Patient Population	Adult patients diagnosed with chronic rhinosinusitis (CRS) scheduled to undergo endoscopic sinus surgery (primary or revision), including bilateral frontal sinus surgery, and in whom placement of the Propel Mini or Propel Nova Sinus Implant is both feasible and medically appropriate.
Key Eligibility Criteria:	General Inclusion Criteria: • Patient has CRS confirmed by CT scan and defined as symptoms lasting longer than 12 consecutive weeks in duration with inflammation of the mucosa of the nose and paranasal sinuses. • Patient has a clinical indication for and has consented to ESS including bilateral frontal sinus surgery. CT Imaging Inclusion Criteria: • Chronic sinusitis diagnosis confirmed and documented by CT scan within 6 months of the procedure. • Patient has bilateral disease in both frontal sinuses confirmed by Lund-Mackay score of ≥1 on each side. Surgical Inclusion Criteria: • Planned sinus surgery includes bilateral ethmoidectomy (if judged necessary) and frontal sinus enlargement using Draf II (A or B) dissection or balloon dilation, with minimum of 5-mm diameter opening created. • Technique used for frontal sinus surgery is the same on both sides (e.g. surgical dissection alone bilaterally, balloon dilation alone bilaterally, or both bilaterally) • 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.
Key Exclusion Criteria:	General Exclusion Criteria: • Known history of immune deficiency such as immunoglobin G or A subclass deficiency, or Human Immunodeficiency Virus (HIV) • Oral-steroid dependent condition such as chronic obstructive pulmonary disease (COPD) or asthma or other condition • Known history of allergy or intolerance to corticosteroids or mometasone furoate • Clinical evidence of acute bacterial sinusitis • Clinical evidence or suspicion of invasive fungal sinusitis (e.g., bone erosion on CT scan, necrotic sinus tissue) • Active viral illness • Concurrent condition requiring active chemotherapy and/or immunotherapy management for the disease • Clinical evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments during the 90 day follow-up period • Currently participating in another clinical trial • History of insulin dependent diabetes mellitus • Patient has previously undergone ESS and experienced a CSF leak or has compromised vision as a result of a complication in a prior ESS procedure Intra-operative Exclusion Criteria: • Significant complication during the current frontal sinus surgery procedure such as excessive blood loss, CSF leak or punctured lamina papyracea • Current ESS including frontal sinus surgery is aborted for any reason. • At least one side is not amenable for implant placement.
Treatment Strategy:	• The implant will be assigned randomly to one sinus (left or right) and placed in the FSO at the end of successful frontal sinus surgery. • Septal splints, if used, should be trimmed to avoid contact with the middle turbinate and/or study Implants. • No hemostatic packing materials of any kind should be placed within the implants unless medically necessary. Packing such as the Merocel tampon may be placed in the nasal cavity, if necessary. • For purposes of the study, any visible remnants of the implant will be removed by Day 21 to allow for a blinded assessment at Day 30.
Concomitant Medications:	• Leading up to frontal sinus surgery there will be no restriction for oral or intranasal steroid use. • A 10-day course of antibiotics beginning on the day of surgery (+/- 1 day) will be required • Intranasal steroids will be allowed starting day 14 following surgery at the investigator's discretion. • Orally-inhaled steroids for control of asthma, for example, will be permitted. • Patients will be encouraged to use saline sprays or irrigation as needed

	during follow-up.
Medical Interventions:	Oral steroid intervention (sinus-related)**:** • If in clinician's opinion, a clinically significant increase in sinus inflammation, edema and/or polyposis occurs in the frontal recess/FSO in either sinus, and oral steroids are determined to be warranted, such intervention may be commenced. The frontal sinus side warranting intervention will be noted on the endoscopic scoring form. Other Medication Intervention (non-sinus related)**:** • If oral steroids are required for reasons other than and not including sinus inflammation of the frontal recess/FSO, a regimen will be allowed after Day 30. • If infection is suspected at any time during the study, treatment with antibiotics will be allowed. • Reason for any medication will be noted on the Concomitant Medication form and localized to sinus and side wherever possible.
Patient Follow-Up:	Patients will undergo post-operative assessment prior to discharge. Protocol-required follow-up visits will take place at Days 7, 21, 30 and 90.

2.0 STUDY FLOW DIAGRAM PER COHORT



3.0 BACKGROUND INFORMATION

3.1 Literature Review: Chronic Sinusitis and Functional Endoscopic Sinus Surgery

Chronic rhinosinusitis (CRS) is one of the most common health problems in the United States and there is evidence that it is increasing in its prevalence and incidence. An estimated 16% of the adult population (>30 million people) is affected annually[1]. Chronic sinusitis causes significant physical symptoms, negatively affects quality of life, and can substantially impair daily functioning. A conservative estimate is that chronic sinusitis results in 18 to 22 million U.S. physician office visits annually, and all forms of sinusitis result in significant health care expenditures[2].

The inflammatory response to CRS manifests itself in patient-reported symptoms such as facial pain and pressure, nasal congestion, edema of various local tissues, headache and a variety of other symptoms. Addressing the underlying causes of sinusitis and controlling the symptoms caused by the inflammatory process is the focus of medical therapy. Patients who are recalcitrant to medical therapy may be referred for functional endoscopic sinus surgery (ESS) to improve ventilation and drainage and to remove polyps.

Several hundred thousand ESS procedures are performed in the U.S. annually and this number appears to be increasing. Primary ESS typically involves uncinectomy, ethmoidectomy, maxillary antrostomy, and frequently, frontal recess dissection and frontal sinus surgery (sinusotomy). Typical anterior ethmoidectomy involves dissection and removal of the bulla ethmoidalis (the first and most constant ethmoid cell in a highly variable anatomy), anterior ethmoidal cells and agger nasi cells (**Figure 1**). These structures are part of the ethmoid sinus labyrinth, which includes the frontal recess. Removal of these structures allows access to the posterior ethmoid cells and exposes the frontal sinus opening (**Figure 2**). Complete ethmoidectomy is accomplished by extending the dissection through the basal lamella to reach and remove septations of the posterior ethmoid cells and to reach the sphenoid sinus.

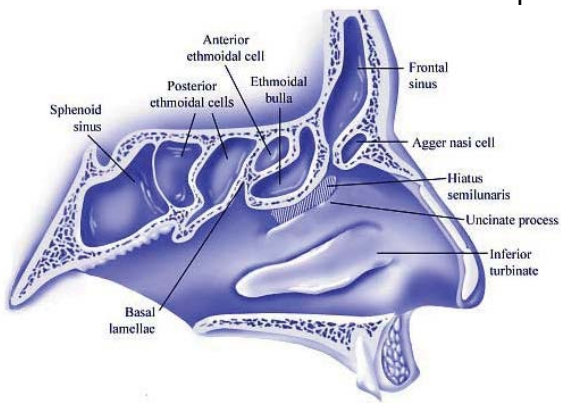


Figure 1. Normal sinus anatomy from the nose toward the back of the head

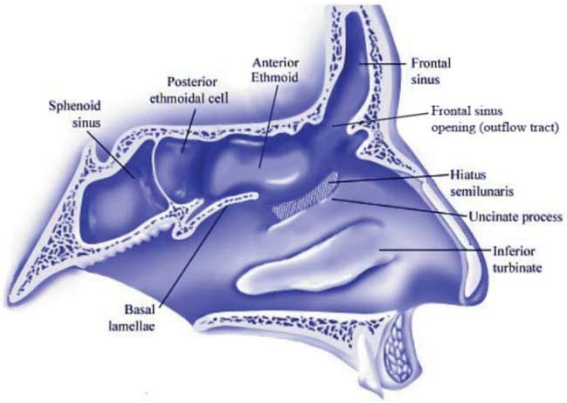


Figure 2. Post-ESS sinus anatomy from the nose toward the back of the head

Endoscopic surgical approaches to the frontal sinus have been developed. A popular and commonly used algorithm is based on anatomical drainage patterns as described by Draf[3,4]. These include (1) anterior ethmoidectomy (which includes frontal recess dissection) without alteration of the frontal ostium itself, (2) anterior ethmoidectomy with further enlargement of the frontal ostium and possible removal of the frontal sinus floor

on a given side, and (3) trans-septal frontal sinus surgery with wide removal of the frontal sinus floor on both sides. A Draf I or Draf II procedure, in effect, surgically addresses the variable frontal sinus drainage pathway referred to as the frontal recess.

While ESS has been demonstrated to be effective in reducing patient-reported symptoms in the short term, and longer term success rates have been reported in the range of 76% to 98%[5], a relatively large number of patients continue to be symptomatic or experience recurrent symptoms or revision surgery within one to two years. Causes of surgical failure are numerous and include lateralization of the middle turbinate, adhesion formation between the middle turbinate and lateral nasal wall, ostial stenosis, persisting or recurrent mucosal edema, and polyposis. The same post-operative failure mechanisms within the ethmoid sinus apply to the frontal recess and frontal sinus opening. These include formation of scarring, adhesions, synechiae, recurrent inflammation, and polyposis.

Many surgeons consider the postoperative treatment regimen to be as important as the surgery itself[6]. There is strong evidence that postoperative endoscopic examination of the sinonasal cavity provides prognostic information concerning the potential for future episodes of sinusitis and that patients whose cavities became normal post-operatively are less likely to require revision[7]. Meticulous post-operative care following ESS involves several follow-up visits over the ensuing months. Maintenance of the surgical result is accomplished by routine endoscopic examination, meticulous cleaning of the cavity using saline rinses, debridement or other manipulations to remove adhesions, and adjustments in pharmacotherapy. Formation of adhesions, scarring, synechiae, middle turbinate lateralization, ostial stenosis and edema are major concerns often addressed by use of sinus stents and injectable gels.

To address these post-operative issues, Intersect ENT developed the Propel, Propel Mini and Propel Nova mometasone furoate sinus implants. The Propel Sinus Implant was approved by the United States Food and Drug Administration (FDA) on August 11, 2011, for placement in the ethmoid sinus following sinus surgery. The Propel Mini Sinus Implant is a smaller (16 mm nominal length) version of the original Propel Sinus Implant, and it was approved by the FDA on September 21, 2012, for the same indication.

The Propel Nova Sinus Implant is currently an investigational device. It represents a smaller version of the Propel and Propel Mini implants and is composed of the same materials and drug content. Propel Nova is formed in a different shape and is designed specifically for placement in the sinus ostium. The implant is supplied with an applicator that allows access and deployment in the post-surgical (e.g. by balloon dilation or traditional surgical techniques) frontal sinus ostium. The deployment mechanism for Propel Nova is similar to the mechanism used for Propel and Propel Mini.

The Propel family of sinus implants (Propel, Propel Mini, Propel Nova) is intended for use in adult patients with CRS who have undergone ESS. The Propel implants are designed to be placed following sinus surgery to maintain patency of the sinus. The implants are coated with a small amount (370 μg total drug content) of the corticosteroid mometasone furoate. This coating is designed to provide a local anti-inflammatory agent to aid in minimizing edema, inflammation, and polyposis within the supported tissues of the sinuses. The Propel family of implants are combination products with the primary mode of action being a device.

The safety and efficacy of Propel, when used in adult patients with CRS undergoing endoscopic sinus surgery (ESS), was studied in in 205 patients in three prospective clinical trials conducted in the U.S.[8,9,10] The study protocols required complete ethmoidectomy with middle meatal antrostomy, prior to implant placement. Sixty percent (60%) of patients in the studies also underwent concurrent frontal sinus surgery as part of the surgical procedure. As described above, anterior ethmoidectomy involves dissection and removal of the structures immediately inferior to the frontal sinus opening, termed the frontal recess in surgical parlance. The present study is being conducted to evaluate the safety and efficacy of placement of Propel Mini and Propel Nova Sinus Implants in the frontal sinus opening.

3.2 Description of the Sinus Implants

Summary descriptions of the Propel Mini and Propel Nova Sinus Implant are provided below. For more detailed delivery system and implant information, refer to the Instructions for Use (IFU).

3.2.1 Propel Mini Intended 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 edema. The implant reduces the need for post-operative intervention such as surgical adhesion lysis and/or use of oral steroids.

3.2.2 Propel Mini Sinus Implant

The Propel Mini Sinus Implant is designed to accommodate the size and variability of the human sinus anatomy. The implant is intended to be inserted by a physician under endoscopic visualization and once positioned, is designed to be self-retaining against the mucosal surface in the area of the frontal recess/FSO.

The Propel Mini Sinus Implant is fabricated from a bioabsorbable monofilament polymer material commonly used in a variety of medical products, including dissolvable sutures. The monofilament is approximately 0.35 mm in diameter.

Figure 3 depicts the structure design features of the Propel Mini Sinus Implant including: the semi-crystalline fiber material, articulated crown-like shape (9 crown points), and the spring-like loops placed at each articulation. The fiber is joined at each intersection to help maintain the shape of the implant. The resulting self-expanding nature of the implant provides uniform outward force against the mucosal surfaces, conforming to variable sinus anatomy. The length of each individual strut between two crown points is 18 mm.

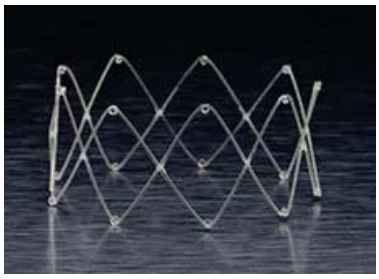


Figure 3. Propel Mini Sinus Implant

3.2.3 Propel Mini Drug Coating

The top coating on the Propel Mini Sinus Implant is composed of mometasone furoate (the active ingredient), poly (DL-lactide-co-glycolide) (PLG) and polyethylene glycol (PEG). Both PLG and PEG are bioabsorbable polymers with a long history of use in medical devices. The top coating on the implant contains 370 μg of mometasone furoate and is designed to release >80% of the total content within 14 days. The coating is added to provide a secondary role in minimizing edema/inflammation. Based on the *in-vivo* drug release rates demonstrated in animal studies, the estimated average daily drug release for the device over the initial 14 days is ≤27 μg / day.

3.2.4 Propel Mini Delivery System

The Propel Mini Sinus Implant is provided with a single use delivery system (**Figure 4**). The delivery system comprises the ergonomic handle, a pusher that is spring loaded and is depressed against the inner push rod to deploy the sinus implant, and an outer sheath. The tip of the outer sheath has a spoon curvature to facilitate placement. The delivery system is used by the physician to access the sinus and then deploy the implant in the desired location by depressing the pusher on the delivery system to release the implant.

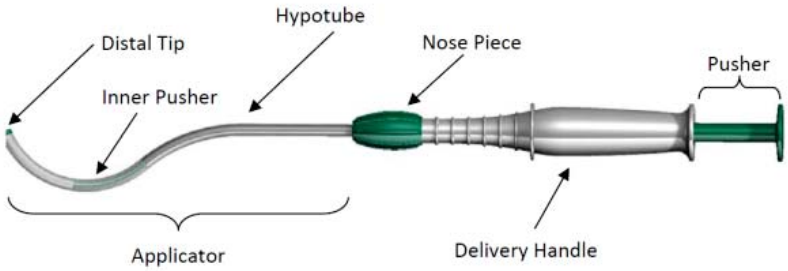


Figure 4. Schematic of the Propel Mini delivery system

The Propel Mini Sinus Implant is provided with a crimper to compress the implant prior to loading into the delivery system.

3.2.5 Propel Mini Implant Deployment

The Propel Mini Sinus Implant is compressed and placed into the delivery system (**Figure 5**), which enables a low profile mode of entry into the sinus facilitating placement in the desired location. The Pusher is depressed to deploy the implant from the distal tip of the delivery system. Upon exiting the delivery system, the compressed implant expands radially to conform to and contact the sinus tissue.

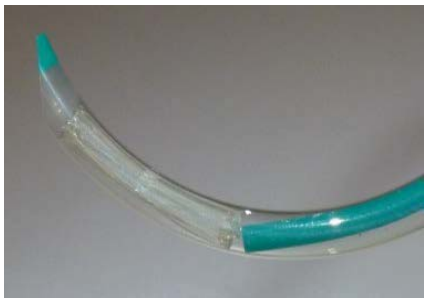


Figure 5. Compressed Propel Mini Implant loaded into distal tip of the delivery system

The delivery system is then retracted out of the patient. Final placement is confirmed by endoscopic visualization. The position of the implant can be adjusted after placement using standard surgical instruments typically available for ESS and for follow-up care.

3.2.6 Propel Nova Intended Use

The Propel Nova Sinus Implant is intended for use in patients ≥ 18 years of age to maintain patency of sinus ostia following sinus surgery. The Propel Nova Sinus Implant separates/dilates mucosal tissues, prevents obstruction by adhesions/scarring, and reduces edema.

3.2.7 Propel Nova Sinus Implant

The Propel Nova Sinus Implant is a self-expanding bioabsorbable implant designed for placement in the frontal sinus ostium to maintain patency post-surgery. The Propel Nova Sinus Implant is a drug-releasing sinus implant that is smaller in size than the Propel Mini Sinus Implant to accommodate the size and variability of the enlarged sinus ostium. The waist of the implant is narrower than the outer diameter to give the implant an hourglass shape, which aids in retention within the sinus ostium. Identical to the Propel and Propel Mini Sinus Implants, the Propel Nova Sinus Implant contains 370 μg of mometasone furoate, which is added to the coating of the device to provide an ancillary function by incorporating a local anti-inflammatory agent to aid in minimizing edema within the supported tissues. Based on the *in-vivo* drug release rates demonstrated in animal studies, the estimated average daily drug release for the device over the initial 14 days is ≤27 μg / day.

The Propel Nova Sinus Implant is manufactured from a synthetic bioabsorbable co-polymer (primarily polylactide co-glycolide [PLG]). This is the same material used to manufacture the Propel and Propel Mini Sinus Implants. The Propel Nova, Propel and Propel Mini Sinus Implants are all formed from an extruded synthetic implant-grade bioabsorbable (PLG) fiber that is wound on a fixture to achieve the desired geometry. The fiber ends (lap joint) and implant strut intersections are bonded with the bioabsorbable polymer poly-(L-lactide-co-ε-caprolactone) (or PLC) to secure the implant geometry.

The Propel Nova Sinus Implant is intended to be inserted by a physician under endoscopic visualization and once positioned, is designed to be self-retaining against the mucosal surface in the area of the enlarged sinus ostium.

Figure 6 is an enlarged view of the implant and **Figure 7** provides a representation of the Propel Nova Sinus Implant deployed in the post-operative frontal sinus ostium.

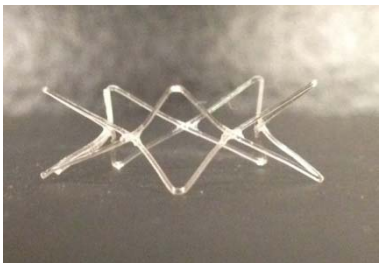


Figure 6. Enlarged view of Propel Nova Sinus Implant

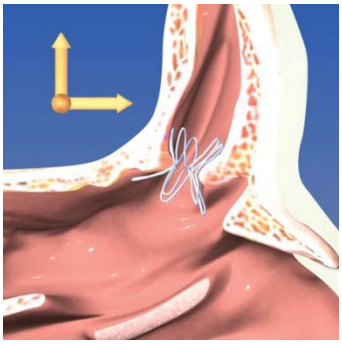


Figure 7. Representation of Propel Nova Sinus Implant placed in frontal sinus ostium

3.2.8 Propel Nova Drug Coating

A small amount of the anti-inflammatory corticosteroid mometasone furoate is formulated onto the implant as a topcoat. This topical/localized drug eluted for a short period of time provides an ancillary function to help reduce post-surgical edema/inflammation of the sinus ostia.

The drug dose and release rate over time are designed to provide a controlled daily drug elution. The total content of the drug constituent is 370 µg. A majority of the drug is released over approximately 14 days.

3.2.9 Propel Nova Delivery System and Applicator

The Propel Nova Sinus Implant is provided with a single use delivery system. The delivery system comprises a handle component and an applicator component. The Propel Nova delivery applicator has a 70 degree bend at the distal end and a beveled distal tip to facilitate access to the sinus ostium. The

Propel Nova applicator is smaller in diameter than the Propel Mini delivery systems to accommodate the decreased implant size and to access smaller sinus anatomy.

3.2.10 Propel Nova Sinus Implant Deployment

Similar to the Propel and Propel Mini delivery systems, the Propel Nova delivery system is utilized by physicians to access the sinus and then deploy the implant in the desired location by depressing the pusher on the delivery system to release the implant. The Propel Nova Sinus Implant is hand crimped (i.e., compressed) into a small bundle, inserted into a funnel at the tip of applicator, and pushed into the applicator through the funnel. The funnel is then removed from the tip of the delivery system for placement in the sinus anatomy.

For endoscopic placement, the delivery system is advanced to the target location, then the pusher on the delivery system is depressed to release the implant from the distal tip of the delivery system into the sinus ostium. Upon release, the Propel Nova Sinus Implant expands radially to conform to and dilate the sinus ostium.

The delivery system is then retracted out of the patient. Final position is confirmed by endoscopic visualization. The position of the Propel Nova Sinus Implant can be adjusted after placement using standard surgical instruments typically available in the office and operating room settings. The Propel Nova Sinus Implant may be removed at the discretion of the physician.

3.3 Summary of Prior Clinical Experience in ESS patients

The Propel Sinus Implant, intended for use in the ethmoid sinus immediately post-ESS recovery period, was studied in three clinical studies in the U.S., totaling 205 patients. All three studies were designated as non-significant risk (NSR) by FDA and multiple IRBs, including IntegReview Ethical Review Board (Austin, TX). As described in Section 3.1 above, all safety, efficacy and performance endpoints were met in these studies. Propel was approved by the FDA for commercialization on August 11, 2011. Propel Mini was approved by FDA on September 21, 2012. Since commercialization, Propel and Propel mini implants have been used in treatment of over 50,000 patients in the US.

The Propel Nova Sinus Implant has been evaluated in a feasibility study called EXCEED. The EXCEED study allowed implant placement in both the frontal and maxillary sinus ostia in either the office or operating room setting following surgical enlargement using traditional surgical instrumentation or balloon sinus dilation. The study enrolled 15 patients at two clinical centers, and was designed to assess the feasibility of the implant placement, evaluate the safety and to collect initial efficacy data. Endoscopic measures included evaluation of sinus patency and inflammation scores. A 98% implant placement success rate was observed and there were no implant-related adverse events. Favorable results were observed in both endoscopic and patient-reported outcome measures over a 90 day follow-up period.

4.0 STUDY OBJECTIVE

The objective of the PROGRESS Study is to assess the safety and efficacy of the Propel Mini and Propel Nova Sinus Implants when placed in the frontal sinus opening following frontal sinus surgery in patients with CRS.

5.0 STUDY DESIGN AND ENDPOINTS

5.1 Study Design

This is a prospective, randomized, blinded, controlled, multicenter study that will enroll two consecutive patient cohorts: the Mini Cohort and the Nova Cohort. Each cohort will enroll 50 to 80 patients who satisfy entry criteria at up to 20 study centers. A maximum of 15 patients may be randomized in each cohort at a single study center.

For each cohort, the study utilizes an intra-patient control design to assess the safety and efficacy of the implant compared to surgery alone without implant on the contralateral side. The study patients will undergo implant placement on one side following ESS that includes bilateral frontal sinus surgery by traditional surgical technique or balloon dilation. The study is blinded, meaning that patients will be blinded throughout the study duration to which side received the implant. The independent sinus surgeon performing review of the video-endoscopies will also be blinded to which side received the implant.

Patients will return for four follow-up visits at Days 7, 21, 30 and 90. The follow-up assessment will include endoscopic examinations that will be recorded. At Day 21 each implant or its remnants will be removed to allow blinded review of video endoscopies.

5.2 Primary Efficacy Endpoint

The primary efficacy endpoint will be the reduction in need for post-operative interventions at Day 30, as determined by an independent, blinded sinus surgeon based on video-endoscopy reviews.

Post-operative intervention is a composite endpoint that includes:

- Surgical intervention required to debride obstructive adhesions or scar tissue formation* in the FSO, and/or
- Oral steroid intervention warranted to resolve recurrent inflammation or polypoid edema in the frontal recess/FSO.

*defined as grades 2 or 3 on the adhesion/scarring scale (see Definition section)

The primary efficacy endpoint will be evaluated for each study cohort separately .

5.3 Secondary Efficacy Endpoints

Endoscopic outcomes assessed by an independent blinded sinus surgeon based on video-endoscopy review:

- Frequency and severity of adhesion/scarring formation in the FSO at Day 30

- Degree of inflammation in the frontal recess/FSO at Day 30 using a 100-mm Visual Analog Scale (VAS)
- Frequency and grade of polypoid edema in the frontal recess/FSO at Day 30

CT outcomes assessed by an independent blinded sinus surgeon based on CT scan review:
- Patency of the FSO and Lund-Mackay score at Day 90

Endoscopic outcomes assessed by on-site investigators:
- Need for post-operative intervention at Day 30
- Degree of inflammation in the frontal recess/FSO at all time-points through Day 90 using the 100-mm VAS
- Frequency and severity of adhesion/scarring formation in the FSO at all time-points through Day 90
- Frequency and grade of polypoid edema in the frontal recess/FSO at all time-points through Day 90
- Rate of frontal sinus patency at Day 90 determined endoscopically and radiologically (CT scan)
- Implant delivery success rate

The secondary efficacy endpoints will be evaluated for each study cohort separately.

5.4 Safety Measures

- Implant safety will be determined by assessment of adverse events.
- Adverse Events (AE) and Serious Adverse Events (SAEs) will be recorded and tabulated through Day 30 and Day 90. Where possible and if applicable, adverse events will be localized to a sinus location.

The safety measures will be evaluated for each study cohort separately.

6.0 PATIENT POPULATION, ELIGIBILITY, TREATMENT AND FOLLOW-UP

6.1 Patient Population

The study population will comprise adult patients diagnosed with CRS scheduled to undergo ESS (primary or revision), including bilateral frontal sinus surgery, in whom placement of the Propel Mini or Propel Nova Sinus Implant is both feasible and medically appropriate.

6.2 Patient Eligibility Criteria

Inclusion Criteria: Candidates for this study must meet ALL of the following criteria:

General Inclusion Criteria

a. Patient has provided written informed consent using a form approved by the reviewing IRB.
b. Patient is 18 years of age or older.
c. Patient is willing and able to comply with protocol requirements.

d. Patient has CRS confirmed by CT scan and defined as symptoms lasting longer than 12 consecutive weeks in duration with inflammation of the mucosa of the nose and paranasal sinuses.
e. Patient has a clinical indication for and has consented to ESS including bilateral frontal sinus surgery.
f. Patient can tolerate general anesthesia.
g. In the opinion of the investigator, treatment with the Propel Mini or Propel Nova Sinus Implant as an adjunct to ESS is technically feasible and clinically indicated in the frontal sinus openings.
h. Female patients of child-bearing potential must not be pregnant and must agree to not become pregnant during the course of the study.
i. Females of child-bearing potential must agree to use consistent and acceptable method/s of birth control during the course of the study

CT Imaging Inclusion Criteria:
j. Patient has CRS diagnosis confirmed and documented by CT scan within 6 months of the procedure.
k. Patient has bilateral disease in both frontal sinuses confirmed by Lund-Mackay score of ≥1 on each side.

Surgical Inclusion Criteria:
l. 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.
m. 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)
n. Septoplasty for access to the ostio-meatal complex is permitted.
o. 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.

Exclusion Criteria: Candidates will be excluded if ANY of the following apply:

General Exclusion Criteria:
a. Patient has a known history of immune deficiency such as immunoglobin G or A subclass deficiency, or Human Immunodeficiency Virus (HIV).
b. Patient has oral-steroid dependent condition such as chronic obstructive pulmonary disease (COPD), asthma or other condition.
c. Patient has a known history of allergy or intolerance to corticosteroids or mometasone furoate.
d. Patient has clinical evidence of acute bacterial sinusitis (e.g., acute increase in purulent discharge, fever, facial pain, etc.)
e. Patient has clinical evidence or suspicion of invasive fungal sinusitis (e.g., bone erosion on CT scan, necrotic sinus tissue, etc.)
f. Patient has evidence of active viral illness (e.g., tuberculosis, ocular herpes simplex, chickenpox or measles).
g. Patient has concurrent condition requiring active chemotherapy and/or immunotherapy management for the disease (e.g., cancer, HIV, etc.).

h. Patient has clinical evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments during the 90 day follow-up period.
i. Patient is currently participating in another clinical trial.
j. Patient has history of insulin dependent diabetes mellitus.
k. Patient has *previously* undergone ESS and experienced a CSF leak or has compromised vision as a result of a complication in a prior ESS procedure.

Intra-operative Exclusion Criteria:
l. Significant complication during the current ESS including frontal sinus surgery such as excessive blood loss, CSF leak or punctured lamina papyracea.
m. Current ESS including frontal sinus surgery is aborted for any reason.
n. At least one side is not amenable for implant placement.

6.3 Informed Consent, Enrollment and Screening

During the pre-screening phase, the investigator or designee will perform an initial evaluation of potential candidates for study eligibility. This initial pre-screening phase may include review of existing patient information (e.g., previously performed diagnostic measures, laboratory studies, medical history, physical examination) and referral to the treating physician.

If the patient appears to be a potential candidate for the study based on existing information, written informed consent will be obtained. No protocol required testing will be performed solely for the purposes of this study prior to obtaining patient written informed consent.

The investigator or designee will approach the patient to obtain written informed consent. The background of the proposed study, the implant procedure, the follow-up schedule and all potential benefits and risks will be carefully explained to the patient. The investigator or designee obtaining the informed consent shall:

- Avoid any coercion of or undue influence of patients to participate
- Not waive or appear to waive patient's legal rights
- Use language that is non-technical and understandable to the patient
- Provide ample time for the patient to consider participation

The patient must sign and date the approved Informed Consent Form (ICF) prior to screening.

Patients are considered enrolled in the study upon signing the ICF. At the time of enrollment, a unique identifying code will be assigned.

For those patients that agree to participate in the study by signing the ICF, a screening evaluation will be performed (see **Table 1** for a schedule of assessments). If the required screening assessments are performed as part of the patient's routine examinations and medical history, they may not need to be repeated after the patient's informed consent is obtained.

Table 1. Schedule of Assessments

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.

For females of child-bearing potential, discussion and documentation of birth control method/s in use shall be performed by the investigator as part of the screening evaluation and a pregnancy test should be performed prior the surgery/implant placement procedure. Acceptable methods of birth control may include contraceptive pills, injections, patches, intra-uterine devices or vaginal rings, barrier methods or contraceptive implants.

Patients should undergo the investigational procedure within approximately 30 days from signing the ICF.

All patients who provide written informed consent will be tracked and if found to be ineligible they will be terminated from the study and reason for ineligibility will be recorded (“Screen Failures”). This information will be documented on a patient enrollment log. In addition, a copy of all signed informed consent documents will be maintained at the site. This will allow appropriate monitoring of all consented patients and tracking of the rate of ineligibility.

6.4 Concomitant Medications

The standardized medication regimen is as follows:

- Leading up to frontal sinus surgery there will be no restriction for oral or intranasal steroid use.
- A 10-day course of antibiotics beginning on the day of surgery (+/- 1 day) will be required.
- Intranasal steroids will be allowed starting on day 14 following surgery at the investigator's discretion.
- Orally-inhaled steroids for control of asthma, for example, will be permitted.
- Patients will be encouraged to use saline sprays or irrigation as needed during follow-up.

Oral Steroid Intervention - Sinus-related:

If in clinician's opinion, a clinically significant increase in sinus inflammation, edema and/or polyposis occurs in the frontal recess/FSO in either sinus, and oral steroids are determined to be warranted, such intervention may be commenced. The frontal sinus side warranting intervention will be noted on the endoscopic scoring CRF.

Other Medication Intervention – Non-sinus-related:

- If oral steroids are required for reasons other than and not including sinus inflammation of the frontal recess/FSO, a regimen will be allowed after Day 30.
- If infection is suspected at any time during the study, treatment with antibiotics will be allowed.

Reason for any medication will be noted on the CRFs and localized to sinus and side wherever possible.

The investigator or other member of the research staff will review and document the specific medications being taken by the patient at baseline (including the 2 weeks pre-procedure), antibiotics or steroids administered during surgery, and through the study follow-up period to Day 90.

6.5 Treatment Strategy

The investigational treatment phase begins upon introduction of the Propel Mini or Propel Nova Sinus Implant delivery system into the study patient at the time of surgery.

6.5.1 Patient Preparation

The patient should be prepared for the planned surgical procedure according to standard surgery center procedures.

6.5.2 Surgical Extent and Sinus Implant Placement

- Devices and equipment typically required for frontal sinus surgery are required and are to be provided by the site. The Propel Mini and Propel Nova Sinus Implants with delivery systems will be provided by Intersect ENT.

- Draf II (A or B) dissection and/or balloon dilation should result in creation of a FSO with minimum of 5-mm diameter.

- The technique used for frontal sinus surgery should be the same on both sides (e.g. surgical dissection alone bilaterally, balloon dilation alone bilaterally, or both bilaterally).

- Randomization of the sinuses to treatment assignment will occur after successful completion of frontal sinus surgery and after meeting all other study eligibility requirements.

- The Propel Mini and Propel Nova Sinus Implants must be used according to the Instructions for Use (IFU).

- No hemostatic packing materials of any kind should be placed within the implants unless medically necessary. Packing such as the Merocel tampon may be placed in the nasal cavity, if necessary.

- If use of any hemostatic packing material within the Implant is deemed to be medically necessary, the study sponsor should be contacted prior to placement, if possible.

- Septal splints, if used, should be trimmed to avoid contact with the middle turbinate and/or study Implant.

- For purposes of the study, any visible remnants of the implant will be removed by Day 21 to allow for a blinded assessment at Day 30.

Appropriate video recording equipment of the sinus surgery and follow-up endoscopic examination will be required.

6.5.3 Sinus Implant Disposal

The delivery system will be disposed of as per standard institutional practices for biohazard waste.

If the sinus implant, delivery system or other components are associated with a device-related adverse event, malfunction or failure, the implant or its parts should be returned to Intersect ENT for evaluation, if possible. For the return of biohazard product, Intersect ENT must be contacted prior to product return for handling instructions.

6.6 Follow-Up Schedule

The follow-up period begins immediately post-treatment (once the patient exits the operating room). The patient will undergo follow-up assessments including endoscopic examination at four (4) post-operative visits at Days 7, 21, 30 and 90. During the first follow-up visit at Day 21, the implant will be removed to allow blinded assessment at Day 30.

An overview of the assessments to be performed at baseline and each follow-up interval along with required timing is provided in **Table 1**. Protocol-required visits occurring outside of the specified date range will be considered and reported as protocol deviations.

6.7 Endoscopic Recording and Evaluation

A video-endoscopy guideline will be developed to specify endoscopy equipment and video recording parameters at investigational centers. At a minimum, the guideline will address parameters such as the anatomy required to be viewed, type and degree of the scope(s) to be used, lighting and white balancing.

See Section 11.0 of this protocol for description of the endoscopic grading scales.

6.7.1 Operative Timeframe

Pre-Implant Placement

Endoscopic Assessment and Video Recording:

Prior to Surgery:

- Obtain video recording of patient anatomy just prior to surgery
- Indicate polyp grade, adhesions/scarring, patency and inflammation on CRF

After Surgery/Prior to Implant:

- Confirm final patient eligibility (ensure the patient's anatomy and overall condition are appropriate for Propel Mini or Propel Nova Sinus Implant placement)
- Confirm successful bilateral frontal sinus surgery outcome prior to implant placement
- Confirm post-surgical FSO diameter prior to implant placement
- Obtain video record of patient anatomy after surgery and prior to implant placement

Post-Implant Placement

Endoscopic Assessment and Video Recording:

- Obtain video recording of post-surgical anatomy, implant deployment and final placement and positioning
- On CRF, make note of:
  - Apposition of the implant to sinus anatomy (visually estimate percent apposition of implant struts)
  - Surgery performed, including middle turbinate infracture or reduction, if performed (e.g. concha bullosa), extent of frontal sinus surgery and instrumentation used

6.7.2 Follow-up Timeframe

Endoscopic Assessment:

Prior to debridement and/or cleaning of the frontal sinuses, the following endoscopic evaluation and rating will be performed:

- Obstruction by adhesion/scarring of the FSO using a 4-point scale (categorical variable)

After debridement and/or cleaning of the sinus cavities, the following endoscopic evaluation and rating will be performed:

- Inflammation in the FSO using the 100-mm VAS (continuous scale)
- Polypoid edema grade in the frontal recess/FSO using a 3-point scale (categorical variable)
- FSO patency grade on a 3-point scale (categorical variable)
- Whether surgical intervention or oral steroids are warranted based on findings in the FSO.

Radiologic Assessment at Day 90 (CT scan):

- Extent of disease in each frontal sinus on a 3-point radiological scale
- Lund-Mackay score on a 24-point scale
- An estimated measure of the FSO diameter will be captured.

6.7.3 Independent Blinded Review of Endoscopic Videos

Video-endoscopies obtained at Day 30 for all patients will be provided to an independent sinus surgeon for grading and determination of the primary efficacy endpoint. The independent reviewer will be independent from the study (i.e., not from investigational centers). The video-endoscopies will be edited to remove patient-identifying information (e.g. only imaging taken within the nose and sinuses will be provided). Video files will be randomly ordered, and the independent reviewer will be blinded to treatment assignment of the sinus sides.

From the randomized, blinded endoscopic videos, the independent reviewer will evaluate using the same scales as on-site investigators the following outcomes:

- Inflammation in the frontal recess/FSO using a 100-mm VAS
- Adhesion/scarring of the FSO using a 4-point scale
- Polypoid edema grade in the frontal recess/FSO using 3-point scale
- Need for post-operative intervention, either surgical to debride obstructive adhesion or scar tissue formation in the FSO and/or oral steroids to resolve recurrent inflammation or polypoid edema of the FSO

6.8 Study Patient Withdrawal/Termination

Patient participation in the study may be withdrawn or terminated for the following reasons:

- Patient death
- Voluntary withdrawal – meaning that patient voluntarily chooses not to further participate in the study
- Lost to follow-up: the patient is more than 30 days late to a study visit and 3 documented attempts to contact the patient are unsuccessful. A patient who misses a study visit but attends a subsequent visit will no longer be considered lost to follow-up.
- In the investigator's opinion, it is not in the best interest of the patient to continue study participation.
- Whenever possible, patients will be followed for safety to study completion (90 days). Safety follow-up will include a review of adverse events (AEs). A safety follow-up assessment may be performed either via a phone contact or a physician visit.
- Any study patient who does not attend a scheduled follow-up visit should be contacted by site personnel to determine the reason for the missed appointment(s).

The reason for the missed visit should be determined and documented in the patient's study records.

Data collected up to the point of patient withdrawal or termination will be maintained in the electronic database and will be included in analyses as appropriate.

All study patients enrolled (including those withdrawn or lost to follow-up) shall be accounted for and documented.

7.0 ADVERSE EVENTS

Adverse events (AEs) may occur during the investigational procedure or during the follow-up phase. Adverse events occurring during the baseline assessment and/or other pre-investigational procedures will be documented in the patient's medical record, but will not need to be reported in eCRFs and will not count as related to the investigational study, drug, device or procedure.

Each adverse event will be documented and reviewed by Intersect ENT personnel or contractors. Intersect ENT is responsible for ensuring that all adverse events are appropriately captured and when applicable, reported to the government(s), ethics committee(s) and other investigational sites per applicable regulations.

Each adverse event will be recorded in the corresponding patient's eCRF. Participating investigators will make a determination as to relationship of each adverse event to the surgical or endoscopic procedure, comorbidity or the investigational device. For device-related adverse events (anticipated or unanticipated), Intersect ENT may request source documentation for review of such adverse event detail with an independent rhinologist. In addition, the investigator will identify the date of onset, severity and duration. All adverse events will be monitored until they are adequately resolved or explained. See the Investigator Reporting of Adverse Events section 10.11.3 for reporting timelines.

Adverse Events, device-related adverse events, unanticipated adverse device events (UADE), Serious Adverse Events (SAE), are defined in the Definitions section of this protocol.

8.0 RISK/BENEFIT ASSESSMENT

A risk/benefit analysis has been performed and a summary of the results is provided below.

8.1 Potential Risks

Risks associated with the use of the implants in the FSO are anticipated to be similar to those experienced by patients who undergo placement of other sinus stents.

Accordingly, the risks potentially associated with the placement of the Propel Mini or Propel Nova Sinus Implant are:

- Implant may move after being placed in the sinus
- Premature displacement of implant or small implant fragments out the nares
- Swallowing implant or implant fragments
- Adherence of crusting to the 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
- Infection

Risks or side effects associated with intranasal mometasone furoate:

- Nasal irritation
- Hypersensitivity reaction
- Intranasal bleeding
- Localized infection (bacterial, fungal colonization or viral) in the nose or pharynx
- Nasal burning
- Nasal dryness
- Susceptibility to secondary infections due to bacteria, fungi or viruses
- Glaucoma or elevation of intraocular pressure
- Cataracts or change in lens opacities
- Headache
- Pharyngitis

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 or change in lens opacities
- Arthralgia

Inhaled and intranasal mometasone furoate is generally well tolerated in clinical trials and any adverse effects are mild and generally of short duration with similar in incidence to placebo. The proportion of patients discontinuing as a result of adverse events related to treatment is very low and generally <2-5% in most trials[11,12,13,14,15,16,17,18]. Intranasal glucocorticoids may occasionally cause local adverse effects, such as a mild sensation of nasal irritation, crusting, dryness and usually minor epistaxis, however these are transient and do not worsen during long-term treatment[19]. Local mycotic infections and septal perforations with prolonged use of nasal corticosteroids are extremely rare and have not been reported for mometasone furoate[20,21,22]. These findings may be related to the more rapid clearance of the topical corticosteroid by the ciliated nasal epithelium.

The material used to make the implant has been used extensively in the manufacture of suture materials and other implantable medical devices and is not expected to present any new risks.

Any implant remnants not removed at Day 21 will be absorbed over approximately 30 days.

8.2 Minimization of Anticipated Risks

Risks associated with the Propel Mini and Propel Nova Sinus Implants are minimized due to:

- The use of medical grade materials that have a long history of use and have been characterized and tested to assure biocompatibility.
- Incorporation of a very low dose (370 µg) of mometasone furoate, the average daily release of which is below currently FDA approved intranasal doses for allergic rhinitis and nasal polyps
- Pre-clinical evaluation including bench testing, analytical testing and animal studies.
- Instructions for Use that details appropriate implant preparation and placement
- Prior three clinical studies with the Propel Implant including 205 surgical patients and 400 sinuses
- Routine patient follow-up that includes direct endoscopic visualization of the Implant and sinus tissue
- In addition, risks will be minimized by including investigators experienced in performing sinus surgery and nasal endoscopy.

8.3 Potential Risks to Study Patient Confidentiality

In all clinical studies, confidentiality of protected health information may be breached due to study-related activities beyond those of routine clinical care. This risk will be minimized by not collecting personally identifying information on electronic CRFs (eCRFs) or other study related documentation to be provided to the study sponsor. It is the sponsor's policy to redact any patient's personally identifying information from any documentation sent to Intersect ENT that inadvertently contains it.

8.4 Potential Benefits of Study Participation

There may be no direct benefits of study participation. However, study patients will undergo an enhanced level of clinical scrutiny compared to routine clinical care, which may provide some indirect health benefits.

The implants are designed to maintain patency of the surgically created opening to the sinuses by occupying space and preventing obstructive adhesions between healing and/or inflamed mucosal surfaces. Addition of mometasone furoate is intended to minimize post-surgical inflammation, potentially reducing the frequency of adhesion formation and enhancing the wound healing process. Patients may benefit from these actions. Because the implant is bioabsorbable, patients may be able to avoid use of other sinus stents that require removal, which can be uncomfortable.

8.5 Risk/Benefit Conclusion

Based upon the Risk/Benefit Analysis performed by Intersect ENT, the benefits associated with the sinus implant are expected to outweigh the potential risks to the patient.

9.0 STATISTICAL ANALYSIS PLAN

The present version 5.0 of this protocol amends the PROGRESS Study protocol to include a second consecutive cohort of patients referred to as the "Nova Cohort". This cohort of patients will receive the Propel Nova Sinus Implant. The primary efficacy endpoint, all secondary efficacy endpoints and safety evaluations will be analyzed separately for the Mini Cohort and Nova Cohort. The analysis of each cohort stands on its own; achieving the primary objective in one cohort is considered sufficient for demonstrating efficacy in that cohort, regardless of the results of the corresponding analysis in the other cohort.

A detailed Statistical Analysis Plan will be prepared prior to formal analysis of the data obtained from each cohort in this study. Following is a description of the study sampling plan and a summary of the intended analyses.

9.1 Randomization

- The ratio of left to right sinus assignments will be 1:1.
- Randomization will be stratified by site, will follow a blocked scheme with blocks of varying sizes, and will be performed using the envelope method.

9.2 Primary Efficacy Endpoint Definition:

The primary efficacy endpoint will be 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 is a composite endpoint that includes:

- Surgical intervention required to debride obstructive adhesions or scar tissue formation* in the FSO, and/or
- Oral steroid intervention warranted to resolve recurrent inflammation or polypoid edema in the frontal recess/FSO.

*defined as grades 2 or 3 on the adhesion/scarring scale (see Definitions and Accronyms section).

9.3 Primary Efficacy Endpoint Hypothesis and Analysis

The Primary Efficacy Hypothesis is that the steroid-releasing implant will reduce the need for post-operative interventions at Day 30 compared to the control, as determined by an independent blinded sinus surgeon based on video-endoscopy review. The relevant null and alternative hypotheses are:

$$H_0: \quad P_T = P_C$$

$$H_a: \quad P_T \neq P_C$$

where P_T and P_C represent the proportion of patients who warrant post-operative interventions on the treatment and control sides, respectively. Since $P_T = P_{11} + P_{10}$ and $P_C = P_{11}+P_{01}$, where P_{10} is the proportion of patients who warrant surgical intervention only on the steroid-releasing implant side, P_{01} is the corresponding proportion for the control side, and P_{11} is the proportion who warrant interventions for both sides, these hypotheses are equivalent to a test of H_0: $P_{10} = P_{01}$ vs H_a: $P_{10} \neq P_{01}$.

Analysis

The planned analysis is 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. Although the alternative hypothesis is two-sided, evidence of a beneficial effect will only be concluded if statistical significance is achieved and P_T is observed to be less than P_C.

An exact version of the test will be used if the number of discordant pairs is less than 20. The exact version defines the proportion of discordant pairs that favor the steroid-releasing implant side as $P^* = P_{01}/(P_{01}+P_{10})$ and tests H_0: $P^* = 0.50$ vs. H_a: $P^* \neq 0.50$ via an exact binomial calculation.

Sample Size

Sample size is calculated based on the following assumptions:

- Expected proportion of discordant pairs at Day 30: $P_{01}+P_{10} = 35\%^{\diamond}$
- Expected treatment effect: $P_T - P_C = 21.0\%^{\diamond}$
- The two preceding assumptions are equivalent to assuming that $P_{01} = 0.28$, $P_{10} = 0.07$, and thus $P^* = 0.80$. This corresponds to a conditional odds ratio of 4.0 among discordant pairs.
- Target power: ≥ 80%
- Type I error rate: $\alpha = 0.05$, 2-sided
- Sample Size: A binomial probability calculation with $P^* = 0.80$ reveals that 20 discordant pairs are required to achieve at least 80% power. To obtain this, patients will be enrolled and treated until it is known that at least 20 patients have discordant pairs of outcomes. A minimum of 50 patients and a maximum of 80 patients will be enrolled and treated.

NOTE: Assumptions for proportion of discordant pairs and treatment effect are based on results from the ADVANCE II Study, where in assessing the need for postoperative intervention at Day 30, 35 of 96 evaluable patients (36.5%) yielded discordant pairs, and among these discordant pairs, 24 of 35 (68.6%) indicated that intervention was warranted on the control side but not the treatment side. The present study evaluates placement of the Propel Mini and Propel Nova in frontal sinus openings. The frontal recess and frontal sinus drainage pathway are known to be more difficult to access surgically, and to maintain in the post-operative timeframe. As a result, frontal sinus patency rates are known to be lower than that of the other sinuses. Therefore, we have assumed that placement of the Propel Mini and Propel Nova implants will yield a higher proportion of discordant pairs favoring the treatment sides than was observed with placement in the ethmoid sinus. The assumed odds ratio is 4:1, meaning that we assume 80% of discordant pairs will favor treatment sides.

Sampling Plan

Since only discordant pairs contribute to the test of a treatment effect, the observed proportion of discordant pairs is an important consideration. In the ADVANCE II study, 35/96 (36.5%) evaluable pairs of observations were discordant. A 95% confidence interval for this percentage ranges from approximately (27%, 47%). Using this as a guide, it is expected that approximately 20/0.25 = 80 patients would be a maximum and 20/0.40 = 50 patients would be a minimum enrollment size in order to achieve 20 discordant pairs.

When 50 patients have reached Day 30, the total number of discordant pairs will be determined (in a manner that reveals only the count of discordant pairs and not any estimates of the treatment effect). If this number is at least 20, enrollment will stop, and the analysis of the primary objective can proceed once all enrolled patients have completed follow-up. Alternatively, if the number of discordant pairs is less than 20, enrollment will continue until 20 patients are known to yield discordant results, up to a maximum of 80 randomized patients. At the time when enrollment ceases, it is possible that some patients will have < 30 days follow-up and thus have undetermined endpoint status. Once their follow-up is complete, these patients can possibly contribute additional discordant pairs to the analysis, for a total exceeding 20.

The primary objective will be evaluated for each cohort separately at the time when all randomized patients from a particular cohort have completed follow-up.

The primary efficacy analysis will be conducted on an intention-to-treat (ITT) basis. See Population Analysis section below.

9.4 Re-Estimation of Nova Cohort Sample Size

Since the results of the original Mini Cohort are not available at the time of this amendment, the study hypothesis and sample size calculation for the Nova Cohort are identical to the Mini Cohort: 50-80 patients will be enrolled in order to achieve 20 discordant pairs of results. The results from the Mini Cohort are external to the analysis of the Nova Cohort. Once available, the results from the Mini Cohort may be used to re-estimate the sample size of the Nova Cohort.

9.5 Sensitivity Analysis for Primary Efficacy Endpoint

Since the primary efficacy endpoint is determined by an independent blinded sinus surgeon based on review of video-endoscopies taken at Day 30, interventions performed by clinical investigators prior to Day 30 can potentially confound the primary efficacy outcome. Therefore, a sensitivity analysis will be performed to test the robustness of the primary efficacy conclusion, to actual interventions given. Data imputations will be performed as follows:

- If at Day 7 or 21, a clinical investigator indicates on the Endoscopic Scoring Form that either frontal recess/FSO required oral steroids or surgical intervention, and that intervention was actually given, then the grades given by the independent reviewer will be replaced by the grades given by the clinical investigator at the earliest visit (Day 7 or 21) at which such intervention was required.
- If oral steroids were actually prescribed for reasons *other than* either frontal recess/FSO, then the grades given by the independent reviewer will be replaced by the grades given by the clinical investigator at the visit preceding commencement of oral steroids (Day 7 or 21).

9.6 Secondary Efficacy Endpoint Analyses

Categorical data that can be localized to a treated or control side will be analyzed using McNemar's test for correlated proportions. In this intra-patient control study design, only discordant pairs of observations contribute to evidence of a treatment effect. If the number of discordant pairs is less than 20, an exact version of McNemar's test will be used, wherein the proportion of discordant pairs favoring the steroid-releasing implant side (out of all discordant pairs) will be compared against a null value of 0.50. The

appropriate test is an exact binomial calculation, using a 2-sided alpha of 0.05 or a 1-sided alpha of 0.025. In addition, frequency distributions showing findings by treatment side over time (figures and tables) and descriptive statistics (counts, percentages, and where appropriate, exact 95% confidence intervals using the method of Clopper and Pearson) will be used.

Intended categorical items to be analyzed include (determined by an independent blinded sinus surgeon):

- Frequency and severity of adhesion/scarring formation in the FSO at Day 30; for analysis purposes, significant scarring is defined as grades 2 or 3.
- Frequency and grade of polypoid edema in the frontal recess/FSO at Day 30

Intended categorical items to be analyzed include (determined by on-site investigators):

- Need for post-operative interventions at all time-points through Day 90
- Frequency and severity of adhesion/scarring formation in the FSO at all time-points through Day 90
- Frequency and grade of polypoid edema in the frontal recess/FSO at all time-points through Day 90
- Rate of frontal sinus patency at Day 90 as determined endoscopically and radiologically (CT scan)
- Extent of disease in the frontal sinus by Lund-Mackay scale on CT scan at Day 90.
- Implant delivery success rate

Continuous data will be analyzed using descriptive statistics such as means, medians, standard deviations, and where appropriate, 95% confidence intervals for the mean assuming a normal distribution. T-tests will be conducted on the side-to-side difference scores. Where appropriate, graphical representations of the data will be presented.

Intended continuous items to be analyzed include:

- Degree of inflammation in the frontal recess/FSO at Day 30 using a 100-mm VAS (determined by an independent blinded sinus surgeon)
- Endoscopic scores of inflammation in the frontal recess/FSO using a 100-mm VAS at all time-points through Day 90 (determined by on-site investigators)
- Frontal sinus patency and mucosal thickness measured on CT scan at Day 90.

Implant delivery success is defined as successful deployment of the implant to the target sites. The proportion of successful deployments will be defined as a ratio where the numerator is the number of successful deployments and the denominator is the number of sinuses in which a deployment was attempted. Deployment will be considered successful if the implant procedure concludes with a successful implant placement on the intended side, even if a second attempt is required in the procedure. An attempted deployment occurs when the surgeon introduces the delivery system into the patient's nostril with the intent of placing an implant.

9.7 Safety Evaluations

Adverse Events:

The incidence of Adverse Events and Serious Adverse Events (SAEs) through 90 days will be reported. Those events that can be localized to a side will be presented separately according to the affected side (steroid-releasing implant, control). In addition,

a pooled analysis will be presented, where AEs and SAEs will be included without regard for whether the event can be localized to a side.

Analysis Populations

Intent-to-Treat Population
The ITT population will consist of all randomized patients who undergo implant placement (i.e., delivery system inserted into the FSO with intent to place the implant). Patients' sinuses will be analyzed in the treatment group to which they were actually randomized.

Per-Treatment-Evaluable Population
The PTE population will consist of all randomized patients who have received the study implant in the target sinus, who have no major procedural protocol deviations and for whom follow-up data are available.

10.0 STUDY MANAGEMENT

As the study sponsor, Intersect ENT has the overall responsibility for the conduct of the study and will ensure that the study is conducted according to 21 CFR Parts 11, 50, 56 and 812. Personnel who participate in the conduct of this clinical trial will be qualified by education and/or experience to perform their tasks.

10.1 Ethical Considerations

The rights, safety and well-being of clinical investigational participants shall be protected in accordance with the ethical principles described in the Declaration of Helsinki.

It is expected that all parties will share in the responsibility for ethical conduct in accordance with their respective roles in the investigation. The sponsor and the investigator(s) shall avoid improper influence or inducement of the study patient, monitor, the clinical investigator(s) or other parties participating in or contributing to the clinical investigation.

10.2 Sponsor Responsibilities

Intersect ENT has the overall responsibility for the study and will manage the study according to applicable regulations.

10.3 Monitor Responsibilities

Study site monitoring will be performed by Clinical Research Associates from Intersect ENT, or hired and trained by Intersect ENT contract CRAs. Study sites will be visited regularly to ensure that the study is conducted in compliance with 21 CFR Parts 11, 50, 56, 812, the study protocol and other applicable regulations. Study monitors will also ensure that the data reported in EDC system is consistent with the information found in the patient's medical records and source documents (source data verification). Monitoring will include assessment of the site's overall progress, including but not limited to the site's ability to keep accurate records and to report study related data, including AEs, to the study sponsor in a timely fashion. In order to appropriately monitor the progress of the study, the monitor will have access to the source documents and other

information necessary to ensure investigator compliance with the protocol and applicable rules and regulations and to assess the progress of the clinical investigation.

The study monitors will maintain personal contact with investigators and study coordinators by phone, e-mail, mail and on-site visits. Monitoring will be performed concurrently during the period of patient enrollment through final database lock. The frequency of monitoring may occur as often as weekly at clinical sites. The schedule of monitoring at individual clinical sites will be determined on the basis of such factors as enrollment number and rate, presence of new clinical investigators, and individual clinical site needs. The monitor will complete a monitoring report for each visit which will be provided to the sponsor. Letters documenting the visit and relevant findings will be provided to the site. Monitoring will ensure continued protocol compliance and accurate reporting of data, AEs, protocol deviations and product accountability.

10.3.1 Source Data Verification

At a minimum, source data verification will be performed on all primary endpoint and safety data for each patient enrolled in this study.

10.3.2 Site Closeout

At the time of the site close-out visit, the monitor will collect all outstanding study documents, ensure that the investigator's files are accurate and complete, review record retention requirements with the investigator, make a final accounting of all study supplies, and ensure that all applicable requirements are met for the study (this visit will be conducted according to the study sponsor's SOP for close-out visits). Any specific observations and actions made at this visit may be documented in a final report.

10.4 Data Management Responsibilities

Data management and data analyses will be performed by Intersect ENT and independent biostatisticians.

10.4.1 Electronic Data Capture

Electronic Data Capture will be utilized to capture study data using eCRFs. Data entry will be performed by qualified site personnel after completing an appropriate training. Modifications to the EDC will be made if deemed necessary by the study sponsor.

10.4.2 Data Cleaning

The database will be subject to initial audit for omitted data, gross data inconsistencies and deviations. Any deficiencies or deviations will be reviewed and any necessary action determined (e.g., data query, communication with the study center).

Intermittent data review will be performed and any discovered errors will be reported to the study site using the electronic query process (as necessary). The

study site will be expected to review and complete the query. The data cleaning cycle will be repeated until all data are considered clean.

10.4.3 Data Back-up

Incremental computer data back-up will be performed on a regular basis. All media will be stored in a secure location.

10.4.4 Confidentiality and Security

Passwords will be issued to appropriate personnel to ensure confidentiality and protection of data.

10.5 Investigational Product Accountability

An appropriate number of the investigational implants will be provided to the study sites. The sites maintain the investigational product in a locked, secure location. Only investigators participating in the study will have access to the study implants. Dispensing of investigational product will be documented by authorized personnel. Each batch of the investigational product will be assigned a serial/lot number for tracking purposes.

Investigational product inventory logs are maintained by site personnel. These logs are reconciled prior to study closure. Any unused inventory of the investigational product will be returned to Intersect ENT at the direction of the sponsor or at the close of the study.

10.6 Data Collection

Study data will be collected using standardized CRFs/eCRFs. The CRF is designed to accommodate the specific features of the trial design. Modification of the CRF will only be made if deemed necessary by the study sponsor.

10.7 Investigator Responsibilities

The investigator is responsible for ensuring that the investigation is conducted according to all signed agreements, the study protocol, 21 CFR 812, data protection regulations in accordance with 21 CFR Part 11, and any other applicable IRB requirements. The investigator is also responsible for ensuring that informed consent is obtained in accordance with 21 CFR Part 50.

The investigator(s) is responsible for the day to day conduct of the investigation as well as for the rights, safety and welfare of the human subjects involved in the clinical investigation and for the control and supervision of devices under investigation

The investigator is responsible for disclosure of financial obligations to the sponsor.

To ensure proper execution of the study protocol, each investigator should identify a study coordinator for this study. Working with and under the authority of the investigator, the study coordinator assures that all study requirements are fulfilled, and is the contact person at the site for all aspects of study administration.

The investigator will allow auditing of their clinical investigation procedure(s).

10.7.1 Maintenance of Study Records

The investigator is responsible for maintaining medical and study records for every patient participating in the clinical study (including information maintained electronically such as digital imaging). The investigator will also maintain ***original*** source documents from which study-related data are derived, which may include, but are not limited to:

- Clinic progress notes recording patient's medical history and medications
- Medical charts with operative reports and condition of patient upon discharge
- Medical records regarding AEs, including treatment and clinical outcome
- Results of diagnostic examinations
- Imaging (such as x-rays, CT scans), as well as the report of the radiologist's reading/interpretation of diagnostic imaging (hard copy and digital copy of images, as available)
- Notes of phone calls and/or correspondence indicating investigational site's attempts to follow study patients at the required follow-up visits until patient's participation in the study is complete or terminated
- Records relating to patient death (e.g., death certificate, autopsy report)
- Print-outs of source data generated by technical equipment (e.g., CT, endoscopy, MRIs) must be filed with the patient's records.
- Video of endoscopic procedures (treatment and follow up assessments).

The study investigator must ensure that all study patient records and study regulatory documentation pertaining to the clinical study are stored for at least 2 years after approval of a marketing application or at least 2 years have elapsed since the date on which the clinical study is terminated or completed. To avoid error, the study site should contact the study sponsor prior to the destruction of study records to ensure that they no longer need to be retained. In addition, Intersect ENT should be contacted if the investigator plans to leave the investigational site so that arrangements can be made for the handling or transfer of study records.

10.7.2 Required Documents from the Investigational Site

At a minimum, the following documents will be provided by the investigational site to the study sponsor:

- Signed Clinical Trial Agreement
- Signed Investigator Agreement (for each investigator)
- IRB approval
- IRB approved ICF
- Investigator and sub-investigator's current Curriculum Vitae*
- Investigator and sub-investigator's copy of current medical license*

A site may not begin study participation until all of the above listed documents have been provided to the study sponsor and an initiation visit is performed.

* *The study may begin once the CV and medical license of the site PI have been received. No additional investigators may participate until copies of their CV and medical license have been provided to the study sponsor.*

The investigator must keep accurate, complete and current records relating to the conduct of the investigation.

10.8 Training

All investigators will be provided training by Intersect ENT personnel or designee in the use of the device using a bench top model or equivalent to familiarize them with the use of the device prior to their participation in the clinical study.

The study center will undergo site initiation which will include but is not limited to a review of the following:

- Clinical Study Protocol
- Consenting procedures
- IFU
- Reporting requirements
- CRF completion and correction procedures
- Device handling procedures
- Protection of subject confidentiality
- AE reporting procedures

Training will be provided on the endoscopic video protocol to be utilized during the trial. Appropriate representative videos/photos will be included in the training. This training will at a minimum contain the anatomy to videotape and specific endoscope requirements and management of the resulting DVD recordings. Specific instructions related to performance of endoscopic scoring will also be provided.

10.9 Protection of Patient Confidentiality

At all times throughout the clinical investigation, confidentiality will be observed by all parties involved. All data shall be secured against unauthorized access. Privacy and confidentiality of information about each patient shall be preserved in the reports and in any publication. Each patient participating in this study will be assigned a unique identifier. All CRFs will be tracked, evaluated, and stored using only this unique identifier.

Video-endoscopy recordings will be sent to a professional video editor who has a signed non-disclosure agreement. This editor will remove all recognizable facial images, leaving only anatomic features within the nose and sinus cavities.

The investigator will maintain a confidential study patient list identifying all enrolled patients. This list will contain the assigned study patient's unique identifier and name. The investigator bears responsibility for keeping this list confidential. This list will not be provided to the study sponsor and is only to be used at the study center.

Monitors and auditors will have access to the study patient list and other personally identifying information of study patients to ensure that data reported in the CRF corresponds to the person who signed the ICF and the information contained in the original source documents. Such personal identifying information may include, but is not

limited to the patient's name, address, date of birth, gender, race and medical record number.

NOTE: The patient's name, medical record number or address will NOT be recorded in the monitor's visit report or the database; demographic data that may be recorded includes age, race, and gender.

Any source documents copied for monitoring purposes by the sponsor will be identified by using the assigned patient's unique identifier in an effort to protect subject confidentiality. All personally identifiable information will be redacted from source documents.

10.10 Study Suspension or Early Termination

The study can be discontinued at the discretion of the investigator or study sponsor for reasons including, but not limited to, the following:

- Occurrence of adverse events unknown to date in respect to their nature, severity, or duration, or the unexpected incidence of known adverse events
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Insufficient recruitment of subjects
- Unanticipated adverse device effect (UADE) presenting an unreasonable risk to subjects (sponsor may terminate the study immediately)
- Persistent non-compliance with the protocol
- Persistent non-compliance with ethics committee or regulatory requirements

If the study is discontinued or suspended prematurely, the sponsor shall promptly inform all clinical investigator(s)/investigational center(s) of the termination or suspension and the reason(s) for this. The IRB shall also be informed promptly and provided with the reason(s) for the termination or suspension by the sponsor or by the clinical investigator/investigation center(s). Regulatory authorities and the personal physicians of the patients may also need to be informed if deemed necessary.

10.11 Quality Assurance and Supervision by Authorities

All documents and data shall be produced and maintained in such a way to assure control of documents and data to protect the patient's privacy as far as reasonably practicable. The sponsor and representatives of the FDA or other regulatory authorities are permitted to inspect the study documents (e.g., study protocol, CRFs, and original study-relevant medical records/files) as needed. All attempts will be made to preserve patient confidentiality.

The clinical site is subject to audit by study sponsor personnel or designee for protocol adherence, accuracy of CRFs and compliance with applicable regulations. The sponsor will communicate to the site any patterns of non-compliance. The sponsor will work with the site to determine any necessary corrective action, as applicable. The sponsor will continue to monitor the site until compliance has been secured. If the site continues to display non-compliance, further and more serious action may be taken by the study sponsor.

The study protocol, data-recording procedures, data handling as well as study reports are subject to an independent clinical Quality Assurance audit by Intersect ENT, its designee, or health authorities.

10.11.1 Approved Informed Consent

An IRB must review and approve an informed consent form (ICF) specific to this study. Intersect ENT will provide an example ICF. The site, to meet specific requirements, may modify this example ICF; however, the ICF must contain all of the elements required by Intersect ENT. IRB approved ICF and renewed approvals as appropriate will be maintained by the site for the duration of the study. The original, signed and dated ICF for each patient should be retained by the site for monitoring. A copy of the original informed consent will be provided to the patient.

10.11.2 Institutional Review Board Approval

IRB approval is required prior to study commencement. The investigator must also obtain renewal of IRB approval during the entire duration of the study. The investigator is responsible for fulfilling any conditions of approval imposed by the reviewing IRB, such as regular reporting, study timing, etc. The investigator will provide the study sponsor with copies of such approvals and reports.

10.11.3 Investigator Reporting of Adverse Events

An investigator will submit to the sponsor a report of AEs occurring during this investigation as follows:

Type of Report	Submission Schedule
Device Related AE	verbal or written report within 10 working days
Patient Death	verbal report within 24 hours followed by a written report within 2 working days
SAE / UADE	verbal report within 24 hours followed by a written report within 5 working days

The investigator will report all of the above to the reviewing IRB per the IRB's guidelines.

10.11.4 Other Investigator Reports

The investigator is responsible for the generation of the following reports according to the following schedule:

Type of Notification	Timeline
Withdrawal of IRB Approval	verbal report within 24 hours followed by a written report within 5 working days
Informed Consent NOT Obtained	verbal or written report within 24 hours of identification

NOTE: Reports must identify patients using the study's unique identifier to protect patient's confidentiality.

10.12 Final Report

A final report will be completed even if the study is prematurely terminated.

10.13 Publication Policy

At the conclusion of the study, an abstract reporting the results will be prepared and may be presented at a major meeting(s). A manuscript may also be prepared for publication in a peer-reviewed scientific journal. The principal investigator may publish results of the study; however, the study sponsor will be allowed 60 days to review the manuscript before submission to ensure protection of intellectual property.

11.0 DEFINITIONS AND ACRONYMS

Adhesion/Scarring Grading Scale

Obstruction of the FSO by adhesion/scarring will be assessed on a 4-point scale as follows:

Grade	Definition
0	No visible granulation/scarring in the FSO
1	Minimal amount of granulation, scarring or contraction observed but not obstructing the FSO (intervention not warranted)
2	Moderate amount of obstructive granulation, scarring or contraction present in the FSO (intervention is warranted)
3	Significant amount of scarring or contraction causing obstruction of the FSO requiring intervention (likely to compromise patency if not removed)

NOTE: *For analysis purposes, clinically* ***significant scarring is prospectively defined as grades 2 and 3****. For analysis of the composite primary endpoint, grades 2 and 3 will also be counted as scarring requiring intervention.*

Adverse Event (AE)
Any untoward medical occurrence in a study patient.

NOTE: This definition does not imply that there is a relationship between the adverse event and the device under investigation.
Patients with CRS experience a persisting set of symptoms associated with the disease, and may continue to present with a wide range of symptoms during the recovery process after endoscopic sinus surgery. These may include symptoms such as pain and discomfort, headache, return of sense of smell, crusting, epistaxis, and other symptoms. Patients healing appropriately after endoscopic sinus surgery may suffer from acute infectious and/or inflammatory exacerbations unrelated to the implant due to the natural course of their CRS. Therefore, investigators will evaluate the occurrence of adverse events excluding usual post-operative recovery signs and symptoms experienced by study patients, unless corroborated by objective findings and/or requiring specific medical or therapeutic intervention/s (e.g. antibiotics, repeat FESS etc.).

NOTE: the need for in office surgical intervention defined as per the study primary efficacy endpoint will not be considered an *adverse event* as this is already captured in the primary

efficacy analysis. Likewise, other endpoint-defined endoscopic findings such as crusting, polyp formation or middle turbinate lateralization will not be considered *adverse events*.

Case Report Form (CRF)
Document designed to record all data reported to the sponsor on each subject. (See also eCRF)

Chronic Rhinosinusitis (CRS)
The 2015 Multi-disciplinary Adult Sinusitis Guidelines [23] define chronic rhinosinusitis as follows:

- Twelve (12) weeks or longer of two or more of the following signs and symptoms:
  - Mucopurulent drainage (anterior, posterior, or both)
  - Nasal obstruction (congestion)
  - Facial pain-pressure-fullness, or
  - Decreased sense of smell
- AND inflammation is documented by one or more of the following findings:
  - Purulent (not clear) mucus or edema in the middle meatus or ethmoid region,
  - Polyps in nasal cavity or the middle meatus and/or,
  - Radiographic imaging showing inflammation of the paranasal sinuses

Computed Tomography (CT)

Device-Related Adverse Event
Any adverse event (defined above) that is determined by a participating investigator to be directly related to the investigational device.

Device Delivery Success
Successful access and deployment of a sinus implant to the target site. If the clinician feels that the initial deployment of an Implant is suboptimal, and decides to remove and replace the Implant with a second device during the index procedure, and the second device is deployed successfully, this will be considered a device success. If further such replacements are required this will not be counted as a device success. This definition is justifiable for this device because it is a reflection of the ease with which the Implant can be removed and replaced, and is consistent with how other sinus products are handled.

Electronic CRF (eCRF)
Auditable electronic record designed to capture information required by the clinical trial protocol to be reported to the sponsor on each trial subject. A CRF in which related data items and their associated comments, notes and signatures are linked electronically. CRFs or their individual pages will be considered source documents if used for recording of source (original) data."

Endoscopic Sinus Surgery (ESS)

Enrolled
Patients are considered enrolled in the study upon signing of the Informed Consent Form (ICF). Final eligibility to receive study implants will be confirmed after completion of successful sinus surgery and prior to introduction of the delivery system.

Frontal Sinus Opening (FSO)
An opening created through surgical enlargement of the frontal ostium.

Inflammation
For the purpose of this study and the endoscopic scoring method, the term inflammation is a global descriptor defined to include mucosal edema, erythema, hypertrophy and/or polypoid changes.

The degree of inflammation present in the frontal recess/FSO will be evaluated using a 100-mm Visual Analog Scale (VAS) ranging from 0 defined as no visible inflammation to 100 defined as severe inflammation, involving extensive erythema, edema, or polyposis.

Informed Consent Form (ICF)

Institutional Review Board (IRB)
A board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights, safety, and welfare of human subjects. The IRB should be established, operated, and function in conformance with 21 CFR 56. The term has the same meaning as "institutional review committee" in section 520(g) of the FD&C Act.

Instructions for Use (IFU)

Intention-to-Treat (ITT)
The intention-to-treat population consists of all patients who undergo implant placement (i.e., delivery system inserted into the FSO with intent to place the implant)

Patency Endoscopic Grading Scale
Patency of the FSO will be assessed endoscopically on a 3-point grading scale as follows:

Grade	Definition
0	Patent
1	Restenosed/Partially Occluded
2	Occluded

An estimated measure of the FSO diameter will be captured.

Polypoid Edema Grading Scale
Polypoid edema in the frontal recess/FSO will be assessed on a 3-point scale as follows:

Grade	Definition
0	Normal mucosa, no visible polyps at the frontal recess or FSO
1	Minimal amount of mucosal edema at the frontal recess or FSO
2	Expanded amount of polypoid edema at the frontal recess or FSO

Radiological Grading Scale
Extent of disease in each frontal sinus will be assessed on a 3-point scale adopted from the modified method of Lund [4] as follows:

Grade	Definition
1	Mucosal thickening of < 5mm
2	Partial opacification, air-fluid level, or mucosal thickening ≥ 5mm
3	Total opacification

Serious Adverse Event (SAE)
An adverse event is considered serious if it:

- resulted in death,
- resulted in a life-threatening illness or injury,
- resulted in a permanent impairment of a body structure or a body function,
- required hospitalization or prolongation of existing hospitalization,
- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure, or
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

Source Data
All information in original and identified records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation.

Source Documents
Original documents, data and records. This may be, for example, video recordings, hospital or clinic medical records, laboratory reports, pharmacy dispensing records, copies or transcriptions certified after verification as being accurate copies, photographic negatives, radiographs, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical investigation.

Unanticipated Adverse Device Effect (UADE)
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21CFR 812.3.s)

NOTE: The occurrence of a diagnostic or elective surgical procedure for a pre-existing condition, unless the condition becomes more severe or increases in frequency, would not be considered procedure or device-related.

Visual Analog Scale (VAS)
A grading scale to be used by investigators to indicate degree of inflammation that is present in the frontal recess/FSO. The scale is 100 mm in length and is anchored at each end (0 and 100).

12.0 REFERENCES

[1] Slavin RG, Spector SL, Bernstein IL, *et al.* The diagnosis and management of sinusitis: A practice parameter update. *J Allergy Clin Immunol* 2005,116:S13-S47.

[2] Benninger MS. Adult chronic rhinosinusitis: Definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol HNS* 2003,129:s1-s32.

[3] Draf W. Endonasal micro-endoscopic frontal sinus surgery: The fulda concept. *Op Tech Otolaryngol HNS* 1991,2:234-240.

[4] Chandra R, Palmer J, Tangsujarittham T, Kennedy D. Factors associated with failure of frontal sinusotomy in the early follow-up period. *Otolaryngol HNS* 2004,131:514-518.

[5] Ramadan H. Surgical causes of failure in endoscopic sinus surgery. *Am Laryngol, Rhinol & Otalogical Soc.* 1999,109:27-29.

[6] Bugten V, Nordgard S, Steinsvag S. The effects of debridement after endoscopic sinus surgery. *Laryngoscope* 2006,116:2037-2043.

[7] Kennedy D, Wright E, Goldberg A. Objective and subjective outcomes in surgery for chronic sinusitis. *Laryngoscope* 2000,110:29-31.

[8] Forwith K, Chandra R, Yun P, *et al*. ADVANCE: A multisite trial of bioabsorbable steroid-eluting sinus implants. *Laryngoscope* 2011,121:2473-2480.

[9] Marple B, Smith T, Han J, *et al*. Advance II: A prospective, randomized study assessing safety and efficacy of bioabsorbable steroid-releasing sinus implants. *Otolaryngol HNS* 2011,146:1004-1011.

[10] Murr AH, Smith TL, Hwang PH, *et al.* Safety and efficacy of a novel bioabsorbable, steroid-eluting sinus stent. *Int Forum Allergy Rhinol* 2011,1:23-32.

[11] Drouin M, Yang W, Bertrand B, *et al.* Once daily mometasone furoate aqueous nasal spray is as effective as twice daily beclomethasone dipropionate for treating perennial allergic rhinitis patients. *Ann Allergy Asthma Immunol* 1996,77:153-160.

[12] Hebert J, Nolop K, Lutsky B. Once-daily mometasone furoate aqueous nasal spray (Nasonex) in seasonal allergic rhinitis: an active- and placebo-controlled study. *Allergy* 1996,51:569-576.

[13] Davies R, Nelson H. Once-daily mometasone furoate nasal spray: efficacy and safety of a new intranasal glucocorticoid for allergic rhinitis. *Clin Therapeutics* 1997,19:27-38.

[14] Graft D, Aaronson D, Chervinsky P, , *et al.* A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray. *J Allergy Clin Immunol* 1996,98:724-731.

[15] Mandl M, Nolop K, Lutsky B. Comparison of once daily mometasone furoate (Nasonex) and fluticasone propionate aqueous nasal sprays for the treatment of perennial rhinitis. *Ann Allergy Asthma Immunol* 1997,79:370-378.

[16] Nayak A, Settipane G, Pedinoff A, *et al.* Effective dose range of mometasone furoate nasal spray in the treatment of acute rhinosinusitis. *Ann Allergy Asthma Immunol* 2002,89:271-278.

[17] Schenkel E. Features of mometsone furoate nasal spray and its utility in the management of allergic rhinitis. *Expert Opin Pharmacother* 2003,4:1579-1591.

[18] McCormack P, Plosker G. Inhaled mometasone furoate: A review of its use in persistent asthma in adults and adolescents. *Drugs* 2006,66:1151-1168.

[19] Mygind N, Andersson M. Topical glucocorticosteroids in rhinitis: Clinical aspects. *Acta Otolaryngol* 2006,126:1022-1029.

[20] Vogt F. The incidence of oral candidiasis with use of inhaled corticosteroids. *Ann Allergy* 1979,43:205-210.

[21] Van Cauwenberge P, Van Hoecke H, Vandenbulcke L, *et al*. Glucocorticosteroids in allergic inflammation: Clinical benefits in allergic rhinitis, rhinosinusitis, and otitis media. *Immunol Allergy Clin N Am* 2005,25:489-509.

[22] Kyrmizakis D, Papadakis C, Lohuis P, *et al*. Acute candidiasis of the oro- and hypopharynx as the result of topical intranasal steroids administration. *Rhinol* 1999,38:87-89.

[23] Rosenfeld RM, Piccirillo J, Chandrasekhar SS, *et al.* Clinical practice guideline (update): adult sinusitis. *Otolaryngol HNS* 2015, 152(2S):S1-S39.

STATISTICAL ANALYSIS PLAN

Protocol #:	P500-0514
Sponsor:	Intersect ENT 1555 Adams Dr Menlo Park CA 94025
SAP Version #:	2.0
Version Date:	May 28, 2015
Investigational Products:	Propel Mini & Propel Nova Sinus Implants
Intended 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 edema. The implant reduces the need for post-operative intervention such as surgical adhesion lysis and/or use of oral steroids. The Propel Nova Sinus Implant is intended for use in patients ≥ 18 years of age to maintain patency of sinus ostia following sinus surgery. The Propel Nova Sinus Implant separates/dilates mucosal tissues, prevents obstruction by adhesions/scarring, and reduces edema.

The study will be performed in compliance with Good Clinical Practice (GCP), including archival of essential study documents, and 21 CFR Parts 11, 50, 56 and 812.

Statistical Analysis Plan

Sponsor Name:	Intersect ENT
Protocol #:	P500-0514
Protocol Title:	Safety and Efficacy of the Propel Mini and Propel Nova Steroid-Releasing Sinus Implants Following Surgical Opening of the Frontal Sinus for Chronic Sinusitis:A Randomized Blinded Controlled Study
SAP Version #:	2.0
Version Date:	May 28, 2015

Prepared by:

Saling Huang, PhD
Sr. Director, Biostatistics
Advance Research Associates (ARA), Inc.

28 May 2015
Date

APPROVAL SIGNATURES

The signatures below indicate approval of the Statistical Analysis Plan for this study.

Andrew Mugglin, PhD
President & Principal Statistical Consultant
Paradigm Biostatistics, LLC

29 May 2015
Date

James Stambaugh
VP, Clinical Affairs
Intersect ENT

29 May 2015
Date

Amy Wolbeck
VP Regulatory Affairs & Quality
Intersect ENT

28 May 2015
Date

REVISION HISTORY

Version	Date	Summary of Changes/Comments
1.0	26Mar15	Document created
2.0	28May15	Revisions consistent with Rev 5.0 protocol. Provided details on the changes of data presentation.

TABLE OF CONTENTS

1.0 INTRODUCTION

This document presents the Statistical Analysis Plan (SAP) for the PROGRESS Study entitled "Safety and Efficacy of the Propel Mini and Propel Nova Steroid-Releasing Sinus Implants Following Surgical Opening of the Frontal Sinus for Chronic Sinusitis: A Randomized Blinded Controlled Study" conducted under the study protocol P500-0514 version 5.0 (dated April 29, 2015). The purpose of this document is to provide further details regarding the analysis plans.

2.0 STUDY DESIGN

This is a prospective, randomized, blinded, controlled, multicenter study that will enroll two consecutive patient cohorts: the Propel Mini Cohort and the Propel Nova Cohort. Each cohort will enroll 50 to 80 patients who satisfy entry criteria. The study patients will undergo implant placement on one side following ESS that includes bilateral frontal sinus surgery by traditional surgical technique or balloon dilation.

For each cohort, the study utilizes an intra-patient control design to assess the safety and efficacy of the implant compared to surgery alone without implant on the contralateral side. The study is blinded, meaning that patients will be blinded throughout the study duration to which side received the implant. . The independent sinus surgeon performing review of the video-endoscopies will also be blinded to which side received the implant.

Patients will return for four follow-up visits at Days 7, 21, 30 and 90 (see Appendix 1 for Schedule of Assessments). The follow-up assessment will include endoscopic examinations that will be recorded. At Day 21 the implant or its remnants will be removed to allow blinded review of video-endoscopies at Day 30.

3.0 STUDY OBJECTIVE

The objective of the PROGRESS Study is to assess the safety and efficacy of the Propel Mini and Propel Nova Sinus Implants when placed in the frontal sinus opening following frontal sinus surgery in patients with chronic sinusitis.

4.0 DATA MANAGEMENT

Data management will be performed by Intersect ENT according to the Data Management Plan. Data analyses will be performed by independent biostatisticians according to Advance Research Associates' standard operating procedures.

4.1 Clinical Database

An Electronic Data Capture (EDC) System will be utilized to collect study data using electronic case report forms (eCRFs). Data entry will be performed by qualified site personnel after completing appropriate training. Modifications to the EDC will be made if deemed necessary by the study sponsor.

4.2 Data Cleaning

The database will be verified periodically for data omissions, inconsistencies and discrepancies. Any deficiencies or deviations will be reviewed and any necessary actions determined (e.g., data query, communication with the study center). Intermittent data review will be performed and any discovered errors will be reported to the study sites using the electronic query process (as necessary). The study sites will be expected to review and complete the queries. The data cleaning cycle will be repeated until all data are considered clean.

4.3 Data Back-up

Incremental computer data back-up will be performed on a regular basis. All media will be stored in a secure location.

4.4 Confidentiality and Security

Passwords will be issued by the EDC System vendor to appropriate personnel.

5.0 DEFINITION OF ENDPOINTS

5.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be evaluated for each study cohort separately. The primary efficacy endpoint is the reduction in need for post-operative interventions at Day 30, as determined by an independent, blinded sinus surgeon based on video-endoscopy reviews.

Post-operative intervention is a composite endpoint that includes:

- Surgical intervention required to debride obstructive adhesions or scar tissue formation * in the frontal sinus opening (FSO), and/or
- Oral steroid intervention warranted to resolve recurrent inflammation or polypoid edema in the frontal recess/FSO.

* Defined as grades 2 or 3 on the Adhesion/Scarring Scale

5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will be evaluated for each study cohort separately.

Secondary endpoints include:
Endoscopic outcomes assessed by an independent blinded sinus surgeon based on video-endoscopy review:

- Frequency and severity of adhesion/scarring formation in the FSO at Day 30Degree of inflammation in the frontal recess/FSO at Day 30 using a 100-mm Visual Analog Scale (VAS)
- Frequency and grade of polypoid edema in the frontal recess/FSO at Day 30
- A sensitivity analysis will be performed to assess the impact of actual interventions that occur prior to Day 30, upon the assessments made by the independent reviewer at Day 30.

Endoscopic outcomes assessed by on-site investigators:

- Need for post-operative intervention at all time-points through Day 90
- Degree of inflammation in the frontal recess/FSO at all time points through Day 90 using the 100-mm VAS
- Frequency and severity of adhesion/scarring formation in the FSO at all time points through Day 90
- Frequency and grade of polypoid edema in the frontal recess/FSO at all time points through Day 90
- Rate of frontal sinus patency at Day 90 determined endoscopically and radiologically (CT scan)
- Implant delivery success rate

CT outcomes assessed by an independent blinded sinus surgeon based on CT scan review:

- Patency of the FSO and Lund-Mackay score at Day 90
- Extent of the disease in the frontal sinuses using Radiological Grading Scale at Day 90

CT outcomes assessed by on-site investigators based on CT scan review:

- Maximum size of FSO in mm
- Lund-Mackay score at Day 90
- Extent of the disease in the frontal sinuses using Radiological Grading Scale at Day 90

5.3 Safety Measures

The safety measures will be evaluated for each study cohort separately. The safety measures include:

- Implant safety will be determined by assessment of adverse events.
- Adverse Events (AE) and Serious Adverse Events (SAEs) will be recorded and tabulated through Day 30 and Day 90. Where possible and if applicable, adverse events will be localized to a sinus location.

6.0 STATISTICAL METHODS

6.1 Randomization

The ratio of left to right sinus assignments will be 1:1. Randomization will be stratified by site, will follow a blocked scheme with blocks of varying sizes, and will be performed using the envelope method.

6.2 Analysis Populations

Intent-to-Treat Population

The ITT population will consist of all randomized patients who undergo implant placement (i.e., delivery system inserted into the FSO with intent to place the implant). Patients' sinuses will be analyzed in the treatment group to which they were actually randomized.

Per-Treatment-Evaluable Population

The PTE population will consist of all randomized patients who have received the study implant in the target sinus, who have no major procedural protocol deviations and for whom follow-up data are available.

6.3 General Considerations for Statistical Analyses

All analyses described in this plan are considered a priori analyses in that they have been defined prior to locking the database and reviewing unblinded results. All other analyses, if any, designed subsequent to locking the database will be considered post hoc analyses and will be applied as exploratory methodology. Any post hoc analyses will be clearly identified in the clinical study report.

The analysis of each cohort stands on its own; achieving the primary objective in one cohort is considered sufficient for demonstrating efficacy in that cohort, regardless of the results of the corresponding analysis in the other cohort.

The primary efficacy endpoint, all secondary efficacy endpoints and safety evaluations will be analyzed separately for each of the two study cohorts.

All data relating to the study will be summarized using descriptive statistics. Summary statistics will consist of counts and percentages of patients for nominal and ordinal measures, and means, standard deviations, median and ranges for continuous measures. Where meaningful, the results will be presented graphically.

Available data at each time point will be presented. No substitutions for missing data will be made, with the exception of the primary efficacy endpoint sensitivity analyses and missing data sensitivity analysis (Sections 7.3 and 7.5).

Categorical data that can be localized to a treatment or control side will be analyzed using McNemar's test for correlated proportions. In this intra-patient control study design, only discordant pairs of observations contribute to evidence of a treatment effect. If the number of discordant pairs is less than 20, an exact version of McNemar's test will be used, wherein the proportion of discordant pairs favoring the treatment side (out of all discordant pairs) will be compared against a null value of 0.50. The appropriate test is an exact binomial calculation, using a 2-sided alpha of 0.05 or a 1-sided alpha of 0.025. In addition, frequency distributions showing findings by treatment side over time and descriptive statistics (counts, percentages and, where appropriate, exact 95% confidence intervals using the method of Clopper and Pearson) will be used.

Listings of patient data will be provided to facilitate investigation of tabulated values and to allow for clinical review of all primary and secondary endpoints. Patient listings will be sorted by Site Number and Patient ID Number.

Version 9.2 (or higher) of SAS statistical software package will be used to provide all summaries, listings, graphs, and statistical analyses.

Except where explicitly indicated, data will be pooled across study sites within each study cohort for all statistical analyses.

7.0 STATISTICAL ANALYSES

7.1 Demographics and Baseline Characteristics

Demographic data (e.g., gender and age) and clinical information (e.g., number of prior sinus procedures, history of asthma diagnosed by physician, history of aspirin intolerance or aspirin allergy, history of allergies, history of smoking, presence of grade 2 polypoid edema, total Lund-Mackay scores by sinus) will be presented for all patients. Lund-Mackay scores will also be presented by side (treatment vs. control).

A summary table for procedural information will present the count and percentage of patients that underwent each surgery type and frequency of use of other device or types of drug in the ethmoid sinuses during surgery.

7.2 Primary Efficacy Endpoint Hypothesis and Analysis

The Primary Efficacy Hypothesis is that the steroid-releasing implant will reduce the need for post-operative interventions at Day 30 compared to the control, as determined by an independent blinded sinus surgeon based on video-endoscopy review. The relevant null and alternative hypotheses are:

$$H_0: P_T = P_C$$
$$Ha: P_T \neq P_C$$

where P_T and P_C represent the proportion of patients who warrant post-operative interventions on the treatment and control sides, respectively. Since $P_T = P_{11} + P_{10}$ 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, these hypotheses are equivalent to a test of $H_0: P_{10} = P_{01}$ vs $Ha: P_{10} \neq P_{01}$.

Analysis

The planned analysis is 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. Although the alternative hypothesis is two-sided, evidence of a beneficial effect will only be concluded if statistical significance is achieved and P_T is observed to be less than P_C.

An exact version of the test will be used if the number of discordant pairs is less than 20. The exact version defines the proportion of discordant pairs that favor the treatment side as $P^* = P_{01}/(P_{01}+P_{10})$ and tests H_0: $P^* = 0.50$ vs. Ha: $P^* \neq 0.50$ via an exact binomial calculation.

Sample Size

Sample size is calculated based on the following assumptions:

- Expected proportion of discordant pairs at Day 30: $P_{01}+P_{10} = 35\%$
- Expected treatment effect: $P_T–P_C= 21.0\%$
- The two preceding assumptions are equivalent to assuming that $P_{01} = 0.28$, $P_{10} = 0.07$, and thus $P^* = 0.80$. This corresponds to a conditional odds ratio of 4.0 among discordant pairs.
- Target power: $\geq 80\%$
- Type I error rate: $\alpha = 0.05$, 2-sided

Sample Size: A binomial probability calculation with $P^* = 0.80$ reveals that 20 discordant pairs are required to achieve at least 80% power. To obtain this, patients will be enrolled and treated until it is known that at least 20 patients have discordant pairs of outcomes. A minimum of 50 patients and a maximum of 80 patients will be enrolled and treated.

NOTE: Assumptions for proportion of discordant pairs and treatment effect are based on results from the ADVANCE II Study, where in assessing the need for postoperative intervention at Day 30, 35 of 96 evaluable patients (36.5%) yielded discordant pairs, and among these discordant pairs, 24 of 35 (68.6%) indicated that intervention was warranted on the control side but not the treatment side. The present study evaluates placement of the Propel Mini and Propel Nova in frontal sinus openings. The frontal recess and frontal sinus drainage pathway are known to be more difficult to access surgically, and to maintain in the post-operative timeframe. As a result, frontal sinus patency rates are known to be lower

than that of the other sinuses. Therefore, we have assumed that placement of the Propel Mini and Propel Nova Sinus Implants will yield a higher proportion of discordant pairs favoring the treatment sides than was observed with placement in the ethmoid sinus. The assumed odds ratio is 4:1, meaning that we assume 80% of discordant pairs will favor treatment sides.

Sampling Plan

Since only discordant pairs contribute to the test of a treatment effect, the observed proportion of discordant pairs is an important consideration. In the ADVANCE II study, 35/96 (36.5%) evaluable pairs of observations were discordant. A 95% confidence interval for this percentage ranges from approximately 27% to 47%. Using this as a guide, it is expected that approximately 20/0.25 = 80 patients would be a maximum and 20/0.40 = 50 patients would be a minimum enrollment size in order to achieve 20 discordant pairs.

When 50 patients have reached Day 30, the total number of discordant pairs will be determined (in a manner that reveals only the count of discordant pairs and not any estimates of the treatment effect). If this number is at least 20, enrollment will stop, and the analysis of the primary objective can proceed once all enrolled patients have completed follow-up. Alternatively, if the number of discordant pairs is less than 20, enrollment will continue until 20 patients are known to yield discordant results, up to a maximum of 80 randomized patients. At the time when enrollment ceases, it is possible that some patients will have < 30 days follow-up and thus have undetermined endpoint status. Once their follow-up is complete, these patients can possibly contribute additional discordant pairs to the analysis, for a total exceeding 20.

The primary objective will be evaluated for each cohort separately at the time when all randomized patients from a particular cohort have completed follow-up.

Re-Estimation of Nova Cohort Sample Size

Since the results of the original Mini Cohort are not available at the time of this amendment, the study hypothesis and sample size calculation for the Nova Cohort are identical to the Mini Cohort: 50-80 patients will be enrolled in order to achieve 20 discordant pairs of results. The results from the Mini Cohort are external to the analysis of

the Nova Cohort. Once available, the results from the Mini Cohort may be used to re-estimate the sample size of the Nova Cohort.

Analysis Cohort

The primary efficacy analysis will be conducted on the ITT basis, which will consist of all randomized patients who undergo implant placement (i.e., delivery system inserted into the FSO with intent to place the implant). This analysis will be repeated for the PTE population.

7.3 Sensitivity Analysis for Primary Efficacy Endpoint

Since the primary efficacy endpoint is determined by an independent blinded sinus surgeon based on review of video-endoscopies taken at Day 30, interventions performed by clinical investigators prior to Day 30 can potentially confound the primary efficacy outcome. Therefore, a sensitivity analysis will be performed to test the robustness of the primary efficacy conclusion, to actual interventions given. Data imputations will be performed as follows:

- If at Day 7 or Day 21, a clinical investigator indicates on the Endoscopic Scoring Form that either frontal recess/FSO required oral steroids or surgical intervention, and that intervention was actually given, then the grades given by the independent reviewer will be replaced by the grades given by the clinical investigator at the earliest visit (Day 7 or Day 21) at which such intervention was required.
- If oral steroids were actually prescribed for reasons *other than* frontal recess/FSO, then the grades given by the independent reviewer will be replaced by the grades given by the clinical investigator at the visit preceding commencement of oral steroids (Day 7 or Day 21).

7.4 Secondary Efficacy Endpoint Analyses

7.4.1 Endoscopic Outcomes Assessed by Independent Reviewer

The counts and percentages of patients with adhesion/scarring at Day 30 by an independent blinded sinus surgeon will be presented by grade and side (treatment vs. control). For analysis purposes, clinically significant adhesion/scarring is prospectively defined as grades 2 or 3. The counts and percentages of patients with

polypoid edema will be presented by grade and side. In addition, adhesion/scarring and polypoid edema grades will be presented graphically by side in scatter plots. The mean inflammation scores in the frontal recess/FSO and their associated standard deviation will be presented by side and as mean difference between sides (difference is calculated by subtracting the control score from the treatment score).

7.4.2 Endoscopic Outcomes Assessed by Investigators

Frequency and severity of adhesion/scarring rated by on-site clinical investigators will be presented by grade and side (treatment vs. control) for each time point (Days 7, 21, 30 and 90). Similarly, frequency and severity of polypoid edema and patency of the FSO will be presented by side and time point. In addition, adhesion/scarring, polypoid edema and FSO patency grades at Day 30 will be presented graphically by side in scatter plots.

The mean inflammation in the frontal recess/FSO and its associated standard deviation will be presented for each time point by side and mean difference between sides (difference is calculated by subtracting the control score from the treatment score). Similarly, the mean largest estimated FSO diameter and its associated standard deviation will be presented for each time point by side and mean difference between sides.

In addition, a composite analysis of the counts and percentages of patients with *unfavorable clinical outcome in the FSO* will be presented by side and by time point.

An *unfavorable clinical outcome* has occurred if any of the following are true for a given sinus:

- Polypoid edema is grade 2 (expanded amount)
- Adhesion/Scarring is grade 2 (moderate amount warranting intervention) or 3 (significant amount requiring intervention)
- Patency of the FSO is grade 2 (occluded)

7.4.3 Implant Delivery Success Assessed by Investigators

Implant delivery success is defined as successful deployment of the Propel Mini or

Propel Nova Sinus Implant to the intended side. The proportion of successful deployments will be defined as a ratio where the numerator is the number of successful deployments and the denominator is the number of sinuses in which a deployment was attempted. Deployment will be considered successful if the implant procedure concludes with a successful implant placement on the intended side, even if a second attempt is required in the procedure. An attempted deployment occurs when the surgeon introduces the delivery system into the patient's nostril with the intent of placing an implant.

7.4.4 CT Outcomes Assessed by Independent Reviewer

The severity and frequency of frontal sinus disease at Day 90 as determined based on CT scan review by an independent blinded sinus surgeon will be presented as counts and percentages by radiologic grade and side (treatment vs. control). The mean Lund-Mackay total scores, Lund-Mackay score in the frontal sinus and the estimated maximum diameter of the FSO and their associated standard deviation will be presented by side and as mean difference between sides (difference is calculated by subtracting the control score from the treatment score).

7.4.5 CT Outcomes Assessed by Investigators

The severity and frequency of frontal sinus disease at Day 90 as determined based on CT scan review by on-site clinical investigators will be presented as counts and percentages by radiologic grade and side (treatment vs. control). The mean Lund-Mackay total scores, Lund-Mackay score in the frontal sinus and the estimated maximum diameter of the FSO and their associated standard deviation will be presented by side and as mean difference between sides (difference is calculated by subtracting the control value from the treatment value). The change in the mean total and frontal sinus Lund-Mackay scores between Day 90 and baseline will be also presented.

7.5 Sensitivity Analyses for Missing Data

Post-operative intervention for one sinus side consists of two possible interventions (intervention to separate an adhesion, or the need for oral steroids) that can be answered

Yes, No or *Unable to Grade*. In addition to the imputations listed in Section 7.3, the following imputations will be used to assess the sensitivity of conclusions to missing data from the independent reviewer if more than 5% of the primary efficacy data are missing:

- Impute *No, intervention* for all missing values in both components of the composite endpoint (e.g. impute adhesion grade as a 0, and "No" for the need for oral steroids)
- Impute *Yes, intervention* for all missing values in both components of the composite endpoint (e.g. impute adhesion grade as a 2, and "Yes" for the need for oral steroids)
- Impute *Yes, intervention* for missing values in either component of the composite endpoint *only on the control side* and impute *No intervention on the treatment side*
- Impute *Yes, intervention* for missing values in either component of the composite endpoint *only on the treatment side* and impute *No intervention on the control side*

Patients collectively determined to be *unable to grade* or indeterminate due to reasons such as patient missed visit, lost to follow-up or video was lost will be considered as missing data.

7.6 Consistency Across Study Centers

The consistency of implant performance across study centers will be investigated. Statistical tests will be conducted to identify if there are outlier study centers that could affect the primary efficacy endpoint and clinical conclusions. The proportion of patients who warrant post-operative interventions (as determined by an independent, blinded sinus surgeon) on the treatment side across study centers will be tested by Chi-square test at an alpha level of 0.05. Similarly the proportion of patients who warrant post-operative interventions on the control side across study centers will be tested by Chi-square test at an alpha level of 0.05. In the event that p-value is less than or equal to 0.05, the sensitivity analysis that excludes study centers with outlier efficacy results will be performed to determine the robustness of the primary efficacy analysis.

7.7 Subgroup Analyses

The following sub-groups are of interest in assessing the primary efficacy endpoint, sensitivity analysis of the primary efficacy endpoint, post-operative interventions by treatment group by investigators and endoscopic outcomes assessed by investigators by time point. The primary efficacy endpoint analysis and the count and percentage of

patients with adhesion grade 1 or higher and grade 2 or higher analyses may be performed for the following sub-groups if they consist of more than 10% of the ITT population:

A. Patients who did not receive high dose steroids (ie, exclude those patients who received high-dose steroids).

B. Patients who did not receive surgical interventions (i.e., exclude those patients who had in-office debridement of FSO at day 21 or later, or repeat ESS of FSO at any time).

C. Patients who did not commence topical intranasal steroid sprays prior to Day 30.

D. Patients who did not receive high dose steroids and did not receive surgical interventions (patients in Subgroups A + B)

E. Patients who did not receive high dose steroids, did not receive surgical interventions and did not commence topical intranasal steroid sprays prior to Day 30 (patients in Subgroups **A**+**B**+**C)**

F. Patients who did not receive Propel or Propel Mini Sinus Implants in the ethmoid sinuses.

7.8 Safety Evaluation

Adverse Events

All adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs and Serious Adverse Events (SAEs) through 30 and 90 days will be reported. Those events that can be localized to a side will be presented separately according to the affected side (treatment, control). In addition, a pooled analysis will be presented, where AEs and SAEs will be included without regard for whether the event can be localized to a treatment group.

Concomitant Medications

Prior and concomitant medications will be coded to therapeutic class and preferred term using the World Health Organization (WHO) Drug Dictionary. All concomitant medications will be listed and summarized in a table.

8.0 APPENDICES

APPENDIX 1: SCHEDULE OF ASSESSMENTS

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 to surgery is permitted to confirm chronic sinusitis diagnosis.
[2] Pregnancy test is required for females of child-bearing potential on the surgery day before implant placement.

APPENDIX 2: TABLES

The following tables will be presented for each study cohort separately:
Note: The same set of tables will be repeated for Nova Cohort

Table Number	Table Title
Table 1	Patient Disposition Mini Cohort: All Randomized Patients
Table 2	Demographic and Baseline Characteristics Mini Cohort: Intent-to-Treat Population
Table 3	Procedural Information Mini Cohort: Intent-to-Treat Population
Table 4	Implant Performance Mini Cohort: Intent-to-Treat Population
Table 5	Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer and by Investigators Mini Cohort: Intent-to-Treat Population
Table 5.1	Frequency Table of Post-Operative Intervention at Day 30 by Independent Reviewer and Investigators Mini Cohort: Intent-to-Treat Population
Table 5.2	Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer Mini Cohort: Per-Treatment Evaluable Population
Table 5.3	Frequency Table of Post-Operative Intervention at Day 30 by Independent Reviewer Mini Cohort: Per-Treatment Evaluable Population
Table 5.4	Sensitivity Analysis for Primary Efficacy Endpoint: Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Sinus Surgeon Mini Cohort: Intent-to-Treat Population
Table 5.5	Sensitivity Analysis for Missing Data with Imputation Method #1: Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer Mini Cohort: Intent-to-Treat Population
Table 5.6	Sensitivity Analysis for Missing Data with Imputation Method #2: Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer Mini Cohort: Intent-to-Treat Population
Table 5.7	Sensitivity Analysis for Missing Data with Imputation Method #3: Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer Mini Cohort: Intent-to-Treat Population
Table 5.8	Sensitivity Analysis for Missing Data with Imputation Method #4: Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer Mini Cohort: Intent-to-Treat Population
Table 6	Frequency of Post-Operative Interventions by Treatment Group by Investigators Mini Cohort: Intent-to-Treat Population
Table 7	Endoscopic Outcomes at Day 30 by Independent Reviewer Mini Cohort: Intent-to-Treat Population
Table 8	Endoscopic Outcomes by Time Point by Investigators Mini Cohort: Intent-to-Treat Population
Table 9	Endoscopic Outcomes at Day 30 by Independent Reviewer – Inflammation Mini Cohort: Intent-to-Treat Population
Table 10	Endoscopic Outcomes by Time Point by Investigators – Inflammation, FSO Diameter Mini Cohort: Intent-to-Treat Population
Table 11	CT Outcomes at Day 90 by Independent Reviewer and Investigators – Lund-Mackay Scores Mini Cohort: Intent-to-Treat Population
Table 12	CT Outcomes at Day 90 by Independent Reviewer and Investigators - Radiological Grades Mini Cohort: Intent-to-Treat Population

Note: Tables 5.5 to 5.8 will not be presented in text table format

APPENDIX 3: LISTINGS

The following listings will be presented for each study cohort separately:

Note: The same set of listings will be repeated for Nova Cohort

Number	Title
Listing 1	Patient Disposition [Mini Cohort]
Listing 2	Analysis Populations [Mini Cohort]
Listing 3	Demographics and Baseline Characteristics[Mini Cohort]
Listing 4	Procedure - Anesthesia and Endoscopic Procedures (Part 1) [Mini Cohort]
Listing 4.1	Procedure - Anesthesia and Surgery (Part 2) [Mini Cohort]
Listing 4.2	Procedure - Implant Placement (Part 3) [Mini Cohort]
Listing 4.3	Procedure – Post-Operative Treatments (Part 4) [Mini Cohort]
Listing 5	Follow-up Assessments [Mini Cohort]
Listing 6	Endoscopic Outcomes by Independent Reviewer – Day 30[Mini Cohort]
Listing 7	Endoscopic Outcomes by Investigators (Part 1) [Mini Cohort]
Listing 7.1	Endoscopic Outcomes by Investigators (Part 2) [Mini Cohort]
Listing 8	CT Outcomes by Independent Reviewer – Day 90 (Part 1) [Mini Cohort]
Listing 8.1	CT Outcomes by Independent Reviewer – Day 90 (Part 2) [Mini Cohort]
Listing 9	CT Outcomes by Investigators – Baseline & Day 90 (Part 1) [Mini Cohort]
Listing 9.1	CT Outcomes by Investigators – Baseline & Day 90 (Part 2) [Mini Cohort]
Listing 10	Adverse Events [Mini Cohort]
Listing 11	Prior and Concomitant Medication [Mini Cohort]
Listing 12	Protocol Deviations [Mini Cohort]
Listing 13	Comments or Narrative [Mini Cohort]

APPENDIX 4: FIGURES

The following figures will be presented for each study cohort separately

Note: The same set of figures will be repeated for Nova Cohort

Figure Number	Figure Title
Figure 1	Scatter Plot of Adhesion/Scarring Grades at Day 30 by Treatment Group *Judged by Independent Reviewer (Mini Cohort: Intent-to-Treat)*
Figure 2	Scatter Plot of Polypoid Edema Grades at Day 30 by Treatment Group *Judged by Independent Reviewer (Mini Cohort: Intent-to-Treat)*
Figure 3	Scatter Plot of Adhesion/Scarring Grades at Day 30 by Treatment Group *Judged by Investigators (Mini Cohort: Intent-to-Treat)*
Figure 4	Scatter Plot of Polypoid Edema Grades at Day 30 by Treatment Group *Judged by Investigators (Mini Cohort: Intent-to-Treat)*
Figure 5	Scatter Plot of Patency of the FSO Grades at Day 30 by Treatment Group *Judged by Investigators (Mini Cohort: Intent-to-Treat)*

Table Mockups - Table of Contents

Table 1
Patient Disposition
Mini Cohort: All Randomized Patients

	All Patients
Intent-to-Treat Population [1]	xx
Per-Treatment Evaluable Population [2]	xx
Primary Reason for Termination [3]	
Adverse Event	xx (xx.x%)
Investigator's order	xx (xx.x%)
Lost to follow-up	xx (xx.x%)
Death	xx (xx.x%)
Patient withdrew from study	xx (xx.x%)
Primary Reason for Early Termination [3]	
Unable to gain access	xx (xx.x%)
Other	xx (xx.x%)

[1] Intent-to-Treat Population consists of all patients who undergo implant placement (i.e., delivery system inserted into the FSO with intent to place the implant).
[2] Per-Treatment Evaluable Population is defined as all randomized patients who have received the study implant in the target sinus, who have no major procedural protocol deviations and for whom follow-up data are available.
[3] Percentage is calculated based on Intent-to-Treat Population.

Reference: Listing x.x.x

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 2
Demographic and Baseline Characteristics
Mini Cohort: Intent-to-Treat Population

	All Patients (N=xx)
Age	
N	xx
Mean (SD)	xx.x (xx.xx)
Median	xx.xx
Min-Max	xx.x – xx.x
Gender [1]	
Male	xx (xx.x%)
Female	xx (xx.x%)
Number of Prior ESS	
N	xx
0	xx (xx.x%)
1	xx (xx.x%)
2	xx (xx.x%)
3	xx (xx.x%)
>= 4	xx (xx.x%)
History of Aspirin Intolerance or Allergy	
Yes	xx (xx.x%)
History of Asthma Diagnosed by Physician	
Yes	xx (xx.x%)
History of Samter’s Triad	
Yes	xx (xx.x%)
History of Smoking	
Yes	
Current	xx (xx.x%)
Former	xx (xx.x%)
Polypoid Edema Grade 2 [2]	
Yes	xx (xx.x%)
Lund Mackay Score	
Overall Total (left+right)	
N	xx
Mean (SD)	xxx.x (xxx.xx)
Median	xxx.xx
Min-Max	xxx.x – xxx.x

[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
Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 2
Demographic and Baseline Characteristics (Part 2)
Mini Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)
Lund Mackay Score		
Total (all sinuses on each side)		
N	xx	xx
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median	xxx.xx	xxx.xx
Min-Max	xxx.x – xxx.x	xxx.x – xxx.x
Frontal Sinus		
N	xx	xx
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median	xxx.xx	xxx.xx
Min-Max	xxx.x – xxx.x	xxx.x – xxx.x
Maxillary		
N	xx	xx
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median	xxx.xx	xxx.xx
Min-Max	xxx.x – xxx.x	xxx.x – xxx.x
Anterior Ethmoid		
N	xx	xx
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median	xxx.xx	xxx.xx
Min-Max	xxx.x – xxx.x	xxx.x – xxx.x
Posterior Ethmoid		
N	xx	xx
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median	xxx.xx	xxx.xx
Min-Max	xxx.x – xxx.x	xxx.x – xxx.x

[1] Percentage is calculated based on Intent-to-Treat Population.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 2
Demographic and Baseline Characteristics (Part 2)
Mini Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)
Sphenoid		
N	xx	xx
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median	xxx.xx	xxx.xx
Min-Max	xxx.x – xxx.x	xxx.x – xxx.x
Osteometal Complex		
N	xx	xx
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median	xxx.xx	xxx.xx
Min-Max	xxx.x – xxx.x	xxx.x – xxx.x
Polypoid Edema Grade 2		
Yes	xx (xx.x%)	xx (xx.x%)

[1] Percentage is calculated based on Intent-to-Treat Population.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 3
Procedural Information
Mini Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)	All Patients (N=xx)
Procedure Duration (min)			
N			xx
Mean (SD)			xxx.x (xxx.xx)
Median			xxx.xx
Min-Max			xxx.x – xxx.x
Endoscopic Procedures Performed:			
Anterior Ethmoidectomy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Posterior Ethmoidectomy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Frontal Sinusotomy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Frontal balloon dilation			
Maxillary antrostomy			
Maxillary balloon dilation			
Sphenoidotomy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Inferior Turbinate Reduction	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Middle Turbinate Reduction	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Polypectomy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Septoplasty			xx (xx.x%)
Instrumentation Used			
Rigid Surgical Instrument	xx (xx.x%)	xx (xx.x%)	
Balloon Dilation	xx (xx.x%)	xx (xx.x%)	
Both	xx (xx.x%)	xx (xx.x%)	
Content of Dissection			
Draf I	xx (xx.x%)	xx (xx.x%)	
Draf IIa	xx (xx.x%)	xx (xx.x%)	
Draf IIb	xx (xx.x%)	xx (xx.x%)	
None	xx (xx.x%)	xx (xx.x%)	
Post-operative Treatments in Ethmoid Sinuses			
Propel	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Propel Mini	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Hemostatic agent, spacer or packing material, with no steroid added	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Hemostatic agent, spacer or packing material, with steroid added	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 4
Implant Performance
Mini Cohort: Intent-to-Treat Population

By Sinus	Treatment Side (N=xx)
Implant Delivery Success [1]	
Number of Attempts	xx (xx.x%)
Implant Delivery Success	xx (xx.x%)
Implant Status (%)	
Day 7	
N [2]	xx (xx.x%)
Absent	xx (xx.x%)
Present	xx (xx.x%)
Completely Open [3]	xx (xx.x%)
Partially Open [3]	xx (xx.x%)
Collapsed [3]	xx (xx.x%)
Mechanical Integrity Remains [3]	xx (xx.x%)
Softening [3]	xx (xx.x%)
Fragmenting [3]	xx (xx.x%)
Completely Removed	xx (xx.x%)
Partially Removed	xx (xx.x%)
Unable to View	xx (xx.x%)
Repeat for Day 21 and 30 for implant status	

[1] Implant procedure concludes with a successful placement even if a second attempt is required. Calculated as ratio of number of successful deployments over number of sinuses attempted.
[2] Based on number of successful deployment
[3] Based on number of status=”Present”

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 5
Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer and by Investigators
Mini Cohort: Intent-to-Treat Population

		Treatment Side (N=xx)	Control Side (N=xx)
Patients with Both Sinuses Evaluable for Post-Op Intervention [1]		xx	xx
Sinuses Requiring Post-Operative Intervention by Independent Reviewer			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Surgical Intervention by Independent Reviewer		xx	xx
Sinuses Requiring Surgical Intervention by Independent Reviewer			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Oral Steroid Intervention by Independent Reviewer		xx	xx
Sinuses Warranting Oral Steroid Intervention by Independent Reviewer			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	

[1] Post-Operative Intervention is a composite endpoint that includes: surgical intervention required to debride obstructive adhesions or scar tissue formation in the FSO (defined as grade 2 or 3 on the adhesion/scarring scale), and/or oral steroid intervention warranted to resolve recurrent inflammation and polypoid edema in the frontal recess/FSO.
[2] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[3] McNemar's test was performed to obtain the 2-sided p-value.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 5
Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer and by Investigators (Part 2)
Mini Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)
Sinuses Requiring Post-Operative Intervention by Investigators		
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Surgical Intervention by Investigators	xx	xx
Sinuses Requiring Surgical Intervention by Investigators		
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Oral Steroid Intervention by Investigators	xx	xx
Sinuses Warranting Oral Steroid Intervention by Investigators		
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [3]	0.xxxx	

[1] Post-Operative Intervention is a composite endpoint that includes: surgical intervention required to debride obstructive adhesions or scar tissue formation in the FSO (defined as grade 2 or 3 on the adhesion/scarring scale), and/or oral steroid intervention warranted to resolve recurrent inflammation and polypoid edema in the frontal recess/FSO.
[2] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[3] McNemar's test was performed to obtain the 2-sided p-value.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 5.1
Frequency Table of Post-Operative Intervention at Day 30 by Independent Reviewer and Investigators
Mini Cohort: Intent-to-Treat Population

	Post-Operative Interventions (N=xx)	Surgical Intervention (N=xx)	Oral Steroid Intervention (N=xx)
Number of Patients in ITT Population			
Patients Requiring Intervention by Indpependent Reviewer	xx	xx	
Yes on T but No on C	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No on T but Yes on C	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Yes on T and Yes on C	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No on T and No on C	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Patients Requiring Intervention by Investigators	xx	xx	
Yes on T but No on C	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No on T but Yes on C	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Yes on T and Yes on C	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No on T and No on C	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Post-Operative Intervention is a composite endpoint that includes: surgical intervention required to debride obstructive adhesions or scar tissue formation in the FSO (defined as grade 2 or 3 on the adhesion/scarring scale), and/or oral steroid intervention warranted to resolve recurrent inflammation and polypoid edema in the frontal recess/FSO.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 5.2
Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer
Mini Cohort: Per-Treatment Evaluable Population

Repeat Tables 5.0 for Per-Treatment Evaluable Population

Table 5.3
Frequency Table of Post-Operative Intervention at Day 30 by Independent Reviewer
Mini Cohort: Per-Treatment Evaluable Population

Repeat Tables 5.1 for Per-Treatment Evaluable Population

Table 5.4
Sensitivity Analysis for Primary Efficacy Endpoint:
Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Sinus Surgeon
Mini Cohort: Intent-to-Treat Population

		Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population			
Patients with Both Sinuses Evaluable for Post-Op Intervention [1]		xx	xx
Sinuses Requiring Post-Operative Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Surgical Intervention		xx	xx
Sinuses Requiring Surgical Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Oral Steroid Intervention		xx	xx
Sinuses Requiring Oral Steroid Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	

Note:
[1] Data imputations: If at Day 7 or 21, a clinical investigator indicates that either frontal recess/FSO required oral steroids or surgical intervention, and that intervention was actually given, then the grades given by the independent reviewer will be replaced by the grades given by the clinical investigator at the earliest visit (Day 7 or 21) at which such intervention was required; If oral steroids were actually prescribed for reasons other than either frontal recess/FSO, then the grades given by the independent reviewer will be replaced by the grades given by the clinical investigator at the visit preceding commencement of oral steroids (Day 7 or 21).
[2] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[3] McNemar's test was performed to obtain the 2-sided p-value.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 5.5
Sensitivity Analysis for Missing Data with Imputation Method #1:
Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer
Mini Cohort: Intent-to-Treat Population

		Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population			
Patients with Both Sinuses Evaluable for Post-Op Intervention [1]		xx	xx
Sinuses Requiring Post-Operative Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Surgical Intervention		xx	xx
Sinuses Requiring Surgical Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Oral Steroid Intervention		xx	xx
Sinuses Requiring Oral Steroid Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	

[1] Missing data will be imputed as:impute No, intervention for all missing values in both components of the composite endpoint (e.g. impute adhesion grade as a 0, and “No” for the need for oral steroids)
[2] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[3] McNemar's test was performed to obtain the 2-sided p-value.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 5.6
Sensitivity Analysis for Missing Data with Imputation Method #2:
Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer
Mini Cohort: Intent-to-Treat Population

		Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population			
Patients with Both Sinuses Evaluable for Post-Op Intervention [1]		xx	xx
Sinuses Requiring Post-Operative Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Surgical Intervention		xx	xx
Sinuses Requiring Surgical Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Oral Steroid Intervention		xx	xx
Sinuses Requiring Oral Steroid Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	

[1] Missing data will be imputed as: •impute Yes, intervention for all missing values in both components of the composite endpoint (e.g. impute adhesion grade as a 2, and “Yes” for the need for oral steroids)
[2] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[3] McNemar's test was performed to obtain the 2-sided p-value.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 5.7
Sensitivity Analysis for Missing Data with Imputation Method #3:
Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer
Mini Cohort: Intent-to-Treat Population

		Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population			
Patients with Both Sinuses Evaluable for Post-Op Intervention [1]		xx	xx
Sinuses Requiring Post-Operative Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Surgical Intervention		xx	xx
Sinuses Requiring Surgical Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Oral Steroid Intervention		xx	xx
Sinuses Requiring Oral Steroid Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	

[1] Missing data will be imputed as: impute Yes, intervention for missing values in either component of the composite endpoint only on the control side and impute No intervention on the treatment side
[2] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[3] McNemar's test was performed to obtain the 2-sided p-value.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 5.8
Sensitivity Analysis for Missing Data with Imputation Method #4:
Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer
Mini Cohort: Intent-to-Treat Population

		Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population			
Patients with Both Sinuses Evaluable for Post-Op Intervention [1]		xx	xx
Sinuses Requiring Post-Operative Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Surgical Intervention		xx	xx
Sinuses Requiring Surgical Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Oral Steroid Intervention		xx	xx
Sinuses Requiring Oral Steroid Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	

[1] Missing data will be imputed as: impute Yes, intervention for missing values in either component of the composite endpoint only on the treatment side and impute No intervention on the control side
[2] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[3] McNemar's test was performed to obtain the 2-sided p-value.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 6
Frequency of Post-Operative Interventions by Treatment Group by Investigators
Mini Cohort: Intent-to-Treat Population

		Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population			
Day 7			
Patients with Sinuses Evaluable for Post-Op Intervention [1]		xx	xx
Sinuses Requiring Post-Operative Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Sinuses Requiring Surgical Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
Sinuses Requiring Oral Steroid Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
Day 21			
Patients with Sinuses Evaluable for Post-Op Intervention [1]		xx	xx
Sinuses Requiring Post-Operative Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Sinuses Requiring Surgical Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
Sinuses Requiring Oral Steroid Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)

Note: Repeat the same data presentation for Day 30 and Day 90
[1] Post-Operative Intervention is a composite endpoint that includes: Surgical intervention required to debride obstructive adhesions or scar tissue formation in the FSO, and/or oral steroid intervention warranted to resolve recurrent inflammation, edema and/or polyposis in the frontal recess/FSO
[2] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[3] McNemar's test was performed to obtain the 2-sided p-value.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 7
Endoscopic Outcomes at Day 30 by Independent Reviewer
Mini Cohort: Intent-to-Treat Population

		Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population		xx	xx
Adhesion/Scarring Grade in the FSO			
Grade 1 (Minimal Amount)			
	N	xx	xx
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [2]	0.xxxx	
Grade 2 or 3 (Clinically Significant)			
	N	xx	xx
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [2]	0.xxxx	
Polypoid Edema Grade at the Frontal Recess/FSO			
Grade 1 (Minimal Amount)			
	N	xx	xx
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [2]	0.xxxx	
Grade 2 (Expanded Amount)			
	N	xx	xx
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [2]	0.xxxx	

[1] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[2] McNemar's test was performed to obtain the 2-sided p-value.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 8
Endoscopic Outcomes by Time Point by Investigators
Mini Cohort: Intent-to-Treat Population

		Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population		xx	xx
Baseline / Procedure			
Adhesion/Scarring in the FSO			
Grade 1 (Minimal Amount)			
	N	xx	xx
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [2]	0.xxxx	
Grade 2 or 3 (Clinically Significant)			
	N	xx	xx
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [2]	0.xxxx	
Polypoid Edema at the Frontal Recess/FSO			
Grade 1 (Minimal Amount)			
	N	xx	xx
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [2]	0.xxxx	
Grade 2 (Expanded Amount)			
	N	xx	xx
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [2]	0.xxxx	

[1] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[2] McNemar's test was performed to obtain the 2-sided p-value.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 8
Endoscopic Outcomes by Time Point by Investigators
Mini Cohort: Intent-to-Treat Population

		Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population		xx	xx
Patency of the FSO Grade of 2 (0, 1 versus 2)			
	N	xx	xx
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [2]	0.xxxx	
Patency of the FSO Grade of 1 or 2 (0 versus 1,2)			
	N	xx	xx
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [2]	0.xxxx	
With Unfavorable Clinical Outcome [3]			
	N	xx	xx
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [2]	0.xxxx	
Day 7			
Day 21			
Day 30			
Day 90			

[1] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[2] McNemar's test was performed to obtain the 2-sided p-value.
[3] An unfavorable clinical outcome has occurred if any of the following are true for a given sinus: polypoid edema is grade 2 (expanded amount), Adhesion/Scaring is grade 2 (moderate amount warranting intervention) or 3 (significant amount requiring intervention)or Patency of the FSO is grade 2 (occluded)

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 9
Endoscopic Outcomes at Day 30 by Independent Reviewer – Inflammation
Mini Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)	Difference (Tx-C) (N=xx)
Number of Patients in the Intent-to-Treat			
Inflammation in the Front Recess/FSO(mm)			
Day 30			
N [1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median	xxx.xx	xxx.xx	xxx.xx
Min-Max	xxx.x – xxx.x	xxx.x – xxx.x	xxx.x – xxx.x
95% CI [1]			
P-value [2]			

Note: Inflammation on 100-mm VAS
[1] The 95% CI for mean values was obtained assuming a normal distribution
[2] A paired t-test was used to obtain the p-value for the side to side difference in scores.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 10
Endoscopic Outcomes by Time Point by Investigators – Inflammation, FSO Diameter
Mini Cohort: Intent-to-Treat Population

Inflammation in the Front Recess/FSO(mm)		Treatment Side (N=xx)	Control Side (N=xx)	Difference (Tx-C) (N=xx)
Baseline Procedure				
Inflammation (mm)				
N [1]		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mean (SD)		xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median		xx.x	xx.x	xx.x
Min-Max		xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
	95% CI [1]	xx.x –xx.x	xx.x – xx.x	xx.x – xx.x
	P-value [2]			0.xxx
Estimated FSO Diameter - Largest (mm)				
N [1]				
Mean (SD)		xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median		xx.x	xx.x	xx.x
Min-Max		xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
	95% CI [1]	xx.x –xx.x	xx.x – xx.x	xx.x – xx.x
	P-value [2]			0.xxx
Day 7				
Day 21				
Day 30				
Day 90				

Note: Inflammation on 100-mm VAS
[1] The 95% CI for mean values was obtained assuming a normal distribution
[2] A paired t-test was used to obtain the p-value for the side to side difference in scores.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 11
CT Outcomes at Day 90 by Independent Reviewer and Investigators – Lund-Mackay Scores
Mini Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)	Difference (Tx-C) (N=xx)
Lund-Mackay Score in Frontal Sinus by Independent Reviewer			
N	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
95% CI [1]	xx.x –xx.x	xx.x – xx.x	xx.x – xx.x
P-value [2]			0.xxx
Lund-Mackay Total Score by Independent Reviewer			
N	xx	xx	xx (xx.x%)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
95% CI [1]	xx.x –xx.x	xx.x – xx.x	xx.x – xx.x
P-value [2]			0.xxx
Lund-Mackay Score in Frontal Sinus by Investigators			
N	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
95% CI [1]	xx.x –xx.x	xx.x – xx.x	xx.x – xx.x
P-value [2]			0.xxx
Lund-Mackay Total Score by Investigators			
N	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
95% CI [1]	xx.x –xx.x	xx.x – xx.x	xx.x – xx.x
P-value [2]			0.xxx

[1] The 95% CI for mean values was obtained assuming a normal distribution
[2] A paired t-test was used to obtain the p-value for the side to side difference in scores.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 11
CT Outcomes at Day 90 by Independent Reviewer and Investigators – Lund-Mackay Scores (Part 2)
Mini Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)	Difference (Tx-C) (N=xx)
Estimated Maximum Size of FSO (mm) by Independent Reviewer			
N	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
95% CI [1]	xx.x –xx.x	xx.x – xx.x	xx.x – xx.x
P-value [2]			0.xxx
Estimated Size of FSO (mm)– Maximum by Investigators			
N	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
95% CI [1]	xx.x –xx.x	xx.x – xx.x	xx.x – xx.x
P-value [2]			0.xxx

[1] The 95% CI for mean values was obtained assuming a normal distribution
[2] A paired t-test was used to obtain the p-value for the side to side difference in scores.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 12
CT Outcomes at Day 90 by Independent Reviewer and Investigators - Radiological Grades
Mini Cohort: Intent-to-Treat Population

		Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population		xx	xx
Radiological Grade of 3 (1, 2 versus 3) by Independent Reviewer			
	N	xx	xx
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [2]	0.xxxx	
Radiological Grade of 2 or 3 (1 versus 2, 3) by Independent Reviewer			
	N	xx	xx
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [2]	0.xxxx	
Radiological Grade of 3 (1, 2 versus 3) by Investigators			
	N	xx	xx
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [2]	0.xxxx	
Radiological Grade of 2 or 3 (1 versus 2,3) by Investigators			
	N	xx	xx
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [2]	0.xxxx	

[1] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[2] McNemar's test was performed to obtain the 2-sided p-value.
Radiological Grading Scale: 1 = Mucosal thickening of less than 5mm; 2 = Partial opacification, air-fluid level, or mucosal thickening of 5mm or higher; 3 = Total opacification

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 13
Summary of Interventions at Follow-up
Mini Cohort: Intent-to-Treat Population

	All Patients (N=xx)
Oral Steroid Prescribed for FSO Sinus Obstruction	
Yes n(%)	
Day 7	xx (xx.x%)
Day 21	xx (xx.x%)
Day 30	xx (xx.x%)
Day 90	xx (xx.x%)
Antibiotics Prescribed for Frontal Sinus	
Yes n(%)	
Day 7	xx (xx.x%)
Day 21	xx (xx.x%)
Day 30	xx (xx.x%)
Day 90	xx (xx.x%)
Received Polypectomy	
Yes n(%)	
If Yes, first noted at	
Day 7	xx (xx.x%)
Day 21	xx (xx.x%)
Day 30	xx (xx.x%)
Day 90	xx (xx.x%)
Received Repeat ESS	
Yes n(%)	
If Yes, occurred at	
Day 7	xx (xx.x%)
Day 21	xx (xx.x%)
Day 30	xx (xx.x%)
Day 90	xx (xx.x%)

[1] Percentage is calculated based on ITT Population.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 14
Overall Summary of Adverse Events
Mini Cohort: Intent-to-Treat Population

	All Patients (N=xx)
Patients with Any Adverse Events	xx (xx.x%)
Relationship of Adverse Events	xx (xx.x%)
No Relationship	xx (xx.x%)
Surgical Procedure Related	xx (xx.x%)
Implant Placement Procedure Related	xx (xx.x%)
Implant Related	xx (xx.x%)
Endoscopy Procedure Related	xx (xx.x%)
Morbid or Comorbid Related	xx (xx.x%)
Anasthesia Related	xx (xx.x%)
Patients with Adverse Events Resulting in Discontinuation	xx (xx.x%)
Patients with Adverse Events by Maximum Severity	
Mild	xx (xx.x%)
Moderate	xx (xx.x%)
Severe	xx (xx.x%)
Patients with Implant Related Adverse Events by Maximum Severity	
Mild	xx (xx.x%)
Moderate	xx (xx.x%)
Severe	xx (xx.x%)
Patients with Implant Placement Procedure Related Adverse Events by Maximum Severity	
Mild	xx (xx.x%)
Moderate	xx (xx.x%)
Severe	xx (xx.x%)
Patients with Serious Adverse Events	xx (xx.x%)
Patients with Implant Related Serious Adverse Events	xx (xx.x%)
Patients with Implant Placement Procedure Related Serious Adverse Events	xx (xx.x%)

Note: Adverse events coded using the MedDRA dictionary Version x.x. Given in the table are patient counts and percentages. At each level of summation, patients are counted only once. Patients experiencing adverse events of more than one severity are summarized according to the maximum severity experienced over all episodes of an adverse event.
Reference: Listing x.x.x

Table 15
Summary of Adverse Events by System Organ Class
Mini Cohort: Intent-to-Treat Population

System Organ Class Preferred Term	All Events (N=xx)	Events Localized to Treatment Side (N=xx)	Events Localized to Control Side (N=xx)
Patients with Any Adverse Event	xx (xx%)		
System Organ Class 1	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 1	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 2	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 3	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 4	xx (xx%)	xx (xx%)	xx (xx%)
.			
.			
System Organ Class 2	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 1	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 2	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 3	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 4	xx (xx%)	xx (xx%)	xx (xx%)
.			
.			
.			
Continue to report all reported events			

Note: Adverse events (AEs) coded using the MedDRA dictionary, Version x.x. Given in the table are patient counts and percentages. At each level of summation, patients are counted only once. Patients experiencing adverse events of more than one severity are summarized according to the maximum severity experienced over all episodes of an adverse event.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 16
Summary of Concomitant Medication
Mini Cohort: Intent-to-Treat Population

ATC level Preferred Term	All Patients (N=xx)
Patient Reported Any Concomitant Medication Use	xx (xx.x%)
Drugs for Acid Related Disorders	xx (xx.x%)
Alfacalcidol	xx (xx.x%)
Calcium Acetate	xx (xx.x%)

Note: Concomitant medications are coded using WHO Drug disctionary Version x.x. At each level of summation, patients are counted only once.
Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table of Contents

Listing 1
Patient Disposition
Mini Cohort

Patient ID	Procedure Date(MM-DD-YYYY)	Both FSOs Amenable to Implant?	Patient Met All Eligibility Criteria?	Side	Treatment Group	Implant Deployed	Completed Study? Date Completion/ Discontinuation MM-DD-YYYY	Primary Reason for Early Termination
xx-xxxx				Right Left	Treatment Control		Yes : MM-DD-YYYY No : MM-DD-YYYY	

SOURCE: xxxx SAS 9.2 {program location}{run date/time}

Programming note: This listing will include all patients including screen fails, all other listings should only include patients who enrolled in this study.

Listing 2
Analysis Populations
Mini Cohort

Treatment Side	Patient ID	Population		Reason for Exclusion from PTE
		ITT [1]	PTE [2]	
Right	xx-xxxx	Yes	Yes	
	xx-xxxx	Yes	No	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx Xxxxxxxxx

Reference: eCRF Module
1.Intent-to-Treat (ITT) – All Randomized Patients.
2.Per-Treatment-Evaluable Population (PTE) - All randomized patients who have received the study implant in the target sinus, have no major procedural protocol deviations and follow-up data are available.

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 3
Demographics and Baseline Characteristics
Mini Cohort

Patient ID	Age(yr)	Gender	Ethnicity	Race	Number of Prior ESS	Date of Most Recent ESS (MM-DD-YYYY)	History of Asthma Diagnosed	Hx of Allergic Rhinitis Diagnosed	History of Aspirin Intolerance	History of Samter's Triad	Hx of Allergies	Hx of Smoking
xx-xxxx	xx	Female	Non-Hispanic	White								
	xx	Female	Hispanic or Latino	White								

Note:

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 4
Procedure - Anesthesia and Endoscopic Procedures (Part 1)
Mini Cohort

					Endoscopic Procedure Performed										
Patient ID	Procedure Date	Type of Anesthesia Used	Anesthesia Start Time/Stop Time	Side	Anterior ethmoidectomy	Posterior ethmoidectomy	Frontal sinusotomy	Frontal balloon dilation	Maxillary antrostomy	Maxillary balloon dilation	Sphenoidotomy	Inferior turbinate reduction	Middle turbinate reduction	Polypectomy	Septoplasty
xx-xxx		XXXXXXX XX	08:25/ xx:xx												
xx-xxx															

Note:

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 4.1
Procedure - Anesthesia and Surgery (Part 2)
Mini Cohort

Treated Side	Patient ID	Surgeon Name	Side	Instrumentation Used	Maker/Diameter/Length/Pressure if Balloon Used	Extent of Frontal Sinus Surgical Dissection	Both FSOs Amenable to Implant?
	xx-xxx		R L				
	xx-xxx						

Note:

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 4.2
Procedure - Implant Placement (Part 3)
Mini Cohort

Treated Side	Patient ID	Procedure Start/ End Time	Lot #	Able to Deploy Implant?	Reason if Not	Implant Malfunction?	Additional Implant Used?	Able to Place Additional Implant at Target Location?	Reason if not	Implant Malfunction for the Additional Implant?	% Apposition of Implant to FSO	Degree of Manipulation
	xx-xxxx	08:05am/09:10pm										
	xx-xxxx											

Note:

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 4.3
Procedure – Post-Operative Treatments (Part 4)
Mini Cohort

Treated Side	Patient ID	Side	Ethmoid	If Ethmoid, Specify	Maxillary	If Maxillary, Specify	Sphenoid	If sphenoid, Specify	Any Procedure AE?
	xx-xxxx								
	xx-xxxx								

Note:

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 5
Follow-up Assessments
Mini Cohort

Treated Side	Patient ID	Visit	Visit Date MM-DD-YYYYMM-DD-YYYY(Day)	New or Worsening Sinus Symptoms?	Change in Medication?	Unscheduled Visit?	List Interventions at this Visit or Since Last Scheduled Visit	AE Occurred Since Last Visit?
	xx-xxxx			x	x		xxxxxxxxxxxxxxx	
				x	x		xxxxxxxx	
	xx-xxxx			xx	xx			xxxxxxxxxx
				xx	xx			xxxxxxxxxxxxxxx
	xx-xxxx							

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 6
Endoscopic Outcomes by Independent Reviewer – Day 30
Mini Cohort

Treated Side	Subject ID	Visit Date (Day)	Side	Polypoid Edema	Adhesions/ Scarring	Inflammation VAS (mm)	Oral Steroid Warranted ? [1]	Surgical Intervention Required? [2]
Right	xx-xxx	yyyy-mm-dd (xxx)	R					
			L					
Right	xx-xxx		R					
			L					
			R					
			L					
			R					
			L					

Reference: eCRF Module

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}
[1] Oral steroid intervention warranted to resolve recurrent inflammation, edema and/or polyposis in the frontal recess/FSO
[2] Surgical intervention required to debride obstructive adhesions or scar tissue formation in the FSO

Listing 7
Endoscopic Outcomes by Investigators (Part 1)
Mini Cohort

Treated Side	Patient ID	Visit	Visit Date (Day) MM-DD-YYYY	Side	Polypoid Edema	Adhesions/Scarring	Patency of FSO	Estimated Diameter-Largest (mm)	Estimated Diameter-Smallest (mm)	Inflammation VAS (mm)	Comments
Right	xx-xxxx	Procedure	MM-DD-YYYY (xxx)	R							
				L							
		Day 7	MM-DD-YYYY (xxx)	R							
				L							
		Day 21	MM-DD-YYYY (xxx)	R							
				L							
		Day 30	MM-DD-YYYY (xxx)	R							
				L							
		Day 90	MM-DD-YYYY (xxx)	R							
				L							
Right	xx-xxxx			R							
				L							

Reference: eCRF Module

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 7.1
Endoscopic Outcomes by Investigators (Part 2)
Mini Cohort

Treated Side	Patient ID	Visit	Visit Date (Day) MM-DD-YYYY	Implant Current Status	Implant Opening	Implant Integrity	Implant Removed at this Visit?	Oral Steroid Warranted? [1]	Oral Steroids Prescribed?	Surgical Intervention Required? [2]	Surgical Intervention Performed?	Comments
Right	xx-xxxxx	Day 7	MM-DD-YYYY (xxx)									
		Day 21	MM-DD-YYYY (xxx)									
		Day 30	MM-DD-YYYY (xxx)									
		Day 90	MM-DD-YYYY (xxx)									
Right	xx-xxxx											

Reference: eCRF Module
[1] Oral steroid intervention warranted to resolve recurrent inflammation, edema and/or polyposis in the frontal recess/FSO
[2] Surgical intervention required to debride obstructive adhesions or scar tissue formation in the FSO

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 8
CT Outcomes by Independent Reviewer – Day 90 (Part 1)
Mini Cohort

				Lund-Mackay Score						
Treated Side	Patient ID	Assessment Date (Day)	Side	Frontal	Maxillary	Anterior Ethmoid	Posterior Ethmoid	Sphenoid	Osteomeatal Complex	Total
Right	xx-xxxx	MM-DD-YYYY (xxx)	R	xx	xx	xx	xx	xx	xx	xx
			L	xx	xx	xx	xx	xx	xx	xx
			Total	xx	xx	xx	xx	xx	xx	xx
Right	xx-xxxx	MM-DD-YYYY (xxx)	R							
			L							
			Total							

Reference: eCRF Module

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 8.1
CT Outcomes by Independent Reviewer – Day 90 (Part 2)
Mini Cohort

Treated Side	Patient ID	Assessment Date (Day)	Side	Estimated Maximum Size of FSO (mm)	Radiological Grade
Right	xx-xxxx	MM-DD-YYYY (xxx)	R	xx	
			L		
			R		
			L		

Reference: eCRF Module

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 9
CT Outcomes by Investigators – Baseline & Day 90 (Part 1)
Mini Cohort

Treated Side	Patient ID	Assessment Date (Day) MM-DD-YYYY	Visit	Side	Lund-Mackay Score						
					Frontal	Maxillary	Anterior Ethmoid	Posterior Ethmoid	Sphenoid	Osteomeatal Complex	Total
Right	xx-xxxx	MM-DD-YYYY (xxx)	Baseline	R							
			Day 90	L							
				R							
				L							

Reference: eCRF Module

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 9.1
CT Outcomes by Investigators – Baseline & Day 90 (Part 2)
Mini Cohort

Treated Side	Patient ID	Assessment Date (Day) MM-DD-YYYY	Side	Size of FSO (mm)	Radiological Grading
		MM-DD-YYYY	R		
	xx-xxx	(xxx)			
			L		
			R		
			L		

Reference: eCRF Module

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 10
Adverse Events
Mini Cohort

Patient ID	Treated Side	System Organ Class/ Preferred Term/ Adverse Event Term	Location	Start Date MM-DD-YYYY (Day)	Stop Date MM-DD-YYYY (Day)	Intensity	SAE?	Relationship	AE Treatment/Primary AE outcome
xx-xxxx	Right	NTE xxxxxxxxxxxxxx/		MM-DD-YYYY (xx)					None/
		xxxxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx		MM-DD-YYYY (xx)					Recovered with Sequelae
xx-xxxx		xxxxxxxxxxxx/ xxxxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxxxxxxxx							
xx-xxx		None							

Note: If a patient has no AEs then "None" will be displayed. Adverse Events are coded in MedDRA Vxx.x.
Reference: eCRF Module AE
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Programming Note:

1. If Ongoing is checked then list “Continuing” in the place for “Stop Date (Day)”.

Listing 11
Prior and Concomitant Medication
Mini Cohort

Patient ID	ATC level Preferred Term/ Medication	Start Date MM-DD-YYYY	Start Day	Stop Date MM-DD-YYYY	Stop Day	Indication Med Prescribed for	Dosage (Unit)	Route	Frequency
xx-xxx									
xx-xxx									

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Programming Note:

1. If Ongoing is checked ”Yes” list “Ongoing” under stop date column
2. Concatenate dose and unit for listing, if other unit exists then list it for units
3. Route, if Other Route is not blank, list it under “Route” column
4. Frequency, if Other Frequency is not blank, list it under ‘Frequency” Column

Listing 12
Protocol Deviations
Mini Cohort

Patient ID	Date/Time Point	Deviation Date MM-DD-YYYY	Reason for Deviation	Explanation	Pre-approved by Sponsor	Date Approved	Date Documented
xx-xxxx	MM-DD-YYYY/D7						
xx-xxxx							

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 13
Comments or Narrative
Mini Cohort

Patient ID	Form	Time Point	Comments
xx-xxxx	Follow-up	Day 90	xxxxxxxxxxxxxxxxxxxx

Reference: eCRF Module xx

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

STATISTICAL ANALYSIS PLAN

Protocol #:	P500-0514
Sponsor:	Intersect ENT 1555 Adams Dr Menlo Park CA 94025
SAP Version #:	3.0
Version Date:	June 24, 2015
Investigational Products:	Propel Mini & Propel Nova Sinus Implants
Intended 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 edema. The implant reduces the need for post-operative intervention such as surgical adhesion lysis and/or use of oral steroids. The Propel Nova Sinus Implant is intended for use in patients ≥ 18 years of age to maintain patency of sinus ostia following sinus surgery. The Propel Nova Sinus Implant separates/dilates mucosal tissues, prevents obstruction by adhesions/scarring, and reduces edema.

The study will be performed in compliance with Good Clinical Practice (GCP), including archival of essential study documents, and 21 CFR Parts 11, 50, 56 and 812.

Statistical Analysis Plan

Sponsor Name:	Intersect ENT
Protocol #:	P500-0514
Protocol Title:	Safety and Efficacy of the Propel Mini and Propel Nova Steroid-Releasing Sinus Implants Following Surgical Opening of the Frontal Sinus for Chronic Sinusitis:A Randomized Blinded Controlled Study
SAP Version #:	3.0
Version Date:	June 24, 2015

Prepared by:

for Saling Huang — 24 June 2015

Saling Huang, PhD
Sr. Director, Biostatistics
Advance Research Associates (ARA), Inc.

Date

APPROVAL SIGNATURES

The signatures below indicate approval of the Statistical Analysis Plan for this study.

25 JUN 2015

Andrew Mugglin, PhD
President & Principal Statistical Consultant
Paradigm Biostatistics, LLC

Date

for James Stambaugh — 25 JUN 2015

James Stambaugh
VP, Clinical Affairs
Intersect ENT

Date

for — 6/30/15

Amy Wolbeck
VP Regulatory Affairs & Quality
Intersect ENT

Date

REVISION HISTORY

Version	Date	Summary of Changes/Comments
1.0	26Mar15	Document created
2.0	28May15	Revisions consistent with Rev 5.0 protocol. Provided details on the changes of data presentation.
3.0	24June15	Revisions in response to the FDA's feedback in Sections 7.2 and 7.7

TABLE OF CONTENTS

1.0 INTRODUCTION

This document presents the Statistical Analysis Plan (SAP) for the PROGRESS Study entitled "Safety and Efficacy of the Propel Mini and Propel Nova Steroid-Releasing Sinus Implants Following Surgical Opening of the Frontal Sinus for Chronic Sinusitis: A Randomized Blinded Controlled Study" conducted under the study protocol P500-0514 version 5.0 (dated April 29, 2015). The purpose of this document is to provide further details regarding the analysis plans.

2.0 STUDY DESIGN

This is a prospective, randomized, blinded, controlled, multicenter study that will enroll two consecutive patient cohorts: the Propel Mini Cohort and the Propel Nova Cohort. Each cohort will enroll 50 to 80 patients who satisfy entry criteria. The study patients will undergo implant placement on one side following ESS that includes bilateral frontal sinus surgery by traditional surgical technique or balloon dilation.

For each cohort, the study utilizes an intra-patient control design to assess the safety and efficacy of the implant compared to surgery alone without implant on the contralateral side. The study is blinded, meaning that patients will be blinded throughout the study duration to which side received the implant. . The independent sinus surgeon performing review of the video-endoscopies will also be blinded to which side received the implant.

Patients will return for four follow-up visits at Days 7, 21, 30 and 90 (see Appendix 1 for Schedule of Assessments). The follow-up assessment will include endoscopic examinations that will be recorded. At Day 21 the implant or its remnants will be removed to allow blinded review of video-endoscopies at Day 30.

3.0 STUDY OBJECTIVE

The objective of the PROGRESS Study is to assess the safety and efficacy of the Propel Mini and Propel Nova Sinus Implants when placed in the frontal sinus opening following frontal sinus surgery in patients with chronic sinusitis.

4.0 DATA MANAGEMENT

Data management will be performed by Intersect ENT according to the Data Management Plan. Data analyses will be performed by independent biostatisticians according to Advance Research Associates' standard operating procedures.

4.1 Clinical Database

An Electronic Data Capture (EDC) System will be utilized to collect study data using electronic case report forms (eCRFs). Data entry will be performed by qualified site personnel after completing appropriate training. Modifications to the EDC will be made if deemed necessary by the study sponsor.

4.2 Data Cleaning

The database will be verified periodically for data omissions, inconsistencies and discrepancies. Any deficiencies or deviations will be reviewed and any necessary actions determined (e.g., data query, communication with the study center). Intermittent data review will be performed and any discovered errors will be reported to the study sites using the electronic query process (as necessary). The study sites will be expected to review and complete the queries. The data cleaning cycle will be repeated until all data are considered clean.

4.3 Data Back-up

Incremental computer data back-up will be performed on a regular basis. All media will be stored in a secure location.

4.4 Confidentiality and Security

Passwords will be issued by the EDC System vendor to appropriate personnel.

5.0 DEFINITION OF ENDPOINTS

5.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be evaluated for each study cohort separately. The primary efficacy endpoint is the reduction in need for post-operative interventions at Day 30, as determined by an independent, blinded sinus surgeon based on video-endoscopy reviews.

Post-operative intervention is a composite endpoint that includes:

- Surgical intervention required to debride obstructive adhesions or scar tissue formation * in the frontal sinus opening (FSO), and/or
- Oral steroid intervention warranted to resolve recurrent inflammation or polypoid edema in the frontal recess/FSO.

* Defined as grades 2 or 3 on the Adhesion/Scarring Scale

5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will be evaluated for each study cohort separately.

Secondary endpoints include:
Endoscopic outcomes assessed by an independent blinded sinus surgeon based on video-endoscopy review:

- Frequency and severity of adhesion/scarring formation in the FSO at Day 30Degree of inflammation in the frontal recess/FSO at Day 30 using a 100-mm Visual Analog Scale (VAS)
- Frequency and grade of polypoid edema in the frontal recess/FSO at Day 30
- A sensitivity analysis will be performed to assess the impact of actual interventions that occur prior to Day 30, upon the assessments made by the independent reviewer at Day 30.

Endoscopic outcomes assessed by on-site investigators:

- Need for post-operative intervention at all time-points through Day 90
- Degree of inflammation in the frontal recess/FSO at all time points through Day 90 using the 100-mm VAS
- Frequency and severity of adhesion/scarring formation in the FSO at all time points through Day 90
- Frequency and grade of polypoid edema in the frontal recess/FSO at all time points through Day 90
- Rate of frontal sinus patency at Day 90 determined endoscopically and radiologically (CT scan)
- Implant delivery success rate

CT outcomes assessed by an independent blinded sinus surgeon based on CT scan review:

- Patency of the FSO and Lund-Mackay score at Day 90
- Extent of the disease in the frontal sinuses using Radiological Grading Scale at Day 90

CT outcomes assessed by on-site investigators based on CT scan review:

- Maximum size of FSO in mm
- Lund-Mackay score at Day 90
- Extent of the disease in the frontal sinuses using Radiological Grading Scale at Day 90

5.3 Safety Measures

The safety measures will be evaluated for each study cohort separately. The safety measures include:

- Implant safety will be determined by assessment of adverse events.
- Adverse Events (AE) and Serious Adverse Events (SAEs) will be recorded and tabulated through Day 30 and Day 90. Where possible and if applicable, adverse events will be localized to a sinus location.

6.0 STATISTICAL METHODS

6.1 Randomization

The ratio of left to right sinus assignments will be 1:1. Randomization will be stratified by site, will follow a blocked scheme with blocks of varying sizes, and will be performed using the envelope method.

6.2 Analysis Populations

Intent-to-Treat Population

The ITT population will consist of all randomized patients who undergo implant placement (i.e., delivery system inserted into the FSO with intent to place the implant). Patients' sinuses will be analyzed in the treatment group to which they were actually randomized.

Per-Treatment-Evaluable Population

The PTE population will consist of all randomized patients who have received the study implant in the target sinus, who have no major procedural protocol deviations and for whom follow-up data are available.

6.3 General Considerations for Statistical Analyses

All analyses described in this plan are considered a priori analyses in that they have been defined prior to locking the database and reviewing unblinded results. All other analyses, if any, designed subsequent to locking the database will be considered post hoc analyses and will be applied as exploratory methodology. Any post hoc analyses will be clearly identified in the clinical study report.

The analysis of each cohort stands on its own; achieving the primary objective in one cohort is considered sufficient for demonstrating efficacy in that cohort, regardless of the results of the corresponding analysis in the other cohort.

The primary efficacy endpoint, all secondary efficacy endpoints and safety evaluations will be analyzed separately for each of the two study cohorts.

All data relating to the study will be summarized using descriptive statistics. Summary statistics will consist of counts and percentages of patients for nominal and ordinal measures, and means, standard deviations, median and ranges for continuous measures. Where meaningful, the results will be presented graphically.

Available data at each time point will be presented. No substitutions for missing data will be made, with the exception of the primary efficacy endpoint sensitivity analyses and missing data sensitivity analysis (Sections 7.3 and 7.5).

Categorical data that can be localized to a treatment or control side will be analyzed using McNemar's test for correlated proportions. In this intra-patient control study design, only discordant pairs of observations contribute to evidence of a treatment effect. If the number of discordant pairs is less than 20, an exact version of McNemar's test will be used, wherein the proportion of discordant pairs favoring the treatment side (out of all discordant pairs) will be compared against a null value of 0.50. The appropriate test is an exact binomial calculation, using a 2-sided alpha of 0.05 or a 1-sided alpha of 0.025. In addition, frequency distributions showing findings by treatment side over time and descriptive statistics (counts, percentages and, where appropriate, exact 95% confidence intervals using the method of Clopper and Pearson) will be used.

Listings of patient data will be provided to facilitate investigation of tabulated values and to allow for clinical review of all primary and secondary endpoints. Patient listings will be sorted by Site Number and Patient ID Number.

Version 9.2 (or higher) of SAS statistical software package will be used to provide all summaries, listings, graphs, and statistical analyses.

Except where explicitly indicated, data will be pooled across study sites within each study cohort for all statistical analyses.

7.0 STATISTICAL ANALYSES

7.1 Demographics and Baseline Characteristics

Demographic data (e.g., gender and age) and clinical information (e.g., number of prior sinus procedures, history of asthma diagnosed by physician, history of aspirin intolerance or aspirin allergy, history of allergies, history of smoking, presence of grade 2 polypoid edema, total Lund-Mackay scores by sinus) will be presented for all patients. Lund-Mackay scores will also be presented by side (treatment vs. control).

A summary table for procedural information will present the count and percentage of patients that underwent each surgery type and frequency of use of other device or types of drug in the ethmoid sinuses during surgery.

7.2 Primary Efficacy Endpoint Hypothesis and Analysis

The Primary Efficacy Hypothesis is that the steroid-releasing implant will reduce the need for post-operative interventions at Day 30 compared to the control, as determined by an independent blinded sinus surgeon based on video-endoscopy review. The relevant null and alternative hypotheses are:

$$H_0: P_T = P_C$$
$$Ha: P_T \neq P_C$$

where P_T and P_C represent the proportion of patients who warrant post-operative interventions on the treatment and control sides, respectively. Since $P_T = P_{11} + P_{10}$ 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, these hypotheses are equivalent to a test of $H_0: P_{10} = P_{01}$ vs $Ha: P_{10} \neq P_{01}$.

Analysis

The planned analysis is 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. Although the alternative hypothesis is two-sided, evidence of a beneficial effect will only be concluded if statistical significance is achieved and P_T is observed to be less than P_C.

An exact version of the test will be used. The exact version defines the proportion of discordant pairs that favor the treatment side as $P^* = P_{01}/(P_{01}+P_{10})$ and tests H_0: $P^* = 0.50$ vs. Ha: $P^* \neq 0.50$ via an exact binomial calculation.

Sample Size

Sample size is calculated based on the following assumptions:

- Expected proportion of discordant pairs at Day 30: $P_{01}+P_{10} = 35\%$
- Expected treatment effect: $P_T–P_C= 21.0\%$
- The two preceding assumptions are equivalent to assuming that $P_{01} = 0.28$, $P_{10} = 0.07$, and thus $P^* = 0.80$. This corresponds to a conditional odds ratio of 4.0 among discordant pairs.
- Target power: $\geq 80\%$
- Type I error rate: $\alpha = 0.05$, 2-sided

Sample Size: A binomial probability calculation with $P^* = 0.80$ reveals that 20 discordant pairs are required to achieve at least 80% power. To obtain this, patients will be enrolled and treated until it is known that at least 20 patients have discordant pairs of outcomes. A minimum of 50 patients and a maximum of 80 patients will be enrolled and treated.

NOTE: Assumptions for proportion of discordant pairs and treatment effect are based on results from the ADVANCE II Study, where in assessing the need for postoperative intervention at Day 30, 35 of 96 evaluable patients (36.5%) yielded discordant pairs, and among these discordant pairs, 24 of 35 (68.6%) indicated that intervention was warranted on the control side but not the treatment side. The present study evaluates placement of the Propel Mini and Propel Nova in frontal sinus openings. The frontal recess and frontal sinus drainage pathway are known to be more difficult to access surgically, and to maintain in the post-operative timeframe. As a result, frontal sinus patency rates are known to be lower than that of the other sinuses. Therefore, we have assumed that placement of the Propel

Mini and Propel Nova Sinus Implants will yield a higher proportion of discordant pairs favoring the treatment sides than was observed with placement in the ethmoid sinus. The assumed odds ratio is 4:1, meaning that we assume 80% of discordant pairs will favor treatment sides.

Sampling Plan

Since only discordant pairs contribute to the test of a treatment effect, the observed proportion of discordant pairs is an important consideration. In the ADVANCE II study, 35/96 (36.5%) evaluable pairs of observations were discordant. A 95% confidence interval for this percentage ranges from approximately 27% to 47%. Using this as a guide, it is expected that approximately 20/0.25 = 80 patients would be a maximum and 20/0.40 = 50 patients would be a minimum enrollment size in order to achieve 20 discordant pairs.

When 50 patients have reached Day 30, the total number of discordant pairs will be determined (in a manner that reveals only the count of discordant pairs and not any estimates of the treatment effect). If this number is at least 20, enrollment will stop, and the analysis of the primary objective can proceed once all enrolled patients have completed follow-up. Alternatively, if the number of discordant pairs is less than 20, enrollment will continue until 20 patients are known to yield discordant results, up to a maximum of 80 randomized patients. At the time when enrollment ceases, it is possible that some patients will have < 30 days follow-up and thus have undetermined endpoint status. Once their follow-up is complete, these patients can possibly contribute additional discordant pairs to the analysis, for a total exceeding 20.

The primary objective will be evaluated for each cohort separately at the time when all randomized patients from a particular cohort have completed follow-up.

Re-Estimation of Nova Cohort Sample Size

Since the results of the original Mini Cohort are not available at the time of this amendment, the study hypothesis and sample size calculation for the Nova Cohort are identical to the Mini Cohort: 50-80 patients will be enrolled in order to achieve 20 discordant pairs of results. The results from the Mini Cohort are external to the analysis of

the Nova Cohort. Once available, the results from the Mini Cohort may be used to re-estimate the sample size of the Nova Cohort.

Analysis Cohort

The primary efficacy analysis will be conducted on the ITT basis, which will consist of all randomized patients who undergo implant placement (i.e., delivery system inserted into the FSO with intent to place the implant). This analysis will be repeated for the PTE population.

7.3 Sensitivity Analysis for Primary Efficacy Endpoint

Since the primary efficacy endpoint is determined by an independent blinded sinus surgeon based on review of video-endoscopies taken at Day 30, interventions performed by clinical investigators prior to Day 30 can potentially confound the primary efficacy outcome. Therefore, a sensitivity analysis will be performed to test the robustness of the primary efficacy conclusion, to actual interventions given. Data imputations will be performed as follows:

- If at Day 7 or Day 21, a clinical investigator indicates on the Endoscopic Scoring Form that either frontal recess/FSO required oral steroids or surgical intervention, and that intervention was actually given, then the grades given by the independent reviewer will be replaced by the grades given by the clinical investigator at the earliest visit (Day 7 or Day 21) at which such intervention was required.
- If oral steroids were actually prescribed for reasons *other than* frontal recess/FSO, then the grades given by the independent reviewer will be replaced by the grades given by the clinical investigator at the visit preceding commencement of oral steroids (Day 7 or Day 21).

7.4 Secondary Efficacy Endpoint Analyses

7.4.1 Endoscopic Outcomes Assessed by Independent Reviewer

The counts and percentages of patients with adhesion/scarring at Day 30 by an independent blinded sinus surgeon will be presented by grade and side (treatment vs. control). For analysis purposes, clinically significant adhesion/scarring is prospectively defined as grades 2 or 3. The counts and percentages of patients with

polypoid edema will be presented by grade and side. In addition, adhesion/scarring and polypoid edema grades will be presented graphically by side in scatter plots. The mean inflammation scores in the frontal recess/FSO and their associated standard deviation will be presented by side and as mean difference between sides (difference is calculated by subtracting the control score from the treatment score).

7.4.2 Endoscopic Outcomes Assessed by Investigators

Frequency and severity of adhesion/scarring rated by on-site clinical investigators will be presented by grade and side (treatment vs. control) for each time point (Days 7, 21, 30 and 90). Similarly, frequency and severity of polypoid edema and patency of the FSO will be presented by side and time point. In addition, adhesion/scarring, polypoid edema and FSO patency grades at Day 30 will be presented graphically by side in scatter plots.

The mean inflammation in the frontal recess/FSO and its associated standard deviation will be presented for each time point by side and mean difference between sides (difference is calculated by subtracting the control score from the treatment score). Similarly, the mean largest estimated FSO diameter and its associated standard deviation will be presented for each time point by side and mean difference between sides.

In addition, a composite analysis of the counts and percentages of patients with *unfavorable clinical outcome in the FSO* will be presented by side and by time point.

An *unfavorable clinical outcome* has occurred if any of the following are true for a given sinus:

- Polypoid edema is grade 2 (expanded amount)
- Adhesion/Scarring is grade 2 (moderate amount warranting intervention) or 3 (significant amount requiring intervention)
- Patency of the FSO is grade 2 (occluded)

7.4.3 Implant Delivery Success Assessed by Investigators

Implant delivery success is defined as successful deployment of the Propel Mini or

Propel Nova Sinus Implant to the intended side. The proportion of successful deployments will be defined as a ratio where the numerator is the number of successful deployments and the denominator is the number of sinuses in which a deployment was attempted. Deployment will be considered successful if the implant procedure concludes with a successful implant placement on the intended side, even if a second attempt is required in the procedure. An attempted deployment occurs when the surgeon introduces the delivery system into the patient's nostril with the intent of placing an implant.

7.4.4 CT Outcomes Assessed by Independent Reviewer

The severity and frequency of frontal sinus disease at Day 90 as determined based on CT scan review by an independent blinded sinus surgeon will be presented as counts and percentages by radiologic grade and side (treatment vs. control). The mean Lund-Mackay total scores, Lund-Mackay score in the frontal sinus and the estimated maximum diameter of the FSO and their associated standard deviation will be presented by side and as mean difference between sides (difference is calculated by subtracting the control score from the treatment score).

7.4.5 CT Outcomes Assessed by Investigators

The severity and frequency of frontal sinus disease at Day 90 as determined based on CT scan review by on-site clinical investigators will be presented as counts and percentages by radiologic grade and side (treatment vs. control). The mean Lund-Mackay total scores, Lund-Mackay score in the frontal sinus and the estimated maximum diameter of the FSO and their associated standard deviation will be presented by side and as mean difference between sides (difference is calculated by subtracting the control value from the treatment value). The change in the mean total and frontal sinus Lund-Mackay scores between Day 90 and baseline will be also presented.

7.5 Sensitivity Analyses for Missing Data

Post-operative intervention for one sinus side consists of two possible interventions (intervention to separate an adhesion, or the need for oral steroids) that can be answered

Yes, No or *Unable to Grade*. In addition to the imputations listed in Section 7.3, the following imputations will be used to assess the sensitivity of conclusions to missing data from the independent reviewer if more than 5% of the primary efficacy data are missing:

- Impute *No, intervention* for all missing values in both components of the composite endpoint (e.g. impute adhesion grade as a 0, and "No" for the need for oral steroids)
- Impute *Yes, intervention* for all missing values in both components of the composite endpoint (e.g. impute adhesion grade as a 2, and "Yes" for the need for oral steroids)
- Impute *Yes, intervention* for missing values in either component of the composite endpoint *only on the control side* and impute *No intervention on the treatment side*
- Impute *Yes, intervention* for missing values in either component of the composite endpoint *only on the treatment side* and impute *No intervention on the control side*

Patients collectively determined to be *unable to grade* or indeterminate due to reasons such as patient missed visit, lost to follow-up or video was lost will be considered as missing data.

7.6 Consistency Across Study Centers

The consistency of implant performance across study centers will be investigated. Statistical tests will be conducted to identify if there are outlier study centers that could affect the primary efficacy endpoint and clinical conclusions. The proportion of patients who warrant post-operative interventions (as determined by an independent, blinded sinus surgeon) on the treatment side across study centers will be tested by Chi-square test at an alpha level of 0.05. Similarly the proportion of patients who warrant post-operative interventions on the control side across study centers will be tested by Chi-square test at an alpha level of 0.05. In the event that p-value is less than or equal to 0.05, the sensitivity analysis that excludes study centers with outlier efficacy results will be performed to determine the robustness of the primary efficacy analysis.

7.7 Subgroup Analyses and Analyses of Special Interest

The following sub-groups are of interest in assessing the primary efficacy endpoint, sensitivity analysis of the primary efficacy endpoint, post-operative interventions by treatment group by investigators and endoscopic outcomes assessed by investigators by time point. The primary efficacy endpoint analysis and the count and percentage of

patients with adhesion grade 1 or higher and grade 2 or higher analyses may be performed for the following sub-groups if they consist of more than 10% of the ITT population:

A. Patients who did not receive high dose steroids (ie, exclude those patients who received high-dose steroids).

B. Patients who did not receive surgical interventions (i.e., exclude those patients who had in-office debridement of FSO at day 21 or later, or repeat ESS of FSO at any time).

C. Patients who did not commence topical intranasal steroid sprays prior to Day 30.

D. Patients who commenced topical intranasal steroids sprays prior to Day 30.

E. Patients who did not receive high dose steroids and did not receive surgical interventions (patients in Subgroups **A+B**)

F. Patients who did not receive high dose steroids, did not receive surgical interventions and did not commence topical intranasal steroid sprays prior to Day 30 (patients in Subgroups **A**+**B**+**C**)

G. Patients who did not receive Propel or Propel Mini Sinus Implants in the ethmoid sinuses.

H. Patients who received Propel or Propel Mini Sinus Implants in the ethmoid sinuses

I. Patients who did not receive Propel or Propel Mini Sinus Implants in the ethmoid sinuses and did not commence topical intranasal sprays prior to Day 30.

J. Patients received Propel or Propel Mini Sinus Implants and/or commenced topical intranasal sprays prior to Day 30.

The effect of the following characteristics on the primary outcome will also be investigated via logistic regression, first on the probability of producing a discordant pair for the primary endpoint, and then among discordant pairs, on the probability of requiring intervention (as defined in the primary endpoint) on the control side but not the treatment side. Characteristics of special interest are:

- Usage of intranasal steroid sprays prior to 30 days
- Presence of Propel or Propel Mini Sinus Implants in the ethmoid sinuses
- Usage of intranasal steroid sprays prior to 30 days AND Presence of Propel or Propel Mini Sinus Implants in the ethmoid sinuses

7.8 Safety Evaluation

Adverse Events

All adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs and Serious Adverse Events (SAEs) through 30 and 90 days will be reported. Those events that can be localized to a side will be presented separately according to the affected side (treatment, control). In addition, a pooled analysis will be presented, where AEs and SAEs will be included without regard for whether the event can be localized to a treatment group.

Concomitant Medications

Prior and concomitant medications will be coded to therapeutic class and preferred term using the World Health Organization (WHO) Drug Dictionary. All concomitant medications will be listed and summarized in a table.

8.0 APPENDICES

APPENDIX 1: SCHEDULE OF ASSESSMENTS

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 to surgery is permitted to confirm chronic sinusitis diagnosis.
[2] Pregnancy test is required for females of child-bearing potential on the surgery day before implant placement.

APPENDIX 2: TABLES

The following tables will be presented for each study cohort separately:
Note: The same set of tables will be repeated for Nova Cohort

Table Number	Table Title
Table 1	Patient Disposition Mini Cohort: All Randomized Patients
Table 2	Demographic and Baseline Characteristics Mini Cohort: Intent-to-Treat Population
Table 3	Procedural Information Mini Cohort: Intent-to-Treat Population
Table 4	Implant Performance Mini Cohort: Intent-to-Treat Population
Table 5	Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer and by Investigators Mini Cohort: Intent-to-Treat Population
Table 5.1	Frequency Table of Post-Operative Intervention at Day 30 by Independent Reviewer and Investigators Mini Cohort: Intent-to-Treat Population
Table 5.2	Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer Mini Cohort: Per-Treatment Evaluable Population
Table 5.3	Frequency Table of Post-Operative Intervention at Day 30 by Independent Reviewer Mini Cohort: Per-Treatment Evaluable Population
Table 5.4	Sensitivity Analysis for Primary Efficacy Endpoint: Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Sinus Surgeon Mini Cohort: Intent-to-Treat Population
Table 5.5	Sensitivity Analysis for Missing Data with Imputation Method #1: Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer Mini Cohort: Intent-to-Treat Population
Table 5.6	Sensitivity Analysis for Missing Data with Imputation Method #2: Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer Mini Cohort: Intent-to-Treat Population
Table 5.7	Sensitivity Analysis for Missing Data with Imputation Method #3: Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer Mini Cohort: Intent-to-Treat Population
Table 5.8	Sensitivity Analysis for Missing Data with Imputation Method #4: Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer Mini Cohort: Intent-to-Treat Population
Table 6	Frequency of Post-Operative Interventions by Treatment Group by Investigators Mini Cohort: Intent-to-Treat Population
Table 7	Endoscopic Outcomes at Day 30 by Independent Reviewer Mini Cohort: Intent-to-Treat Population
Table 8	Endoscopic Outcomes by Time Point by Investigators Mini Cohort: Intent-to-Treat Population
Table 9	Endoscopic Outcomes at Day 30 by Independent Reviewer – Inflammation Mini Cohort: Intent-to-Treat Population
Table 10	Endoscopic Outcomes by Time Point by Investigators – Inflammation, FSO Diameter Mini Cohort: Intent-to-Treat Population
Table 11	CT Outcomes at Day 90 by Independent Reviewer and Investigators – Lund-Mackay Scores Mini Cohort: Intent-to-Treat Population
Table 12	CT Outcomes at Day 90 by Independent Reviewer and Investigators - Radiological Grades Mini Cohort: Intent-to-Treat Population

Table 13 Summary of Interventions at Follow-up Mini Cohort: Intent-to-Treat Population
Table 14 Overall Summary of Adverse Events Mini Cohort: Intent-to-Treat Population
Table 15 Summary of Adverse Events by System Organ Class Mini Cohort: Intent-to-Treat Population
Table 16 Summary of Concomitant Medication Mini Cohort: Intent-to-Treat Population

Note: Tables 5.5 to 5.8 will not be presented in text table format

APPENDIX 3: LISTINGS

The following listings will be presented for each study cohort separately:

Note: The same set of listings will be repeated for Nova Cohort

Number	Title
Listing 1	Patient Disposition [Mini Cohort]
Listing 2	Analysis Populations [Mini Cohort]
Listing 3	Demographics and Baseline Characteristics[Mini Cohort]
Listing 4	Procedure - Anesthesia and Endoscopic Procedures (Part 1) [Mini Cohort]
Listing 4.1	Procedure - Anesthesia and Surgery (Part 2) [Mini Cohort]
Listing 4.2	Procedure - Implant Placement (Part 3) [Mini Cohort]
Listing 4.3	Procedure – Post-Operative Treatments (Part 4) [Mini Cohort]
Listing 5	Follow-up Assessments [Mini Cohort]
Listing 6	Endoscopic Outcomes by Independent Reviewer – Day 30[Mini Cohort]
Listing 7	Endoscopic Outcomes by Investigators (Part 1) [Mini Cohort]
Listing 7.1	Endoscopic Outcomes by Investigators (Part 2) [Mini Cohort]
Listing 8	CT Outcomes by Independent Reviewer – Day 90 (Part 1) [Mini Cohort]
Listing 8.1	CT Outcomes by Independent Reviewer – Day 90 (Part 2) [Mini Cohort]
Listing 9	CT Outcomes by Investigators – Baseline & Day 90 (Part 1) [Mini Cohort]
Listing 9.1	CT Outcomes by Investigators – Baseline & Day 90 (Part 2) [Mini Cohort]
Listing 10	Adverse Events [Mini Cohort]
Listing 11	Prior and Concomitant Medication [Mini Cohort]
Listing 12	Protocol Deviations [Mini Cohort]
Listing 13	Comments or Narrative [Mini Cohort]

APPENDIX 4: FIGURES

The following figures will be presented for each study cohort separately

Note: The same set of figures will be repeated for Nova Cohort

Figure Number	Figure Title
Figure 1	Scatter Plot of Adhesion/Scarring Grades at Day 30 by Treatment Group *Judged by Independent Reviewer (Mini Cohort: Intent-to-Treat)*
Figure 2	Scatter Plot of Polypoid Edema Grades at Day 30 by Treatment Group *Judged by Independent Reviewer (Mini Cohort: Intent-to-Treat)*
Figure 3	Scatter Plot of Adhesion/Scarring Grades at Day 30 by Treatment Group *Judged by Investigators (Mini Cohort: Intent-to-Treat)*
Figure 4	Scatter Plot of Polypoid Edema Grades at Day 30 by Treatment Group *Judged by Investigators (Mini Cohort: Intent-to-Treat)*
Figure 5	Scatter Plot of Patency of the FSO Grades at Day 30 by Treatment Group *Judged by Investigators (Mini Cohort: Intent-to-Treat)*

Protocol P500-0514 PROGRESS

STATISTICAL ANALYSIS PLAN

Doc. Control #: P 28024

SAP Version #: 5.0

Version Date: November 25, 2015

STATISTICAL ANALYSIS PLAN

Protocol #:	P500-0514
Sponsor:	Intersect ENT 1555 Adams Dr Menlo Park CA 94025
SAP Version #:	5.0
Version Date:	November 25, 2015
Investigational Products:	Propel Mini & Propel Nova Sinus Implants
Intended 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 edema. The implant reduces the need for post-operative intervention such as surgical adhesion lysis and/or use of oral steroids. The Propel Nova Sinus Implant is intended for use in patients ≥ 18 years of age to maintain patency of sinus ostia following sinus surgery. The Propel Nova Sinus Implant separates/dilates mucosal tissues, prevents obstruction by adhesions/scarring, and reduces edema. The implant reduces the need for post-operative intervention such as surgical adhesion lysis and/or use of oral steroids.

The study will be performed in compliance with Good Clinical Practice (GCP), including archival of essential study documents, and 21 CFR Parts 11, 50, 56 and 812.

Statistical Analysis Plan

Sponsor Name:	Intersect ENT
Protocol #:	P500-0514
Protocol Title:	Safety and Efficacy of the Propel Mini and Propel Nova Steroid-Releasing Sinus Implants Following Surgical Opening of the Frontal Sinus for Chronic Sinusitis: A Randomized Blinded Controlled Study
SAP Version #:	5.0
Version Date:	November 25, 2015

Prepared by:

Annie Hung, MA
Sr. Director, Biostatistics
Advance Research Associates (ARA), Inc.

11/25/2015
Date

APPROVAL SIGNATURES

The signatures below indicate approval of the Statistical Analysis Plan for this study.

Andrew Mugglin, PhD
President & Principal Statistical Consultant
Paradigm Biostatistics, LLC

~~11/25/2016~~ 11/25/2015
Date

ASM
12/16/15

James Stambaugh
VP, Clinical Affairs
Intersect ENT

11/30/15
Date

Amy Wolbeck
VP Regulatory Affairs & Quality
Intersect ENT

11/30/15
Date

REVISION HISTORY

Version	Date	Summary of Changes/Comments
1.0	26Mar15	Document created
2.0	28May15	Revisions consistent with Rev 5.0 protocol. Provided details on the changes of data presentation.
3.0	24June15	Revisions in response to the FDA's feedback in Sections 7.2 and 7.7
4.0	-	Administrative version under which Rev 3.0 was released by document control without any additional changes.
5.0	25Nov15	Revisions in response to the FDA's feedback in Section 7.4 and Table 17. Additional minor wording changes to increase clarity and consistency. Updated mockup tables and listings for Nova cohort.

TABLE OF CONTENTS

1.0 INTRODUCTION

This document presents the Statistical Analysis Plan (SAP) for the PROGRESS Study entitled "Safety and Efficacy of the Propel Mini and Propel Nova Steroid-Releasing Sinus Implants Following Surgical Opening of the Frontal Sinus for Chronic Sinusitis: A Randomized Blinded Controlled Study" conducted under the study protocol P500-0514 version 5.0 (dated April 29, 2015). The purpose of this document is to provide further details regarding the analysis plans.

2.0 STUDY DESIGN

This is a prospective, randomized, blinded, controlled, multicenter study that will enroll two consecutive patient cohorts: the Propel Mini Cohort and the Propel Nova Cohort. Each cohort will enroll 50 to 80 patients who satisfy entry criteria. The study patients will undergo implant placement on one side following ESS that includes bilateral frontal sinus surgery by traditional surgical technique or balloon dilation.

For each cohort, the study utilizes an intra-patient control design to assess the safety and efficacy of the implant compared to surgery alone without implant on the contralateral side. The study is blinded, meaning that patients will be blinded throughout the study duration to which side received the implant. The independent sinus surgeon performing review of the video-endoscopies will also be blinded to which side received the implant.

Patients will return for four follow-up visits at Days 7, 21, 30 and 90 (see Appendix 1 for Schedule of Assessments). The follow-up assessment will include endoscopic examinations that will be recorded. At Day 21 the implant or its remnants will be removed to allow blinded review of video-endoscopies at Day 30.

3.0 STUDY OBJECTIVE

The objective of the PROGRESS Study is to assess the safety and efficacy of the Propel Mini and Propel Nova Sinus Implants when placed in the frontal sinus opening following frontal sinus surgery in patients with chronic sinusitis.

4.0 DATA MANAGEMENT

Data management will be performed by Intersect ENT according to the Data Management Plan. Data analyses will be performed by independent biostatisticians according to Advance Research Associates' standard operating procedures.

4.1 Clinical Database

An Electronic Data Capture (EDC) System will be utilized to collect study data using electronic case report forms (eCRFs). Data entry will be performed by qualified site personnel after completing appropriate training. Modifications to the EDC will be made if deemed necessary by the study sponsor.

4.2 Data Cleaning

The database will be verified periodically for data omissions, inconsistencies and discrepancies. Any deficiencies or deviations will be reviewed and any necessary actions determined (e.g., data query, communication with the study center). Intermittent data review will be performed and any discovered errors will be reported to the study sites using the electronic query process (as necessary). The study sites will be expected to review and complete the queries. The data cleaning cycle will be repeated until all data are considered clean.

4.3 Data Back-up

Incremental computer data back-up will be performed on a regular basis. All media will be stored in a secure location.

4.4 Confidentiality and Security

Passwords will be issued by the EDC System vendor to appropriate personnel.

5.0 DEFINITION OF ENDPOINTS

5.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be evaluated for each study cohort separately. The primary efficacy endpoint is the reduction in need for post-operative interventions at Day 30, as determined by an independent, blinded sinus surgeon based on video-endoscopy reviews.

Post-operative intervention is a composite endpoint that includes:

- Surgical intervention required to debride obstructive adhesions or scar tissue formation* in the frontal sinus opening (FSO), and/or
- Oral steroid intervention warranted to resolve recurrent inflammation or polypoid edema in the frontal recess/FSO.

* Defined as grades 2 or 3 on the Adhesion/Scarring Scale

5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will be evaluated for each study cohort separately.

Secondary endpoints include:
Endoscopic outcomes assessed by an independent blinded sinus surgeon based on video-endoscopy review:

- Frequency and severity of adhesion/scarring formation in the FSO at Day 30
- Degree of inflammation in the frontal recess/FSO at Day 30 using a 100-mm Visual Analog Scale (VAS)
- Frequency and grade of polypoid edema in the frontal recess/FSO at Day 30
- A sensitivity analysis will be performed to assess the impact of actual interventions that occur prior to Day 30, upon the assessments made by the independent reviewer at Day 30.

Endoscopic outcomes assessed by on-site investigators:

- Need for post-operative intervention at all time-points through Day 90
- Degree of inflammation in the frontal recess/FSO at all time points through Day 90 using the 100-mm VAS
- Frequency and severity of adhesion/scar formation in the FSO at all time points through Day 90
- Frequency and grade of polypoid edema in the frontal recess/FSO at all time points through Day 90
- Rate of frontal sinus restenosis/occlusion (inverse of patency) at Day 90 determined endoscopically
- Implant delivery success rate

CT outcomes assessed by an independent blinded sinus surgeon based on Day 90 CT scan review:

- FSO patency assessed by measuring the maximum diameter of the FSO in mm
- Lund-Mackay score
- Extent of the disease in the frontal sinuses using Radiological Grading Scale

CT outcomes assessed by on-site investigators based on Day 90 CT scan review:

- FSO patency assessed by measuring the maximum diameter of the FSO in mm
- Lund-Mackay score
- Extent of the disease in the frontal sinuses using Radiological Grading Scale

5.3 Safety Measures

The safety measures will be evaluated for each study cohort separately. The safety measures include:

- Implant safety will be determined by assessment of adverse events.
- Adverse Events (AE) and Serious Adverse Events (SAEs) will be recorded and tabulated through Day 30 and Day 90. Where possible and if applicable, adverse events will be localized to a sinus location.

6.0 STATISTICAL METHODS

6.1 Randomization

The ratio of left to right sinus assignments will be 1:1. Randomization will be stratified by site, will follow a blocked scheme with blocks of varying sizes, and will be performed using the envelope method.

6.2 Analysis Populations

Intent-to-Treat Population

The ITT population will consist of all randomized patients who undergo implant placement (i.e., delivery system inserted into the FSO with intent to place the implant). Patients' sinuses will be analyzed in the treatment group to which they were actually randomized.

Per-Treatment-Evaluable Population

The PTE population will consist of all randomized patients who have received the study implant in the target sinus, who have no major procedural protocol deviations and for whom follow-up data are available.

6.3 General Considerations for Statistical Analyses

All analyses described in this plan are considered a priori analyses in that they have been defined prior to locking the database and reviewing unblinded results. All other analyses, if any, designed subsequent to locking the database will be considered post hoc analyses and will be applied as exploratory methodology. Any post hoc analyses will be clearly identified in the clinical study report.

The analysis of each cohort stands on its own; achieving the primary objective in one cohort is considered sufficient for demonstrating efficacy in that cohort, regardless of the results of the corresponding analysis in the other cohort.

The primary efficacy endpoint, all secondary efficacy endpoints and safety evaluations will be analyzed separately for each of the two study cohorts.

All data relating to the study will be summarized using descriptive statistics. Summary statistics will consist of counts and percentages of patients for nominal and ordinal measures, and means, standard deviations, median and ranges for continuous measures. Where meaningful, the results will be presented graphically.

Available data at each time point will be presented. No substitutions for missing data will be made, with the exception of the primary efficacy endpoint sensitivity analyses and missing data sensitivity analysis (Sections 7.3 and 7.5).

Categorical data that can be localized to a treatment or control side will be analyzed using McNemar's test for correlated proportions. In this intra-patient control study design, only discordant pairs of observations contribute to evidence of a treatment effect. If the number of discordant pairs is less than 20, an exact version of McNemar's test will be used, wherein the proportion of discordant pairs favoring the treatment side (out of all discordant pairs) will be compared against a null value of 0.50. The appropriate test is an exact binomial calculation, using a 2-sided alpha of 0.05 or a 1-sided alpha of 0.025. In addition, frequency distributions showing findings by treatment side over time and descriptive statistics (counts, percentages and, where appropriate, exact 95% confidence intervals using the method of Clopper and Pearson) will be used.

Listings of patient data will be provided to facilitate investigation of tabulated values and to allow for clinical review of all primary and secondary endpoints. Patient listings will be sorted by Site Number and Patient ID Number.

Version 9.2 (or higher) of SAS statistical software package will be used to provide all summaries, listings, graphs, and statistical analyses.

Except where explicitly indicated, data will be pooled across study sites within each study cohort for all statistical analyses.

7.0 STATISTICAL ANALYSES

7.1 Demographics and Baseline Characteristics

Demographic data (e.g., gender and age) and clinical information (e.g., number of prior sinus procedures, history of asthma diagnosed by physician, history of aspirin intolerance or aspirin allergy, history of allergies, history of smoking, presence of grade 2 polypoid edema, total Lund-Mackay scores by sinus) will be presented for all patients. Lund-Mackay scores will also be presented by side (treatment vs. control).

A summary table for procedural information will present the count and percentage of patients that underwent each surgery type and frequency of use of other device or types of drug in the ethmoid sinuses during surgery.

7.2 Primary Efficacy Endpoint Hypothesis and Analysis

The Primary Efficacy Hypothesis is that the steroid-releasing implant will reduce the need for post-operative interventions at Day 30 compared to the control, as determined by an independent blinded sinus surgeon based on video-endoscopy review. The relevant null and alternative hypotheses are:

$$H_0: P_T = P_C$$
$$Ha: P_T \neq P_C$$

where P_T and P_C represent the proportion of patients who warrant post-operative interventions on the treatment and control sides, respectively. Since $P_T = P_{11} + P_{10}$ 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, these hypotheses are equivalent to a test of $H_0: P_{10} = P_{01}$ vs $Ha: P_{10} \neq P_{01}$.

Analysis

The planned analysis is 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. Although the alternative hypothesis is two-sided, evidence of a beneficial effect will only be concluded if statistical significance is achieved and P_T is observed to be less than P_C. An exact version of the test will be used. The exact version defines the proportion of discordant pairs that favor the treatment side as $P^* = P_{01}/(P_{01}+P_{10})$ and tests H_0: $P^* = 0.50$ vs. Ha: $P^* \neq 0.50$ via an exact binomial calculation.

Sample Size

Sample size is calculated based on the following assumptions:

- Expected proportion of discordant pairs at Day 30: $P_{01}+P_{10} = 35\%$
- Expected treatment effect: $P_T–P_C= 21.0\%$
- The two preceding assumptions are equivalent to assuming that $P_{01} = 0.28$, $P_{10} = 0.07$, and thus $P^* = 0.80$. This corresponds to a conditional odds ratio of 4.0 among discordant pairs.
- Target power: ≥ 80%
- Type I error rate: $\alpha = 0.05$, 2-sided

Sample Size: A binomial probability calculation with $P^* = 0.80$ reveals that 20 discordant pairs are required to achieve at least 80% power. To obtain this, patients will be enrolled and treated until it is known that at least 20 patients have discordant pairs of outcomes. A minimum of 50 patients and a maximum of 80 patients will be enrolled and treated.

NOTE: Assumptions for proportion of discordant pairs and treatment effect are based on results from the ADVANCE II Study, where in assessing the need for postoperative intervention at Day 30, 35 of 96 evaluable patients (36.5%) yielded discordant pairs, and among these discordant pairs, 24 of 35 (68.6%) indicated that intervention was warranted on the control side but not the treatment side. The present study evaluates placement of the Propel Mini and Propel Nova in frontal sinus openings. The frontal recess and frontal sinus drainage pathway are known to be more difficult to access surgically, and to maintain in the post-operative timeframe. As a result, frontal sinus patency rates are known to be lower than that of the other sinuses. Therefore, we have assumed that placement of the Propel Mini and

Propel Nova Sinus Implants will yield a higher proportion of discordant pairs favoring the treatment sides than was observed with placement in the ethmoid sinus. The assumed odds ratio is 4:1, meaning that we assume 80% of discordant pairs will favor treatment sides.

Sampling Plan

Since only discordant pairs contribute to the test of a treatment effect, the observed proportion of discordant pairs is an important consideration. In the ADVANCE II study, 35/96 (36.5%) evaluable pairs of observations were discordant. A 95% confidence interval for this percentage ranges from approximately 27% to 47%. Using this as a guide, it is expected that approximately 20/0.25 = 80 patients would be a maximum and 20/0.40 = 50 patients would be a minimum enrollment size in order to achieve 20 discordant pairs.

When 50 patients have reached Day 30, the total number of discordant pairs will be determined (in a manner that reveals only the count of discordant pairs and not any estimates of the treatment effect). If this number is at least 20, enrollment will stop, and the analysis of the primary objective can proceed once all enrolled patients have completed follow-up. Alternatively, if the number of discordant pairs is less than 20, enrollment will continue until 20 patients are known to yield discordant results, up to a maximum of 80 randomized patients. At the time when enrollment ceases, it is possible that some patients will have < 30 days follow-up and thus have undetermined endpoint status. Once their follow-up is complete, these patients can possibly contribute additional discordant pairs to the analysis, for a total exceeding 20.

The primary objective will be evaluated for each cohort separately at the time when all randomized patients from a particular cohort have completed follow-up.

Re-Estimation of Nova Cohort Sample Size

Since the results of the original Mini Cohort were not available at the time of the SAP version 3.0 amendment (wherein the analysis plans for the Nova Cohort were added), the study hypothesis and sample size calculation for the Nova Cohort were identical to the Mini Cohort: 50-80 patients will be enrolled in order to achieve 20 discordant pairs of results. The results from the Mini Cohort are external to the analysis of the Nova Cohort. Once available,

the results from the Mini Cohort were used to re-estimate the sample size of the Nova Cohort. The sample size of the Nova Cohort was not changed.

Analysis Cohort

The primary efficacy analysis will be conducted on the ITT basis, which will consist of all randomized patients who undergo implant placement (i.e., delivery system inserted into the FSO with intent to place the implant). This analysis will be repeated for the PTE population.

7.3 Sensitivity Analysis for Primary Efficacy Endpoint

Since the primary efficacy endpoint is determined by an independent blinded sinus surgeon based on review of video-endoscopies taken at Day 30, interventions performed by clinical investigators prior to Day 30 can potentially confound the primary efficacy outcome. Therefore, a sensitivity analysis will be performed to test the robustness of the primary efficacy conclusion, to actual interventions given. Data imputations will be performed as follows:

- If at Day 7 or Day 21, a clinical investigator indicates on the Endoscopic Scoring Form that either frontal recess/FSO required oral steroids or surgical intervention, and that intervention was actually given, then the grades given by the independent reviewer will be replaced by the grades given by the clinical investigator at the earliest visit (Day 7 or Day 21) at which such intervention was required.
- If oral steroids were actually prescribed for reasons *other than* frontal recess/FSO, then the grades given by the independent reviewer will be replaced by the grades given by the clinical investigator at the visit preceding commencement of oral steroids (Day 7 or Day 21).

7.4 Secondary Efficacy Endpoint Analyses

The company intends to present inferential statistical results to support product labeling claims for 6 secondary endpoints. This section describes the methods that will be used to control the familywise type 1 error rate (FWER) among the tests of these 6 secondary endpoints. All other secondary endpoints will be viewed as exploratory or explanatory in nature; these may be clinically interesting but are not intended to support labeling claims.

If and only if the primary efficacy objective is met, Holm's step-down procedure will be used to control the FWER at a two-sided significance level of 0.05 for the following six secondary endpoints:

- Degree of inflammation in the frontal recess/FSO by endoscopy (100-mm VAS) at Day 30 by clinical investigator judgment
  - Test: H_0: $\mu_T = \mu_C$ *vs* H_A: $\mu_T \neq \mu_C$, by paired t-test
- Rate of frontal sinus restenosis/occlusion (inverse of patency) by endoscopy at Day 30 by clinical investigator judgment.
  - Test: H_0: $P_T = P_C$ *vs* H_A: $P_T \neq P_C$, by McNemar's test (exact version)
- Rate of frontal sinus restenosis/occlusion (inverse of patency) by endoscopy at Day 90 by clinical investigator judgment.
  - Test: H_0: $P_T = P_C$ *vs* H_A: $P_T \neq P_C$, by McNemar's test (exact version)
- Need for Post-Operative Intervention at Day 30 by clinical investigator judgment
  - Test: H_0: $P_T = P_C$ *vs* H_A: $P_T \neq P_C$, by McNemar's test (exact version)
- Need for surgical intervention at Day 30 by clinical investigator judgment
  - Test: H_0: $P_T = P_C$ *vs* H_A: $P_T \neq P_C$, by McNemar's test (exact version)
- Need for oral steroid intervention at Day 30 by clinical investigator judgment
  - Test: H_0: $P_T = P_C$ *vs* H_A: $P_T \neq P_C$, by McNemar's test (exact version)

Let $p_{(1)} \leq p_{(2)} \leq \ldots \leq p_{(m)}$ be the m=6 p-values resulting from the above 6 tests, after being placed in ascending order. Adjusted p-values $\tilde{p}_{(1)}, \ldots, \tilde{p}_{(m)}$ from Holm's step-down procedure will be calculated as follows:

$$\tilde{p}_{(i)} = \begin{cases} m p_{(1)} & \text{for } i = 1 \\ \max\left(\tilde{p}_{(i-1)}, (m-i+1)\, p_{(i)}\right) & \text{for } i = 2, \ldots, m \end{cases}$$

Source: SAS Institute Inc. 2008. *SAS/STAT® 9.22 User's Guide*. Cary, NC: SAS Institute Inc., p 4839.

If any adjusted p-value exceeds 1, it is set to 1. Using this procedure, any adjusted p-value that is < 0.05 is statistically significant and supports a claim for the corresponding endpoint, while any adjusted p-value ≥ 0.05 is not statistically significant. Both adjusted and unadjusted p-values will be reported.

7.4.1 Endoscopic Outcomes Assessed by Independent Reviewer

The counts and percentages of patients with adhesion/scarring at Day 30 by an independent blinded sinus surgeon will be presented by grade and side (treatment vs. control). For analysis purposes, clinically significant adhesion/scarring is prospectively defined as grades 2 or 3. The counts and percentages of patients with polypoid edema will be presented by grade and side. In addition, adhesion/scarring and polypoid edema grades will be presented graphically by side in scatter plots. The mean inflammation scores in the frontal recess/FSO and their associated standard deviation will be presented by side and as mean difference between sides (difference is calculated by subtracting the control score from the treatment score).

7.4.2 Endoscopic Outcomes Assessed by Investigators

Frequency and severity of adhesion/scarring rated by on-site clinical investigators will be presented by grade and side (treatment vs. control) for each time point (Days 7, 21, 30 and 90). Similarly, frequency and severity of polypoid edema and patency of the FSO will be presented by side and time point. In addition, adhesion/scarring, polypoid edema and FSO patency grades at Day 30 will be presented graphically by side in scatter plots.

The mean inflammation in the frontal recess/FSO and its associated standard deviation will be presented for each time point by side and mean difference between sides (difference is calculated by subtracting the control score from the treatment score). Similarly, the mean largest estimated FSO diameter and its associated standard deviation will be presented for each time point by side and mean difference between sides.

In addition, a composite analysis of the counts and percentages of patients with *unfavorable clinical outcome in the FSO* will be presented by side and by time point.

An *unfavorable clinical outcome* has occurred if any of the following are true for a given sinus:

- Polypoid edema is grade 2 (expanded amount)
- Adhesion/Scarring is grade 2 (moderate amount warranting intervention) or 3 (significant amount requiring intervention)
- Patency of the FSO is grade 2 (occluded)

7.4.3 Implant Delivery Success Assessed by Investigators

Implant delivery success is defined as successful deployment of the Propel Mini or Propel Nova Sinus Implant to the intended side. The proportion of successful deployments will be defined as a ratio where the numerator is the number of successful deployments and the denominator is the number of sinuses in which a deployment was attempted. Deployment will be considered successful if the implant procedure concludes with a successful implant placement on the intended side, even if a second attempt is required in the procedure. An attempted deployment occurs when the surgeon introduces the delivery system into the patient's nostril with the intent of placing an implant.

7.4.4 CT Outcomes Assessed by Independent Reviewer

The severity and frequency of frontal sinus disease at Day 90 as determined based on CT scan review by an independent blinded sinus surgeon will be presented as counts and percentages by radiologic grade and side (treatment vs. control). The mean Lund-Mackay total scores, Lund-Mackay score in the frontal sinus and the mean maximum diameter of the FSO and its associated standard deviation, as well as the mean Radiologic Grading score will be presented by side and as mean difference between sides (difference is calculated by subtracting the control score from the treatment score).

7.4.5 CT Outcomes Assessed by Investigators

The severity and frequency of frontal sinus disease at Day 90 as determined based on CT scan review by on-site clinical investigators will be presented as counts and percentages by radiologic grade and side (treatment vs. control). The mean Lund-

Mackay total scores, Lund-Mackay score in the frontal sinus and the mean maximum diameter of the FSO and its associated standard deviation, as well as the mean Radiologic Grading score will be presented by side and as mean difference between sides (difference is calculated by subtracting the control value from the treatment value).

7.5 Sensitivity Analyses for Missing Data

Post-operative intervention for one sinus side consists of two possible interventions (intervention to separate an adhesion, or the need for oral steroids) that can be answered *Yes, No* or *Unable to Grade*. In addition to the imputations listed in Section 7.3, the following imputations will be used to assess the sensitivity of conclusions to missing data from the independent reviewer if more than 5% of the primary efficacy data are missing:

- Impute *No, intervention* for all missing values in <u>both</u> components of the composite endpoint (e.g. impute adhesion grade as a 0, and "No" for the need for oral steroids)
- Impute *Yes, intervention* for all missing values in <u>both</u> components of the composite endpoint (e.g. impute adhesion grade as a 2, and "Yes" for the need for oral steroids)
- Impute *Yes, intervention* for missing values in <u>either</u> component of the composite endpoint *only on the control side* and impute *No intervention on the treatment side*
- Impute *Yes, intervention* for missing values in <u>either</u> component of the composite endpoint *only on the treatment side* and impute *No intervention on the control side*

Patients collectively determined to be *unable to grade* or indeterminate due to reasons such as patient missed visit, lost to follow-up or video was lost will be considered as missing data.

7.6 Consistency Across Study Centers

The consistency of implant performance across study centers will be investigated. Statistical tests will be conducted to identify if there are outlier study centers that could affect the primary efficacy endpoint and clinical conclusions. The proportion of patients who warrant post-operative interventions (as determined by an independent, blinded sinus surgeon) on the treatment side across study centers will be tested by Chi-square test at an alpha level of 0.05. Similarly the proportion of patients who warrant post-operative interventions on the control side across study centers will be tested by Chi-square test at an alpha level of 0.05. In the

event that p-value is less than or equal to 0.05, the sensitivity analysis that excludes study centers with outlier efficacy results will be performed to determine the robustness of the primary efficacy analysis.

7.7 Subgroup Analyses and Analyses of Special Interest

The following sub-groups are of interest in assessing the confounding effect of topical steroids on the primary efficacy endpoint. The count and percentage of patients with adhesion grade 1 or higher and grade 2 or higher analyses may be performed if they consist of more than 10% of the ITT population.

A. Patients who did not receive high dose steroids (ie, exclude those patients who received high-dose steroids).
B. Patients who did not receive surgical interventions (i.e., exclude those patients who had in-office debridement of FSO at day 21 or later, or repeat ESS of FSO at any time).
C. Patients who did not commence topical intranasal steroid sprays prior to Day 30.
D. Patients who commenced topical intranasal steroids sprays prior to Day 30.
E. Patients who did not receive high dose steroids and did not receive surgical interventions (patients in Subgroups **A+B**)
F. Patients who did not receive high dose steroids, did not receive surgical interventions and did not commence topical intranasal steroid sprays prior to Day 30 (patients in Subgroups **A**+**B**+**C**)
G. Patients who did not receive Propel or Propel Mini Sinus Implants in the ethmoid sinuses.
H. Patients who received Propel or Propel Mini Sinus Implants in the ethmoid sinuses
I. Patients who did not receive Propel or Propel Mini Sinus Implants in the ethmoid sinuses and did not commence topical intranasal sprays prior to Day 30.
J. Patients received Propel or Propel Mini Sinus Implants and/or commenced topical intranasal sprays prior to Day 30.

The effect of the following characteristics on the primary outcome may also be investigated via logistic regression, first on the probability of producing a discordant pair for the primary endpoint, and then among discordant pairs, on the probability of requiring intervention (as

defined in the primary endpoint) on the control side but not the treatment side. Characteristics of special interest are:

- Usage of intranasal steroid sprays prior to 30 days
- Presence of Propel or Propel Mini Sinus Implants in the ethmoid sinuses
- Usage of intranasal steroid sprays prior to 30 days AND Presence of Propel or Propel Mini Sinus Implants in the ethmoid sinuses

7.8 Safety Evaluation

Adverse Events

All adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs and Serious Adverse Events (SAEs) through 30 and 90 days will be reported. Those events that can be localized to a side will be presented separately according to the affected side (treatment, control). In addition, a pooled analysis will be presented, where AEs and SAEs will be included without regard for whether the event can be localized to a treatment group.

Concomitant Medications

Prior and concomitant medications will be coded to therapeutic class and preferred term using the World Health Organization (WHO) Drug Dictionary. All concomitant medications will be listed and summarized in a table.

8.0 APPENDICES

APPENDIX 1: SCHEDULE OF ASSESSMENTS

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 to surgery is permitted to confirm chronic sinusitis diagnosis.
[2] Pregnancy test is required for females of child-bearing potential on the surgery day before implant placement.

APPENDIX 2: TABLES

The following tables will be presented for each study cohort separately:
Note: The same set of tables will be repeated for Nova Cohort

Table Number	Table Title
Table 1	Patient Disposition Nova Cohort: All Randomized Patients
Table 2	Demographic and Baseline Characteristics Nova Cohort: Intent-to-Treat Population
Table 3	Procedural Information Nova Cohort: Intent-to-Treat Population
Table 4	Implant Performance Nova Cohort: Intent-to-Treat Population
Table 5	Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer and by Investigators Nova Cohort: Intent-to-Treat Population
Table 5.1	Frequency Table of Post-Operative Intervention at Day 30 by Independent Reviewer and Investigators Nova Cohort: Intent-to-Treat Population
Table 5.2	Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer Nova Cohort: Per-Treatment Evaluable Population
Table 5.3	Frequency Table of Post-Operative Intervention at Day 30 by Independent Reviewer Nova Cohort: Per-Treatment Evaluable Population
Table 5.4	Sensitivity Analysis for Primary Efficacy Endpoint: Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Sinus Surgeon Nova Cohort: Intent-to-Treat Population
Table 5.5	Sensitivity Analysis for Missing Data with Imputation Method #1: Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer Nova Cohort: Intent-to-Treat Population
Table 5.6	Sensitivity Analysis for Missing Data with Imputation Method #2: Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer Nova Cohort: Intent-to-Treat Population
Table 5.7	Sensitivity Analysis for Missing Data with Imputation Method #3: Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer Nova Cohort: Intent-to-Treat Population
Table 5.8	Sensitivity Analysis for Missing Data with Imputation Method #4: Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer Nova Cohort: Intent-to-Treat Population
Table 6	Frequency of Post-Operative Interventions by Treatment Group by Investigators Nova Cohort: Intent-to-Treat Population
Table 7	Endoscopic Outcomes at Day 30 by Independent Reviewer Nova Cohort: Intent-to-Treat Population
Table 8	Endoscopic Outcomes by Time Point by Investigators Nova Cohort: Intent-to-Treat Population
Table 9	Endoscopic Outcomes at Day 30 by Independent Reviewer – Inflammation Nova Cohort: Intent-to-Treat Population
Table 10	Endoscopic Outcomes by Time Point by Investigators – Inflammation, FSO Diameter Nova Cohort: Intent-to-Treat Population
Table 11	CT Outcomes at Day 90 by Independent Reviewer and Investigators – Lund-Mackay Scores Nova Cohort: Intent-to-Treat Population
Table 12	CT Outcomes at Day 90 by Independent Reviewer and Investigators - Radiological Grades Nova Cohort: Intent-to-Treat Population

Note: Tables 5.5 to 5.8 will not be presented in text table format

APPENDIX 3: LISTINGS

The following listings will be presented for each study cohort separately:

Note: The same set of listings will be repeated for Nova Cohort

Number	Title
Listing 1	Patient Disposition [Nova Cohort]
Listing 2	Analysis Populations [Nova Cohort]
Listing 3	Demographics and Baseline Characteristics[Nova Cohort]
Listing 4	Procedure - Anesthesia and Endoscopic Procedures (Part 1) [Nova Cohort]
Listing 4.1	Procedure - Anesthesia and Surgery (Part 2) [Nova Cohort]
Listing 4.2	Procedure - Implant Placement (Part 3) [Nova Cohort]
Listing 4.3	Procedure – Post-Operative Treatments (Part 4) [Nova Cohort]
Listing 5	Follow-up Assessments [Nova Cohort]
Listing 6	Endoscopic Outcomes by Independent Reviewer – Day 30[Nova Cohort]
Listing 7	Endoscopic Outcomes by Investigators (Part 1) [Nova Cohort]
Listing 7.1	Endoscopic Outcomes by Investigators (Part 2) [Nova Cohort]
Listing 8	CT Outcomes by Independent Reviewer – Day 90 (Part 1) [Nova Cohort]
Listing 8.1	CT Outcomes by Independent Reviewer – Day 90 (Part 2) [Nova Cohort]
Listing 9	CT Outcomes by Investigators – Baseline & Day 90 (Part 1) [Nova Cohort]
Listing 9.1	CT Outcomes by Investigators – Baseline & Day 90 (Part 2) [Nova Cohort]
Listing 10	Adverse Events [Nova Cohort]
Listing 11	Prior and Concomitant Medication [Nova Cohort]
Listing 12	Protocol Deviations [Nova Cohort]
Listing 13	Comments or Narrative [Nova Cohort]

APPENDIX 4: FIGURES

The following figures will be presented for each study cohort separately

Note: The same set of figures will be repeated for Nova Cohort

Figure Number	Figure Title
Figure 1	Scatter Plot of Adhesion/Scarring Grades at Day 30 by Treatment Group *Judged by Independent Reviewer (Nova Cohort: Intent-to-Treat)*
Figure 2	Scatter Plot of Polypoid Edema Grades at Day 30 by Treatment Group *Judged by Independent Reviewer (Nova Cohort: Intent-to-Treat)*
Figure 3	Scatter Plot of Adhesion/Scarring Grades at Day 30 by Treatment Group *Judged by Investigators (Nova Cohort: Intent-to-Treat)*
Figure 4	Scatter Plot of Polypoid Edema Grades at Day 30 by Treatment Group *Judged by Investigators (Nova Cohort: Intent-to-Treat)*
Figure 5	Scatter Plot of Patency of the FSO Grades at Day 30 by Treatment Group *Judged by Investigators (Nova Cohort: Intent-to-Treat)*

STATISTICAL ANALYSIS PLAN

Protocol P500-0514 Progress

Doc. Control #: P 28024

Appendix 2 (Total 42 Pages)

Table Mockups - Table of Contents

Table 1
Patient Disposition
NovaCohort: All Randomized Patients

	All Patients
Intent-to-Treat Population [1]	xx
Per-Treatment Evaluable Population [2]	xx
Primary Reason for Termination [3]	
Adverse Event	xx (xx.x%)
Investigator's order	xx (xx.x%)
Lost to follow-up	xx (xx.x%)
Death	xx (xx.x%)
Patient withdrew from study	xx (xx.x%)
Primary Reason for Early Termination [4]	
Unable to gain access	xx (xx.x%)
Other	xx (xx.x%)

[1] Intent-to-Treat Population consists of all patients who undergo implant placement (i.e., delivery system inserted into the FSO with intent to place the implant).
[2] Per-Treatment Evaluable Population is defined as all randomized patients who have received the study implant in the target sinus, who have no major procedural protocol deviations and for whom follow-up data are available. [3] Percentage is calculated based on Intent-to-Treat Population.
[4] Percentage is calculated based on all randomized patients.
Reference: Listing x.x.x

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 2
Demographic and Baseline Characteristics
Nova Cohort: Intent-to-Treat Population

	All Patients (N=xx)
Age	
N	xx
Mean (SD)	xx.x (xx.xx)
Median	xx.xx
Min-Max	xx.x – xx.x
Gender [1]	
Male	xx (xx.x%)
Female	xx (xx.x%)
Ethnicity	
Hispanic or Latino	xx (xx.x%)
Not Hispanic or Latino	xx (xx.x%)
Race	
Black or African American	xx (xx.x%)
American Indian or Alaska Native	xx (xx.x%)
Asian	xx (xx.x%)
White	xx (xx.x%)
Native Hawaiian or other Pacific Islander	xx (xx.x%)
Other	
Number of Prior ESS	
N	xx
0	xx (xx.x%)
1	xx (xx.x%)
2	xx (xx.x%)
3	xx (xx.x%)
>= 4	xx (xx.x%)
History of Aspirin Intolerance or Allergy	
Yes	xx (xx.x%)
History of Asthma Diagnosed by Physician	
Yes	xx (xx.x%)
History of Samter’s Triad	
Yes	xx (xx.x%)
History of Smoking	
Yes	
Current	xx (xx.x%)
Former	xx (xx.x%)
Polypoid Edema Grade 2 [2]	

Yes	xx (xx.x%)
Lund Mackay Score	
Overall Total (left+right)	
N	xx
Mean (SD)	xxx.x (xxx.xx)
Median	xxx.xx
Min-Max	xxx.x – xxx.x

[1] Percentage is calculated based on Intent-to-Treat Population.
[2] Patients with Grade 2 polypoid edema on either right sinus or left sinus sides
Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 2
Demographic and Baseline Characteristics (Part 2)
NovaCohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)
Lund Mackay Score		
Total (all sinuses on each side)		
N	xx	xx
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median	xxx.xx	xxx.xx
Min-Max	xxx.x – xxx.x	xxx.x – xxx.x
Frontal Sinus		
N	xx	xx
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median	xxx.xx	xxx.xx
Min-Max	xxx.x – xxx.x	xxx.x – xxx.x
Maxillary		
N	xx	xx
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median	xxx.xx	xxx.xx
Min-Max	xxx.x – xxx.x	xxx.x – xxx.x
Anterior Ethmoid		
N	xx	xx
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median	xxx.xx	xxx.xx
Min-Max	xxx.x – xxx.x	xxx.x – xxx.x
Posterior Ethmoid		
N	xx	xx
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median	xxx.xx	xxx.xx
Min-Max	xxx.x – xxx.x	xxx.x – xxx.x

[1] Percentage is calculated based on Intent-to-Treat Population.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 2
Demographic and Baseline Characteristics (Part 2)
Nova Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)
Sphenoid		
N	xx	xx
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median	xxx.xx	xxx.xx
Min-Max	xxx.x – xxx.x	xxx.x – xxx.x
Osteometal Complex		
N	xx	xx
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median	xxx.xx	xxx.xx
Min-Max	xxx.x – xxx.x	xxx.x – xxx.x
Polypoid Edema Grade 2		
Yes	xx (xx.x%)	xx (xx.x%)

[1] Percentage is calculated based on Intent-to-Treat Population.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 3
Procedural Information
Nova Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)	All Patients (N=xx)
Implant Placement Duration (min)			
N			xx
Mean (SD)			xxx.x (xxx.xx)
Median			xxx.xx
Min-Max			xxx.x – xxx.x
Endoscopic Procedures Performed:			
Anterior Ethmoidectomy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Posterior Ethmoidectomy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Frontal Sinusotomy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Frontal balloon dilation			
Maxillary antrostomy			
Maxillary balloon dilation			
Sphenoidotomy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Inferior Turbinate Reduction	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Middle Turbinate Reduction	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Polypectomy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Septoplasty			xx (xx.x%)
Instrumentation Used			
Rigid Surgical Instrument	xx (xx.x%)	xx (xx.x%)	
Balloon Dilation	xx (xx.x%)	xx (xx.x%)	
Both	xx (xx.x%)	xx (xx.x%)	
Content of Dissection			
Draf I	xx (xx.x%)	xx (xx.x%)	
Draf IIa	xx (xx.x%)	xx (xx.x%)	
Draf IIb	xx (xx.x%)	xx (xx.x%)	
None	xx (xx.x%)	xx (xx.x%)	
Post-operative Treatments in Ethmoid Sinuses			
Propel	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Propel Nova	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Hemostatic agent, spacer or packing material, with no steroid added	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Hemostatic agent, spacer or packing material, with steroid added	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 4
Implant Performance
Nova Cohort: Intent-to-Treat Population

By Sinus	Treatment Side (N=xx)
Implant Delivery Success [1]	
Number of Attempts, including second attempts	xx (xx.x%)
Implant Delivery Success [2]	xx (xx.x%)
Implant Status (%)	
Day 7	
N [2]	xx (xx.x%)
Absent	xx (xx.x%)
Present	xx (xx.x%)
Completely Open [3]	xx (xx.x%)
Partially Open [3]	xx (xx.x%)
Collapsed [3]	xx (xx.x%)
Mechanical Integrity Remains [3]	xx (xx.x%)
Softening [3]	xx (xx.x%)
Fragmenting [3]	xx (xx.x%)
Completely Removed	xx (xx.x%)
Partially Removed	xx (xx.x%)
Unable to View	xx (xx.x%)
Repeat for Day 21 and 30 for implant status	

[1] Implant procedure concludes with a successful placement even if a second attempt is required. Calculated as ratio of number of successful deployments over number of sinuses attempted.
[2] Based on number of successful deployment
[3] Based on number of status=”Present”

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 5
Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer and by Investigators
Nova Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)
Patients with Both Sinuses Evaluable for Post-Op Intervention [1]	xx	xx
Sinuses Requiring Post-Operative Intervention by Independent Reviewer		
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [3]	0.xxxx	
Percent Relative Difference [4]	xx	
Patients with Both Sinuses Evaluable for Surgical Intervention by Independent Reviewer	xx	xx
Sinuses Requiring Surgical Intervention by Independent Reviewer		
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [3]	0.xxxx	
Percent Relative Difference [4]	xx	
Patients with Both Sinuses Evaluable for Oral Steroid Intervention by Independent Reviewer	xx	xx
Sinuses Warranting Oral Steroid Intervention by Independent Reviewer		
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [3]	0.xxxx	
Percent Relative Difference [4]	xx	

[1] Post-Operative Intervention is a composite endpoint that includes: surgical intervention required to debride obstructive adhesions or scar tissue formation in the FSO (defined as grade 2 or 3 on the adhesion/scarring scale), and/or oral steroid intervention warranted to resolve recurrent inflammation and polypoid edema in the frontal recess/FSO.
[2] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[3] McNemar's test was performed to obtain the 2-sided p-value.
[4] Percent relative difference = $\left[\frac{\text{proportion of patients requiring intervention (treatment } - \text{control)}}{\text{proportion of patients requiring intervention (control)}}\right] \times 100$; patients with both, right and left sinuses evaluable were used for this calculation

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 5
Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer and by Investigators (Part 2)
Nova Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)
Sinuses Requiring Post-Operative Intervention by Investigators		
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [3]	0.xxxx	
Percent Relative Difference [4]	xx	
Patients with Both Sinuses Evaluable for Surgical Intervention by Investigators	xx	xx
Sinuses Requiring Surgical Intervention by Investigators		
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [3]	0.xxxx	
Percent Relative Difference [4]	xx	
Patients with Both Sinuses Evaluable for Oral Steroid Intervention by Investigators	xx	xx
Sinuses Warranting Oral Steroid Intervention by Investigators		
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [3]	0.xxxx	
Percent Relative Difference [4]	xx	

[1] Post-Operative Intervention is a composite endpoint that includes: surgical intervention required to debride obstructive adhesions or scar tissue formation in the FSO (defined as grade 2 or 3 on the adhesion/scarring scale), and/or oral steroid intervention warranted to resolve recurrent inflammation and polypoid edema in the frontal recess/FSO.
[2] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[3] McNemar's test was performed to obtain the 2-sided p-value.
[4] Percent relative difference = $\left[\frac{\text{proportion of patients requiring intervention (treatment } - \text{control)}}{\text{proportion of patients requiring intervention (control)}}\right] \times 100$; patients with both, right and left sinuses evaluable were used for this calculation

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 5.1
Frequency Table of Post-Operative Intervention at Day 30 by Independent Reviewer and Investigators
Nova Cohort: Intent-to-Treat Population

	Post-Operative Interventions (N=xx)	Surgical Intervention (N=xx)	Oral Steroid Intervention (N=xx)
Number of Patients in ITT Population			
Patients Requiring Intervention by Indpependent Reviewer	xx	xx	
Yes on T but No on C	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No on T but Yes on C	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Yes on T and Yes on C	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No on T and No on C	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Patients Requiring Intervention by Investigators	xx	xx	
Yes on T but No on C	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No on T but Yes on C	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Yes on T and Yes on C	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No on T and No on C	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Post-Operative Intervention is a composite endpoint that includes: surgical intervention required to debride obstructive adhesions or scar tissue formation in the FSO (defined as grade 2 or 3 on the adhesion/scarring scale), and/or oral steroid intervention warranted to resolve recurrent inflammation and polypoid edema in the frontal recess/FSO.

T – Treatment side; C – Control Side

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 5.2
Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer
Nova Cohort: Per-Treatment Evaluable Population

Repeat Tables 5.0 for Per-Treatment Evaluable Population

Table 5.3
Frequency Table of Post-Operative Intervention at Day 30 by Independent Reviewer
Nova Cohort: Per-Treatment Evaluable Population

Repeat Tables 5.1 for Per-Treatment Evaluable Population

Table 5.4
Sensitivity Analysis for Primary Efficacy Endpoint:
Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Sinus Surgeon
Nova Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population		
Patients with Both Sinuses Evaluable for Post-Op Intervention [1]	xx	xx
Sinuses Requiring Post-Operative Intervention		
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [3]	0.xxxx	
Percent Relative Difference [4]	xx	
Patients with Both Sinuses Evaluable for Surgical Intervention	xx	xx
Sinuses Requiring Surgical Intervention		
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [3]	0.xxxx	
Percent Relative Difference [4]	xx	
Patients with Both Sinuses Evaluable for Oral Steroid Intervention	xx	xx
Sinuses Requiring Oral Steroid Intervention		
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [3]	0.xxxx	
Percent Relative Difference [4]	xx	

[1] Data imputations: If at Day 7 or 21, a clinical investigator indicates that either frontal recess/FSO required oral steroids or surgical intervention, and that intervention was actually given, then the grades given by the independent reviewer will be replaced by the grades given by the clinical investigator at the earliest visit (Day 7 or 21) at which such intervention was required; If oral steroids were actually prescribed for reasons other than either frontal recess/FSO, then the grades given by the independent reviewer will be replaced by the grades given by the clinical investigator at the visit preceding commencement of oral steroids (Day 7 or 21).
[2] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.[3] McNemar's test was performed to obtain the 2-sided p-value.
[4] Percent relative difference = $\left[\frac{\text{proportion of patients requiring intervention (treatment } - \text{control)}}{\text{proportion of patients requiring intervention (control)}}\right] \times 100$; patients with right

and left sinuses evaluable were used for this calculation

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 5.5
Sensitivity Analysis for Missing Data with Imputation Method #1:
Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer
Nova Cohort: Intent-to-Treat Population

		Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population			
Patients with Both Sinuses Evaluable for Post-Op Intervention [1]		xx	xx
Sinuses Requiring Post-Operative Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Surgical Intervention		xx	xx
Sinuses Requiring Surgical Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Oral Steroid Intervention		xx	xx
Sinuses Requiring Oral Steroid Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	

[1] Missing data will be imputed as:impute No, intervention for all missing values in both components of the composite endpoint (e.g. impute adhesion grade as a 0, and “No” for the need for oral steroids)
[2] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[3] McNemar's test was performed to obtain the 2-sided p-value.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 5.6
Sensitivity Analysis for Missing Data with Imputation Method #2:
Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer
Nova Cohort: Intent-to-Treat Population

		Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population			
Patients with Both Sinuses Evaluable for Post-Op Intervention [1]		xx	xx
Sinuses Requiring Post-Operative Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Surgical Intervention		xx	xx
Sinuses Requiring Surgical Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Oral Steroid Intervention		xx	xx
Sinuses Requiring Oral Steroid Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	

[1] Missing data will be imputed as: •impute Yes, intervention for all missing values in both components of the composite endpoint (e.g. impute adhesion grade as a 2, and “Yes” for the need for oral steroids)
[2] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[3] McNemar's test was performed to obtain the 2-sided p-value.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 5.7
Sensitivity Analysis for Missing Data with Imputation Method #3:
Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer
Nova Cohort: Intent-to-Treat Population

		Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population			
Patients with Both Sinuses Evaluable for Post-Op Intervention [1]		xx	xx
Sinuses Requiring Post-Operative Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Surgical Intervention		xx	xx
Sinuses Requiring Surgical Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Oral Steroid Intervention		xx	xx
Sinuses Requiring Oral Steroid Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	

[1] Missing data will be imputed as: impute Yes, intervention for missing values in either component of the composite endpoint only on the control side and impute No intervention on the treatment side
[2] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[3] McNemar's test was performed to obtain the 2-sided p-value.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 5.8
Sensitivity Analysis for Missing Data with Imputation Method #4:
Frequency of Post-Operative Interventions by Treatment Group at Day 30 by Independent Reviewer
Nova Cohort: Intent-to-Treat Population

		Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population			
Patients with Both Sinuses Evaluable for Post-Op Intervention [1]		xx	xx
Sinuses Requiring Post-Operative Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Surgical Intervention		xx	xx
Sinuses Requiring Surgical Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	
Patients with Both Sinuses Evaluable for Oral Steroid Intervention		xx	xx
Sinuses Requiring Oral Steroid Intervention			
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [3]	0.xxxx	

[1] Missing data will be imputed as: impute Yes, intervention for missing values in either component of the composite endpoint only on the treatment side and impute No intervention on the control side
[2] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[3] McNemar's test was performed to obtain the 2-sided p-value.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 6
Frequency of Post-Operative Interventions by Treatment Group by Investigators
Nova Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population		
Day 7		
Patients with Sinuses Evaluable for Post-Op Intervention [1]	xx	xx
Sinuses Requiring Post-Operative Intervention		
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [3]	0.xxxx	
Percent Relative Difference [4]	xx	
Sinuses Requiring Surgical Intervention		
N (%)	xx (xx.x%)	xx (xx.x%)
Sinuses Requiring Oral Steroid Intervention		
N (%)	xx (xx.x%)	xx (xx.x%)
Day 21		
Patients with Sinuses Evaluable for Post-Op Intervention [1]	xx	xx
Sinuses Requiring Post-Operative Intervention		
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [2]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [3]	0.xxxx	
Percent Relative Difference [4]	xx	
Sinuses Requiring Surgical Intervention		
N (%)	xx (xx.x%)	xx (xx.x%)
Sinuses Requiring Oral Steroid Intervention		
N (%)	xx (xx.x%)	xx (xx.x%)

Note: Repeat the same data presentation for Day 30 and Day 90
[1] Post-Operative Intervention is a composite endpoint that includes: Surgical intervention required to debride obstructive adhesions or scar tissue formation in the FSO, and/or oral steroid intervention warranted to resolve recurrent inflammation, edema and/or polyposis in the frontal recess/FSO
[2] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[3] McNemar's test was performed to obtain the 2-sided p-value.
[4] Percent relative difference = $\left[\frac{\text{proportion of patients requiring intervention (treatment } - \text{control)}}{\text{proportion of patients requiring intervention (control)}}\right] \times 100$; patients with both, right and left sinuses evaluable were used for this calculation

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 7
Endoscopic Outcomes at Day 30 by Independent Reviewer
Nova Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population	xx	xx
Adhesion/Scarring Grade in the FSO		
Any Amount (Grade 1, 2, 3 vs. Minimal Amount 0)		
N	xx	xx
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [2]	0.xxxx	
Percent Relative Difference [3]	xx	
Clinically Significant Amount(Grade 2, 3 vs. 0,1)		
N	xx	xx
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [2]	0.xxxx	
Percent Relative Difference [3]	xx	
Polypoid Edema Grade at the Frontal Recess/FSO		
Any Amount (Grade 1, 2 vs. Minimal Amount 0)		
N	xx	xx
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [2]	0.xxxx	
Percent Relative Difference [3]	xx	
Expanded Amount (Grade 2 vs 0,1)		
N	xx	xx
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [2]	0.xxxx	
Percent Relative Difference [3]	xx	

[1] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[2] McNemar's test was performed to obtain the 2-sided p-value.

[3] Percent relative difference = [Proportion of patients with selected grade or outcome (treatment-control)]/Proportion of patients with selected grade or outcome in control group] X 100; patients with both, right and left sinuses evaluable were used for this calculationReference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 8
Endoscopic Outcomes by Time Point by Investigators
Nova Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population	xx	xx
Baseline / Procedure		
Adhesion/Scarring in the FSO		
Any Amount (Grade 1, 2, 3 vs Minimal Amount 0)		
N	xx	xx
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [2]	0.xxxx	
Percent Relative Difference [3]	xx	
Clinically Significant Amount(Grade 2, 3 vs. 0,1)		
N	xx	xx
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [2]	0.xxxx	
Percent Relative Difference [3]	xx	
Polypoid Edema at the Frontal Recess/FSO		
Any Amount (Grade 1, 2 vs Minimal Amount 0)		
N	xx	xx
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [2]	0.xxxx	
Percent Relative Difference [3]	xx	
Expanded Amount (Grade 2 vs 0,1)		
N	xx	xx
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [2]	0.xxxx	
Percent Relative Difference [3]	xx	

[1] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[2] McNemar's test was performed to obtain the 2-sided p-value.

[3] Percent relative difference = [Proportion of patients with selected grade or outcome (treatment-control)]/Proportion of patients with selected grade or outcome in control group] X 100; patients with both right and left sinuses evaluable were used for this calculation

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 8
Endoscopic Outcomes by Time Point by Investigators
Nova Cohort: Intent-to-Treat Population

		Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population		xx	xx
Patency of the FSO			
Occluded (Grade 2 vs. 0,1)			
	N	xx	xx
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [2]	0.xxxx	
	Percent Relative Difference [3]	xx	
Restenosed/ Occluded (Grade 1, 2 vs. 0)			
	N	xx	xx
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [2]	0.xxxx	
	Percent Relative Difference [3]	xx	
With Unfavorable Clinical Outcome [4]			
	N	xx	xx
	N (%)	xx (xx.x%)	xx (xx.x%)
	95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
	P-value [2]	0.xxxx	
	Percent Relative Difference [3]	xx	
Day 7			
Day 21			
Day 30			
Day 90			

[1] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.

[2] McNemar's test was performed to obtain the 2-sided p-value.

[3] Percent Relative Difference = [Proportion of patients with selected grade or outcome (treatment-control)]/Proportion of patients with selected grade or outcome in control group] X 100 ; patients with both, right and left sinuses evaluable were used for this calculation

[4] An unfavorable clinical outcome has occurred if any of the following are true for a given sinus: polypoid edema is grade 2 (expanded amount), Adhesion/Scarring is grade 2 (moderate amount warranting intervention) or 3 (significant amount requiring intervention)or Patency of the FSO is grade 2 (occluded)

Reference: Listing x.x.x

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 9
Endoscopic Outcomes at Day 30 by Independent Reviewer – Inflammation
Nova Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)	Difference (Tx-C) (N=xx)
Number of Patients in the Intent-to-Treat			
Inflammation in the Front Recess/FSO(mm)			
Day 30			
N [1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median	xxx.xx	xxx.xx	xxx.xx
Min-Max	xxx.x – xxx.x	xxx.x – xxx.x	xxx.x – xxx.x
95% CI [1]			
P-value [2]			0.xxxx
Percent Relative Difference [3]			xx

Note: Inflammation on 100-mm VAS
[1] The 95% CI for mean values was obtained assuming a normal distribution
[2] A paired t-test was used to obtain the p-value for the side to side difference in scores.
[3] Percent relative difference = [Mean (treatment – control)/Mean (control)] X 100, Patients with both, right and left sinuses evaluable were used for this calculation
Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 10
Endoscopic Outcomes by Time Point by Investigators – Inflammation, FSO Diameter
Nova Cohort: Intent-to-Treat Population

Inflammation in the Front Recess/FSO(mm)	Treatment Side (N=xx)	Control Side (N=xx)	Difference (Tx-C) (N=xx)
Baseline Procedure			
Inflammation (mm)			
N [1]	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
95% CI [1]	xx.x –xx.x	xx.x – xx.x	xx.x – xx.x
P-value [2]			0.xxxx
Percent Relative Difference [3]			xx
Estimated FSO Diameter - Largest (mm)			
N [1]			
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
95% CI [1]	xx.x –xx.x	xx.x – xx.x	xx.x – xx.x
P-value [2]			0.xxxx
Percent Relative Difference [3]			xx
Day 7			
Day 21			
Day 30			
Day 90			

Note: Inflammation on 100-mm VAS
[1] The 95% CI for mean values was obtained assuming a normal distribution
[2] A paired t-test was used to obtain the p-value for the side to side difference in scores.
[3] Percent relative difference = Percent relative difference = [Mean (treatment – control)/Mean (control)]
X 100, Patients with both, right and left sinuses evaluable were used for this calculation

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 11
CT Outcomes at Day 90 by Independent Reviewer and Investigators – Lund-Mackay Scores
Nova Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)	Difference (Tx-C) (N=xx)
Lund-Mackay Score in Frontal Sinus by Independent Reviewer			
N	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
95% CI [1]	xx.x –xx.x	xx.x – xx.x	xx.x – xx.x
P-value [2]			0.xxxx
Percent Relative Difference [3]			xx
Lund-Mackay Total Score by Independent Reviewer			
N	xx	xx	xx (xx.x%)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
95% CI [1]	xx.x –xx.x	xx.x – xx.x	xx.x – xx.x
P-value [2]			0.xxxx
Percent Relative Difference [3]			xx
Lund-Mackay Score in Frontal Sinus by Investigators			
N	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
95% CI [1]	xx.x –xx.x	xx.x – xx.x	xx.x – xx.x
P-value [2]			0.xxxx
Percent Relative Difference [3]			xx
Lund-Mackay Total Score by Investigators			
N	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
95% CI [1]	xx.x –xx.x	xx.x – xx.x	xx.x – xx.x
P-value [2]			0.xxxx
Percent Relative Difference [3]			xx

[1] The 95% CI for mean values was obtained assuming a normal distribution
[2] A paired t-test was used to obtain the p-value for the side to side difference in scores.

[3] Percent relative difference = [Mean (treatment – control)/Mean (control)] X 100; Patients with both, right and left sinuses evaluable were used for this calculation

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 11
CT Outcomes at Day 90 by Independent Reviewer and Investigators – Lund-Mackay Scores (Part 2)
Nova Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)	Difference (Tx-C) (N=xx)
Estimated Maximum Size of FSO (mm) by Independent Reviewer			
N	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
95% CI [1]	xx.x –xx.x	xx.x – xx.x	xx.x – xx.x
P-value [2]			0.xxxx
Percent Relative Difference [3]			xx
Estimated Size of FSO (mm)– Maximum by Investigators			
N	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min-Max	xx.x – xx.x	xx.x – xx.x	xx.x – xx.x
95% CI [1]	xx.x –xx.x	xx.x – xx.x	xx.x – xx.x
P-value [2]			0.xxxx
Percent Relative Difference [3]			xx

[1] The 95% CI for mean values was obtained assuming a normal distribution
[2] A paired t-test was used to obtain the p-value for the side to side difference in scores.
[3] Percent relative difference =[Mean (treatment – control)/Mean (control)] X 100; Patients with both, right and left sinuses evaluable were used for this calculation

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 12
CT Outcomes at Day 90 by Independent Reviewer and Investigators - Radiological Grades of Frontal Sinuses
Nova Cohort: Intent-to-Treat Population

	Treatment Side (N=xx)	Control Side (N=xx)
Number of Patients in ITT Population	xx	xx
Radiological Grade of 3 (3 vs 1,2) by Independent Reviewer		
N	xx	xx
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [2]	0.xxxx	
Percent Relative difference [3]	xx	
Radiological Grade of 2 or 3 (2,3 vs.1) by Independent Reviewer		
N	xx	xx
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [2]	0.xxxx	
Percent Relative difference [3]	xx	
Radiological Grade of 3 (3 vs 1,2) by Investigators		
N	xx	xx
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [2]	0.xxxx	
Percent Relative difference [3]	xx	
Radiological Grade of 2 or 3 (2,3 vs.1) by Investigators		
N	xx	xx
N (%)	xx (xx.x%)	xx (xx.x%)
95% CI [1]	0.xxx, 0.xxx	0.xxx, 0.xxx
P-value [2]	0.xxxx	
Percent Relative difference [3]	xx	

[1] The 95% CI for each treatment group was computed via the method of Clopper and Pearson.
[2] McNemar's test was performed to obtain the 2-sided p-value.
Radiological Grading Scale: 1 = Mucosal thickening of less than 5mm; 2 = Partial opacification, air-fluid level, or mucosal thickening of 5mm or higher; 3 = Total opacification

[3] Percent relative difference = [Proportion (treatment – control)/Proportion (control)] X 100;Patients with right and left sinuses evaluable were used for this calculation

Reference: Listing x.x.x

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 13
Summary of Interventions at Follow-up
Nova Cohort: Intent-to-Treat Population

	All Patients (N=xx)
Oral Steroid Prescribed for FSO Sinus Obstruction	
Yes n(%)	
Day 7	xx (xx.x%)
Day 21	xx (xx.x%)
Day 30	xx (xx.x%)
Day 90	xx (xx.x%)
Antibiotics Prescribed for Frontal Sinus	
Yes n(%)	
Day 7	xx (xx.x%)
Day 21	xx (xx.x%)
Day 30	xx (xx.x%)
Day 90	xx (xx.x%)
Received Polypectomy	
Yes n(%)	
If Yes, first noted at	
Day 7	xx (xx.x%)
Day 21	xx (xx.x%)
Day 30	xx (xx.x%)
Day 90	xx (xx.x%)
Received Repeat ESS	
Yes n(%)	
If Yes, occurred at	
Day 7	xx (xx.x%)
Day 21	xx (xx.x%)
Day 30	xx (xx.x%)
Day 90	xx (xx.x%)

[1] Percentage is calculated based on ITT Population.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 14
Overall Summary of Adverse Events
Nova Cohort: Intent-to-Treat Population

	All Patients (N=xx)
Patients with Any Adverse Events	xx (xx.x%)
Relationship of Adverse Events	xx (xx.x%)
No Relationship	xx (xx.x%)
Surgical Procedure Related	xx (xx.x%)
Implant Placement Procedure Related	xx (xx.x%)
Implant Related	xx (xx.x%)
Endoscopy Procedure Related	xx (xx.x%)
Morbid or Comorbid Related	xx (xx.x%)
Anasthesia Related	xx (xx.x%)
Patients with Adverse Events Resulting in Discontinuation	xx (xx.x%)
Patients with Adverse Events by Maximum Severity	
Mild	xx (xx.x%)
Moderate	xx (xx.x%)
Severe	xx (xx.x%)
Patients with Implant Related Adverse Events by Maximum Severity	
Mild	xx (xx.x%)
Moderate	xx (xx.x%)
Severe	xx (xx.x%)
Patients with Implant Placement Procedure Related Adverse Events by Maximum Severity	
Mild	xx (xx.x%)
Moderate	xx (xx.x%)
Severe	xx (xx.x%)
Patients with Serious Adverse Events	xx (xx.x%)
Patients with Implant Related Serious Adverse Events	xx (xx.x%)
Patients with Implant Placement Procedure Related Serious Adverse Events	xx (xx.x%)

Note: Adverse events coded using the MedDRA dictionary Version x.x. Given in the table are patient counts and percentages. At each level of summation, patients are counted only once. Patients experiencing adverse events of more than one severity are summarized according to the maximum severity experienced over all episodes of an adverse event.
Reference: Listing x.x.x

Table 15
Summary of Adverse Events by System Organ Class
Nova Cohort: Intent-to-Treat Population

System Organ Class Preferred Term	All Events (N=xx)	Events Localized to Treatment Side (N=xx)	Events Localized to Control Side (N=xx)
Patients with Any Adverse Event	xx (xx%)		
System Organ Class 1	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 1	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 2	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 3	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 4	xx (xx%)	xx (xx%)	xx (xx%)
.			
.			
System Organ Class 2	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 1	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 2	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 3	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 4	xx (xx%)	xx (xx%)	xx (xx%)
.			
.			
.			
Continue to report all reported events			

Note: Adverse events (AEs) coded using the MedDRA dictionary, Version x.x. Given in the table are patient counts and percentages. At each level of summation, patients are counted only once. Patients experiencing adverse events of more than one severity are summarized according to the maximum severity experienced over all episodes of an adverse event.

Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 16
Summary of Concomitant Medication
Nova Cohort: Intent-to-Treat Population

ATC level Preferred Term	All Patients (N=xx)
Patient Reported Any Concomitant Medication Use	xx (xx.x%)
Drugs for Acid Related Disorders	xx (xx.x%)
Alfacalcidol	xx (xx.x%)
Calcium Acetate	xx (xx.x%)

Note: Concomitant medications are coded using WHO Drug disctionary Version x.x. At each level of summation, patients are counted only once.
Reference: Listing x.x.x
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Table 17
Secondary Endpoints by Clinical Investigator Judgement Adjusted for Multiplicity Using Holm's Step Down Method
Nova Cohort Only: Intent-to-Treat Population

	p-value in ascending order	Adjusted p-value
Degree of inflammation in the frontal recess/FSO by endoscopy (100-mm VAS) at Day 30	x.xxxx	x.xxxx
Rate of frontal sinus restenosis/occlusion (inverse of patency; 1, 2 versus 0) by Endoscopy at Day 30	x.xxxx	x.xxxx
Rate of frontal sinus restenosis/occlusion (inverse of patency; 1, 2 versus 0) by Endoscopy at Day 90	x.xxxx	x.xxxx
Patients with evaluable sinuses requiring Post-Operative Intervention at Day 30	x.xxxx	x.xxxx
Patients with evaluable sinuses requiring surgical intervention at Day 30	x.xxxx	x.xxxx
Patients with evaluable sinuses requiring oral steroid intervention at Day 30	x.xxxx	x.xxxx

Reference: Table 6, Table 8, Table 9
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

STATISTICAL ANALYSIS PLAN

Protocol P500-0514 Progress

Doc. Control #: P 28024

Appendix 3 (Total 21 Pages)

Table of Contents

Listing 1
Patient Disposition
Nova Cohort

Patient ID	Procedure Date(MM-DD-YYYY)	Both FSOs Amenable to Implant?	Patient Met All Eligibility Criteria?	Side	Treatment Group	Implant Deployed	Completed Study? Date Completion/ Discontinuation MM-DD-YYYY	Primary Reason for Early Termination
xx-xxxx				Right Left	Treatment Control		Yes : MM-DD-YYYY No : MM-DD-YYYY	

SOURCE: xxxx SAS 9.2 {program location}{run date/time}

Programming note: This listing will include all patients including screen fails, all other listings should only include patients who enrolled in this study.

Listing 2
Analysis Populations
Mini Cohort

Treatment Side	Patient ID	Population		Reason for Exclusion from PTE
		ITT [1]	PTE [2]	
Right	xx-xxxx	Yes	Yes	
	xx-xxxx	Yes	No	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx Xxxxxxxxx

Reference: eCRF Module
1.Intent-to-Treat (ITT) – All Randomized Patients.
2.Per-Treatment-Evaluable Population (PTE) - All randomized patients who have received the study implant in the target sinus, have no major procedural protocol deviations and follow-up data are available.

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 3
Demographics and Baseline Characteristics
Nova Cohort

Patient ID	Age(yr)	Gender	Ethnicity	Race	Number of Prior ESS	Date of Most Recent ESS (MM-DD-YYYY)	History of Asthma Diagnosed	Hx of Allergic Rhinitis Diagnosed	History of Aspirin Intolerance	History of Samter's Triad	Hx of Allergies	Hx of Smoking
xx-xxxx	xx	Female	Non-Hispanic	White								
	xx	Female	Hispanic or Latino	White								

Note:

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 4
Procedure - Anesthesia and Endoscopic Procedures (Part 1)
Mini Cohort

				Endoscopic Procedure Performed										
Procedure Date	Type of Anesthesia Used	Anesthesia Start Time/Stop Time	Side	Anterior ethmoidectomy	Posterior ethmoidectomy	Frontal sinusotomy	Frontal balloon dilation	Maxillary antrostomy	Maxillary balloon dilation	Sphenoidotomy	Inferior turbinate reduction	Middle turbinate reduction	Polypectomy
	XXXXXXXXX	08:25/ xx:xx											

Note:

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 4.1
Procedure - Anesthesia and Surgery (Part 2)
Nova Cohort

Treated Side	Patient ID	Surgeon Name	Side	Instrumentation Used	Maker/Diameter/Length/Pressure if Balloon Used	Extent of Frontal Sinus Surgical Dissection	Both FSOs Amenable to Implant?
	xx-xxx		R L				
	xx-xxx						

Note:

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 4.2
Procedure - Implant Placement (Part 3)
Mini Cohort

Treated Side	Patient ID	Procedure Start/ End Time	Lot #	Able to Deploy Implant?	Reason if Not	Implant Malfunction?	Additional Implant Used?	Able to Place Additional Implant at Target Location?	Reason if not	Implant Malfunction for the Additional Implant?	% Apposition of Implant to FSO	Degree of Manipulation
	xx-xxxx	08:05am/09:10pm										
	xx-xxxx											

Note:

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 4.3
Procedure – Post-Operative Treatments (Part 4)
Nova Cohort

Treated Side	Patient ID	Side	Ethmoid	If Ethmoid, Specify	Maxillary	If Maxillary, Specify	Sphenoid	If sphenoid, Specify	Any Procedure AE?
	xx-xxxx								
	xx-xxxx								

Note:

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 5
Follow-up Assessments
Mini Cohort

Treated Side	Patient ID	Visit	Visit Date MM-DD-YYYYMM-DD-YYYY(Day)	New or Worsening Sinus Symptoms?	Change in Medication?	Unscheduled Visit?	List Interventions at this Visit or Since Last Scheduled Visit	AE Occurred Since Last Visit?
	xx-xxxx			x	x		xxxxxxxxxxxxxxx	
				x	x		xxxxxxxx	
	xx-xxxx			xx	xx			xxxxxxxxxx
				xx	xx			xxxxxxxxxxxxxxx
	xx-xxxx							

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 6
Endoscopic Outcomes by Independent Reviewer – Day 30
Nova Cohort

Treated Side	Subject ID	Visit Date (Day)	Side	Polypoid Edema	Adhesions/ Scarring	Inflammation VAS (mm)	Oral Steroid Warranted? [1]	Surgical Intervention Required? [2]
Right	xx-xxx	yyyy-mm-dd (xxx)	R					
			L					
Right	xx-xxx		R					
			L					
			R					
			L					
			R					
			L					

Reference: eCRF Module

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}
[1] Oral steroid intervention warranted to resolve recurrent inflammation, edema and/or polyposis in the frontal recess/FSO
[2] Surgical intervention required to debride obstructive adhesions or scar tissue formation in the FSO

Listing 7
Endoscopic Outcomes by Investigators (Part 1)
Mini Cohort

Treated Side	Patient ID	Visit	Visit Date (Day) MM-DD-YYYY	Side	Polypoid Edema	Adhesions/Scarring	Patency of FSO	Estimated Diameter-Largest (mm)	Estimated Diameter-Smallest (mm)	Inflammation VAS (mm)	Comments
Right	xx-xxxx	Procedure	MM-DD-YYYY (xxx)	R							
				L							
		Day 7	MM-DD-YYYY (xxx)	R							
				L							
		Day 21	MM-DD-YYYY (xxx)	R							
				L							
		Day 30	MM-DD-YYYY (xxx)	R							
				L							
		Day 90	MM-DD-YYYY (xxx)	R							
				L							
Right	xx-xxxx			R							
				L							

Reference: eCRF Module

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 7.1
Endoscopic Outcomes by Investigators (Part 2)
Nova Cohort

Treated Side	Patient ID	Visit	Visit Date (Day) MM-DD-YYYY	Implant Current Status	Implant Opening	Implant Integrity	Implant Removed at this Visit?	Oral Steroid Warranted? [1]	Oral Steroids Prescribed?	Surgical Intervention Required? [2]	Surgical Intervention Performed?	Comments
Right	xx-xxxxx	Day 7	MM-DD-YYYY (xxx)									
		Day 21	MM-DD-YYYY (xxx)									
		Day 30	MM-DD-YYYY (xxx)									
		Day 90	MM-DD-YYYY (xxx)									
Right	xx-xxxx											

Reference: eCRF Module
[1] Oral steroid intervention warranted to resolve recurrent inflammation, edema and/or polyposis in the frontal recess/FSO
[2] Surgical intervention required to debride obstructive adhesions or scar tissue formation in the FSO

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 8
CT Outcomes by Independent Reviewer – Day 90 (Part 1)
Nova Cohort

				Lund-Mackay Score						
Treated Side	Patient ID	Assessment Date (Day)	Side	Frontal	Maxillary	Anterior Ethmoid	Posterior Ethmoid	Sphenoid	Osteomeatal Complex	Total
Right	xx-xxxx	MM-DD-YYYY (xxx)	R	xx	xx	xx	xx	xx	xx	xx
			L	xx	xx	xx	xx	xx	xx	xx
			Total	xx	xx	xx	xx	xx	xx	xx
Right	xx-xxxx	MM-DD-YYYY (xxx)	R							
			L							
			Total							

Reference: eCRF Module

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 8.1
CT Outcomes by Independent Reviewer – Day 90 (Part 2)
Mini Cohort

Treated Side	Patient ID	Assessment Date (Day)	Side	Estimated Maximum Size of FSO (mm)	Radiological Grade
Right	xx-xxxx	MM-DD-YYYY (xxx)	R	xx	
			L		
			R		
			L		

Reference: eCRF Module

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 9
CT Outcomes by Investigators – Baseline & Day 90 (Part 1)
Nova Cohort

Treated Side	Patient ID	Assessment Date (Day) MM-DD-YYYY	Visit	Side	Lund-Mackay Score						
					Frontal	Maxillary	Anterior Ethmoid	Posterior Ethmoid	Sphenoid	Osteomeatal Complex	Total
Right	xx-xxxx	MM-DD-YYYY (xxx)	Baseline	R							
			Day 90	L							
				R							
				L							

Reference: eCRF Module

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 9.1
CT Outcomes by Investigators – Baseline & Day 90 (Part 2)
Mini Cohort

Treated Side	Patient ID	Assessment Date (Day) MM-DD-YYYY	Side	Size of FSO (mm)	Radiological Grading
		MM-DD-YYYY	R		
	xx-xxx	(xxx)			
			L		
			R		
			L		

Reference: eCRF Module

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 10
Adverse Events
Nova Cohort

Patient ID	Treated Side	System Organ Class/ Preferred Term/ Adverse Event Term	Location	Start Date MM-DD-YYYY (Day)	Stop Date MM-DD-YYYY (Day)	Intensity	SAE?	Relationship	AE Treatment/Primary AE outcome
xx-xxxx	Right			MM-DD-YYYY					None/
		NTE xxxxxxxxxxxxxx/		(xx)					
				MM-DD-YYYY					Recovered with
		xxxxxxxxxxxxxxxxxx/		(xx)					Sequelae
		xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx							
xx-xxxx		xxxxxxxxxxxx/							
		xxxxxxxxxxxxxxxxxx/							
		xxxxxxxxxxxxxxxxxxxxxxx							
xx-xxx		None							

Note: If a patient has no AEs then "None" will be displayed. Adverse Events are coded in MedDRA Vxx.x.
Reference: eCRF Module AE
SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Programming Note:

1. If Ongoing is checked then list “Continuing” in the place for “Stop Date (Day)”.

Listing 11
Prior and Concomitant Medication
Mini Cohort

Patient ID	ATC level Preferred Term/ Medication	Start Date MM-DD-YYYY	Start Day	Stop Date MM-DD-YYYY	Stop Day	Indication	Med Prescribed for	Dosage (Unit)	Route	Frequency
xx-xxx										
xx-xxx										

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Programming Note:

1. If Ongoing is checked ”Yes” list “Ongoing” under stop date column
2. Concatenate dose and unit for listing, if other unit exists then list it for units
3. Route, if Other Route is not blank, list it under “Route” column
4. Frequency, if Other Frequency is not blank, list it under ‘Frequency” Column

Listing 12
Protocol Deviations
Nova Cohort

Patient ID	Date/Time Point	Deviation Date MM-DD-YYYY	Reason for Deviation	Explanation	Pre-approved by Sponsor	Date Approved	Date Documented
xx-xxxx	MM-DD-YYYY/D7						
xx-xxxx							

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}

Listing 13
Comments or Narrative
Nova Cohort

Patient ID	Form	Time Point	Comments
xx-xxxx	Follow-up	Day 90	xxxxxxxxxxxxxxxxxxxx

Reference: eCRF Module xx

SOURCE: xxxxx SAS 9.2 {program location}{run date/time}