CLINICAL STUDY PROTOCOL

1 TITLE PAGE

Study Title	The ENCORE Study: Safety Evaluation of Repeat Placement of the Corticosteroid-Releasing S8 Sinus Implant in Chronic Sinusitis Patients with Nasal Polyps
Protocol Number	P500-0717
Doc. Control Number	CP-00015
Investigational Product	S8 Sinus Implant (mometasone furoate, 1350 mcg)
Study Design	Prospective, non-randomized, open-label, multicenter clinical trial
Sponsor's Name and Address	Intersect ENT, Inc. 1555 Adams Drive Menlo Park, CA 94025 Tel: +1 650-641-2100 Fax: +1 650-641-2053
IND Number	116042
Phase of Development	Phase IIIB
Principal Investigators	R. Peter Manes, MD Yale School of Medicine New Haven, CT 06519-1369
Data Management and Study Monitoring	Intersect ENT
Biostatistics and Data Analysis	Intersect ENT

This study will be conducted under the guidance of the International Council on Harmonisation (ICH) Good Clinical Practice, Clinical investigation of medical devices for human subjects - Good clinical practice (BS EN ISO14155: 2011) and other applicable local and federal regulations, including the archiving of essential documents.

CONFIDENTIALITY STATEMENT

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2 LIST OF ABBREVIATIONS

Abbreviations	Expansion
AE	adverse event
AS	acute sinusitis
CFR	Code of Federal Regulations
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRA	clinical research associate
CRF	case report form
CS	chronic sinusitis
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
EDC	electronic data capture
e.g.	'exempli gratia' in Latin, meaning 'for example'
ESS	endoscopic sinus surgery
et al	'et alia' in Latin, meaning 'and others'
FDA	Food and Drug Administration
GCP	good clinical practice
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council on Harmonisation
i.e.	'id est' in Latin, meaning 'that is'
INCS	intranasal corticosteroids
IRB	institutional review board
IUD	intrauterine device
MFNS	mometasone furoate nasal spray
MRI	magnetic resonance imaging
RESS	repeat endoscopic sinus surgery
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SNOT-22	sino-nasal outcome test (22 items)
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
UADE	unanticipated adverse device effect

3 DEFINITIONS OF TERMS

Term	Definition
Acute sinusitis (AS)	Per the 2016 "International Consensus Statement on Allergy and Rhinology" definition, patient must have inflammation lasting < 4 weeks associated with the sudden onset of symptoms such as nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior) and facial pain/pressure or reduction/loss of smell.
Adverse event (AE)	Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. [21 CFR 312; BN ES ISO14155]
Adhesion grading scale	Adhesion severity graded on a 5-point scale from 0 to 4 at the screening and baseline visits, as follows: 0: None 1: Small but non-obstructing (no separation required) 2: Obstructing, but easily separated 3: Dense and obstructing, separation difficult 4: Severe: complete adhesion of the middle turbinate to the lateral nasal wall
Bilateral polyp grade	Sum of left and right polyp grades (see - *scale* below), resulting in a bilateral polyp grade of 0 to 8
Case report form (CRF)	Standardized forms designed to capture monitored data as required by the protocol.
Chronic rhinosinusitis with nasal polyps	Per the 2016 "International Consensus Statement on Allergy and Rhinology" definition, patient must have ≥ 12 weeks of: • Two or more of the following symptoms: o Mucopurulent discharge (rhinorrhea or postnasal drip) o Nasal obstruction and congestion o Decreased/absent sense of smell o Facial pressure/pain • And one or more of the following findings: o Evidence of inflammation on paranasal sinus examination or computed tomography o Evidence of purulence coming from paranasal sinuses or ostiomeatal complex • And presence of polyps.
Enrolled	Subjects are considered enrolled upon signing the informed consent form.
High-dose steroids	The following steroids are considered as high-dose in the study: oral, parenteral, injections, budesonide or other sinus steroid irrigations, rinses or drops, nebulized steroids administered nasally.
Implant delivery success	Successful deployment of the S8 Sinus Implant to the target site. Deployment is considered successful if the procedure concludes with a successful placement in the target sinus, even if a second attempt is required. Implant delivery success rate is calculated as proportion of successful deployments of the S8 Sinus Implant to the target site per total number of sinuses attempted including the baseline and repeat placement procedures.

Term	Definition
Malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instruction for use or clinical investigation plan. [BS EN ISO14155] Failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed. [21CFR 803]
Nasal obstruction/congestion scale	A 4-point scale defined as follows: 0: No symptoms 1: Mild symptoms, clearly present but minimal awareness and easily tolerated 2: Moderate symptoms, definite awareness of symptoms that is bothersome but tolerable 3: Severe symptoms, hard to tolerate, cause interference with activities or daily living
Percent ethmoid sinus obstruction	Estimated visually based on endoscopic examination on a scale ranging from 0% (no obstruction) to 100% (complete obstruction of the ethmoid cavity by polyps, edema and/or scarring).
Polyp grading scale	Polyps are assessed endoscopically and graded on an 8-point scale ranging from 0 to 4 defined as follows: 0: No visible sinonasal polyps 1: Small amount of sinonasal polyps confined in middle meatus 1.5: Small amount of sinonasal polyps confined in middle meatus with expanded amount of polypoid edema obstructing ≥ 25% of the ethmoid sinus cavity 2: Expanded amount of sinonasal polyps confined in middle meatus 2.5: Expanded amount of sinonasal polyps confined in middle meatus with expanded amount of polypoid edema obstructing ≥ 50% of the ethmoid sinus cavity 3: Sinonasal polyps extending beyond middle meatus but not totally obstructing the nasal cavity 3.5: Sinonasal polyps extending beyond middle meatus with expanded amount of polypoid edema obstructing ≥ 75% of the ethmoid sinus cavity 4: Sinonasal polyps extending beyond middle meatus and completely obstructing the nasal cavity
Serious adverse event (SAE) or serious suspected adverse reaction (SSAR)	Adverse events are considered "serious" if, in the view of either the investigator or sponsor, they result in any the following outcomes: • Death; or • A life-threatening adverse event; or • Inpatient hospitalization or prolongation of existing hospitalization; or

Term	Definition
	• A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or • A congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. [21 CFR 312]
Suspected unexpected serious adverse reaction (SUSAR)	Any SSAR that is unexpected. [21 CFR 312]
Suspected adverse reaction (SAR)	Any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction (SAR) implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. [21 CFR 312]
Sino-Nasal Outcome Test (SNOT-22)	A validated, disease-specific, symptom-scoring instrument consisting of 22 questions, each scored on a scale of 0 to 5 defined as follows: 0: No problem 1: Very mild problem 2: Mild or slight problem 3: Moderate problem 4: Severe problem 5: Problem as bad as it can be
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.
Source documents	Original documents, data, and records. Printed, optical or electronic document containing source data.
Subject	An individual who participates in a clinical investigation.
Treatment emergent adverse event (TEAE)	Any event not present prior to the treatment or an event already present that worsens either in intensity or frequency following the treatment.
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, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. [BS EN ISO 14155]
Unanticipated Serious Adverse Device Effect (USADE)	Any serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. [21 CFR 812]
Unexpected adverse event or suspected adverse reaction	An AE/SAR is considered 'unexpected' if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed. Unexpected events also refer to AE/SARs that are mentioned in the investigator brochure as occurring with a class of product or as anticipated from the pharmacological properties of the

Term	Definition
	product, but are not specifically mentioned as occurring with the particular investigational product. [21 CFR 312]

4 PROTOCOL SUMMARY

Study Title	The ENCORE Study: Safety Evaluation of Repeat Placement of the Corticosteroid-Releasing S8 Sinus Implant in Chronic Sinusitis Patients with Nasal Polyps
Objective	To assess the safety of repeat placement of the S8 Sinus Implant when used in chronic sinusitis (CS) patients with recurrent nasal polyps
Investigational Product	The S8 Sinus Implant (mometasone furoate, 1350 mcg) is a bioabsorbable, corticosteroid-eluting implant studied for the treatment of nasal polyps in patients ≥ 18 years of age who have had ethmoid sinus surgery. The S8 Sinus Implant is placed in the ethmoid sinus under endoscopic visualization. The implant may be left in the sinus to gradually release the corticosteroid over approximately 90 days. The implant must be removed by 90 days after placement or may be removed earlier at the investigator's discretion, using standard surgical instruments.
Study Design	A prospective, non-randomized, open-label, multicenter clinical trial, consisting of three phases: <u>Screening</u> • Patients who sign the institutional-review board (IRB) approved informed consent form will be considered enrolled into the study. • All consented subjects will undergo a screening assessment consisting of an endoscopic examination. <u>Baseline/Procedure</u> • Eligible subjects will undergo a baseline assessment. • Subject meeting all eligibility criteria will undergo an in-office bilateral placement of the S8 Sinus Implant in the ethmoid sinuses. <u>Follow-up</u> • Subjects will return for **7** follow-up visits at Days 30, 60, 90, 120, 150, 180 and 365. • At the **Day 90** visit, subjects will undergo **repeat in-office placement** of the S8 Sinus Implant in each ethmoid sinus with nasal polyps (grade ≥ 1). Repeat placement will not be performed if polyp grade is < 1, or if the subject declines the procedure.
Subject Enrollment	A total of **50** subjects will be treated at up to **10** study centers across the U.S. with a maximum of 15 treated subjects at a single center.
Study Population	Patients ≥ 18 years of age with CS who have undergone prior endoscopic sinus surgery (ESS), including bilateral total ethmoidectomy, and present with bilateral ethmoid polyposis, and in whom bilateral placement of the S8 Sinus Implant is both feasible and medically appropriate.

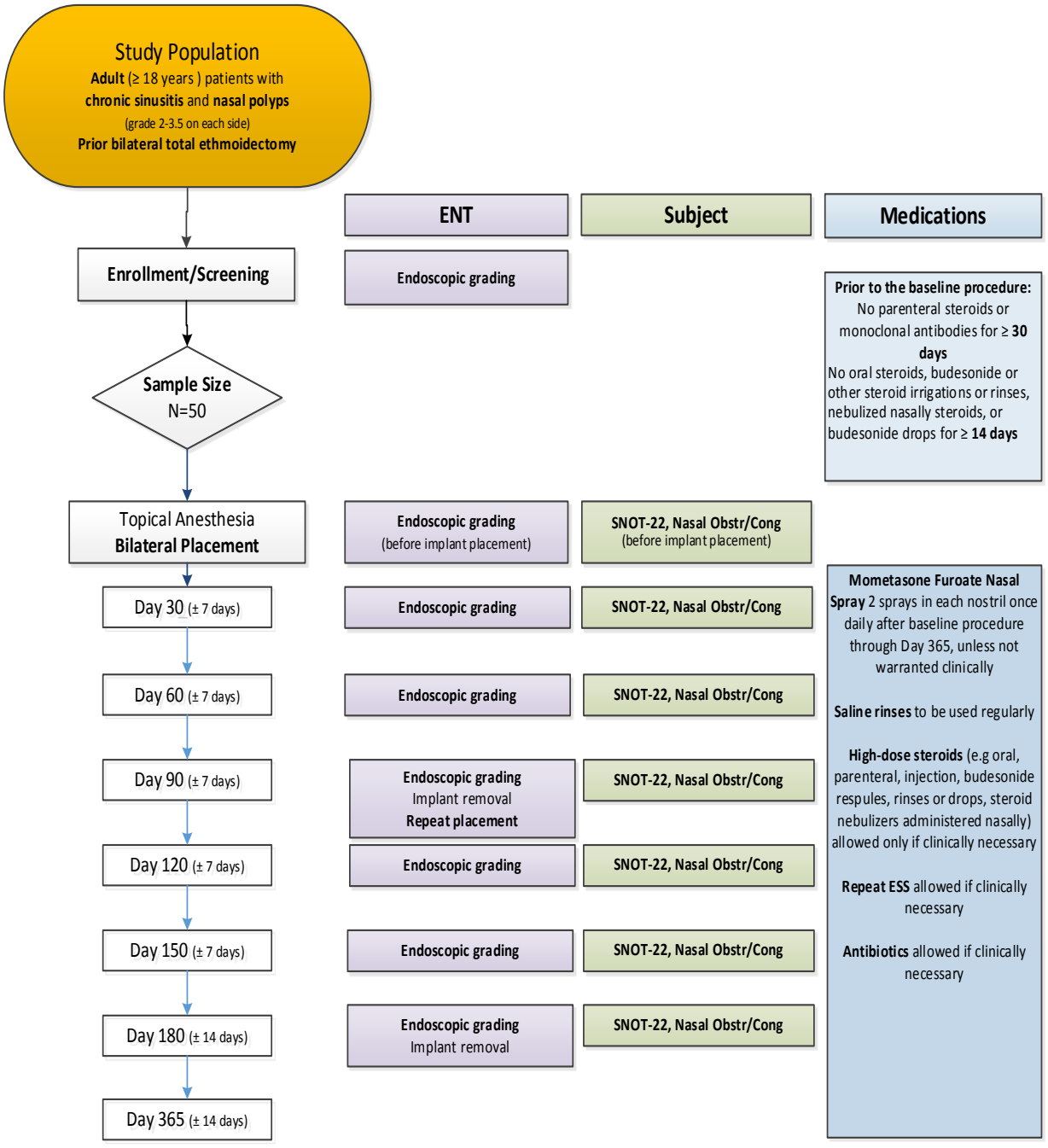
Eligibility Criteria	**Key inclusion criteria:**
	• Confirmed diagnosis of CS with nasal polyps. Per the 2016, "International Consensus Statement on Allergy and Rhinology" definition, patient must have ≥ 12 weeks of:
	  ○ Two or more of the following symptoms:
	  ▪ Mucopurulent discharge (rhinorrhea or postnasal drip)
	  ▪ Nasal obstruction and congestion
	  ▪ Decreased/absent sense of smell
	  ▪ Facial pressure/pain
	  ○ And one or more of the following findings:
	  ▪ Evidence of inflammation on paranasal sinus examination or computed tomography
	  ▪ Evidence of purulence coming from paranasal sinuses or ostiomeatal complex
	  ○ And presence of polyps.
	• Previous ESS including bilateral total ethmoidectomy at least 90 days prior to screening.
	• Patient must have evidence of bilateral ethmoid sinus polyps (grade ≥ 2 on each side)
	• Ethmoid sinus anatomy is amenable to bilateral placement of the S8 Sinus Implant (20 mm nominal length, 7 mm compressed diameter)
	Key exclusion criteria:
	• Extensive ethmoid sinus polyps (grade 4 on at least one side)
	• Extensive adhesions/synechiae (grade 3 or 4)
	• Oral-steroid dependent condition
	• History of allergy or intolerance to corticosteroids or mometasone furoate
	• Physical obstruction that would preclude access to or placement of the S8 Sinus Implant in the middle meatus
	• Evidence of acute sinusitis (AS), invasive fungal sinusitis or another disease or condition expected to compromise survival or ability to complete assessments during the 180-day follow-up period
	• Use of parenteral and injected steroids (e.g., Kenalog injection) 30 days prior to the baseline procedure
	• Use of monoclonal antibodies (e.g., Dupoxent, Nucala, Xolair) for treatment for asthma, allergies or nasal polyps 30 days prior to the baseline procedure

	• Use of oral steroids, budesonide or other sinus steroid irrigations/rinses, nebulized steroids administered nasally or budesonide drops 14 days prior to the baseline procedure
Safety Evaluation	All adverse events reported by subjects between consent and the Day 365 follow-up visit (end of study) will be tabulated. Each adverse event will be evaluated by investigators in terms of seriousness, severity (i.e., mild, moderate, severe) and strength of relationship (i.e., not related, unlikely related, possibly related, related) to study drug, study device, and implant procedure.
Efficacy Endpoints	**Patient-reported endpoints**: • Change from baseline to each time-point (Days 30, 60, 90, 120, 150, 180) in the mean **nasal obstruction/congestion** score (scale 0 to 3) based on a reflective questionnaire • Change from baseline to each time-point (Days 30, 60, 90, 120, 150, 180) in **SNOT-22** total score (scale 0 to 110), domain scores and individual symptom scores (scale 0 to 5) **Endoscopic endpoints:** • Change from baseline to each time-point (Days 30, 60, 90, 120, 150, 180) in **bilateral polyp grade** (scale 0 to 8) • Change from baseline to each time-point (Days 30, 60, 90, 120, 150, 180) in **ethmoid sinus obstruction** (scale 0% to 100%)
Other Endpoints	**Implant delivery success rate**: • Proportion of successful deployments of the S8 Sinus Implant to the target site including the baseline and repeat placement procedures. See *Section 3 Definition of terms* **Interventions received**: • Proportion of subjects who **received interventions** (i.e., sinus-related medications, systemic steroid interventions, surgical interventions for sinusitis) through Day 365
Concomitant Medications	• After the baseline procedure, subjects will be encouraged to use **saline rinses** regularly through Day 365. • After the baseline procedure, subjects will be required to use **MFNS** 200 mcg (two sprays in each nostril) once daily throughout the whole duration of the follow-up, unless the use of MFNS is not warranted clinically. Both the generic version of MFNS by Apotex or Novartis and the brand-name version by Merck (Nasonex) can be used. • **High-dose steroids** (e.g., oral, parenteral, injections, budesonide or other sinus steroid irrigations/rinses or drops, nebulized steroids administered nasally) will be allowed during the study

	follow-up only if clinically necessary. (see *Medical and Surgical Interventions*) • **Orally-inhaled steroids** for control of asthma will be permitted. • If infection is suspected at any time during the study, treatment with **antibiotics** will be permitted. • Use of **monoclonal antibodies** is prohibited throughout the 365-day follow-up period. • To the extent possible, subjects will be maintained on stable regimens of leukotriene inhibitors and/or **immunotherapy** for allergies, if currently on such regimens; however, use of breath-powered or other methods of intranasal steroid delivery for allergies is not permitted during the study. • Use of **drug-eluting implants** (PROPEL®, PROPEL® Mini, PROPEL® Contour) is prohibited during the baseline procedure and throughout the 365-day follow-up unless placed immediately following repeat ESS performed in the operating room setting.
Medical and Surgical Interventions	**Medical interventions**: • During the study follow-up, **high-dose steroids** (e.g., oral, parenteral, injection, budesonide or other sinus steroid irrigations, rinses or drops, nebulized steroids administered nasally) may be used as a medical intervention in cases where a clinically significant increase or persistence in ethmoid sinus polyposis occurs, leading to subject seeking intervention. • High-dose steroids may be used for reasons other than ethmoid sinus obstruction, if medically necessary. • In either case, high-dose steroid interventions and reasons of their use will be recorded on the concomitant medication and follow-up case report forms (CRF). **Surgical interventions**: • During the study follow-up, surgical intervention (e.g., repeat ESS, office polypectomy) may be required in cases where a clinically significant increase or persistence in ethmoid sinus polyposis occurs.
Follow-up	Each subject will return for **7** follow-up visits: • Day 30 (± 7 days) • Day 60 (± 7 days) • Day 90 (± 7 days) implant removal & repeat placement • Day 120 (± 7 days) • Day 150 (± 7 days) • Day 180 (± 14 days) implant removal • Day 365 (± 14 days)

	Subjects may come in for additional **unscheduled office visits** if necessary. Circumstances that may warrant additional visits include, but are not limited to worsening of sinus symptoms, sinus-related adverse events requiring medical evaluation, and implant migration.
Study Duration	The anticipated timeline for this study is as follows: • Enrollment start: November 2017 • Enrollment end: January 2018 • Follow-up end: November 2018
Duration of Study Period (per subject)	Screening visit (1 day) + baseline/procedure (1 day) + follow-up (365 days) = Approximately 367 days

5 STUDY FLOW DIAGRAM



Abbreviations: SNOT-22, Sino-Nasal Outcome Test

6 SCHEDULE OF ASSESSMENTS

Assessment	Screening	Baseline/Procedure	Day 30 (± 7 days)	Day 60 (± 7 days)	Day 90 (± 7 days)	Day 120 (± 7 days)	Day 150 (± 7 days)	Day 180 (± 14 days)	Day 365 (± 14 days)
Informed consent	X								
Medical/surgical history	X								
Endoscopic grading & recording	X	X	X	X	X	X	X	X	
Nasal Obstruction/Congestion		X	X	X	X	X	X	X	
Sino-Nasal Outcome Test (SNOT-22)		X	X	X	X	X	X	X	
In-office implant placement (bilateral)		X							
Implant removal					X			X	
In-office repeat placement (unilateral or bilateral)					X[a]				
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events reporting	X	X	X	X	X	X	X	X	X
Pregnancy test (female subjects)	X[b]	X[b]			X[b]				
Documented birth control (female subjects)		X[c]	X	X	X	X	X	X	X

Note: If screening and baseline/procedure visits occur on the same day, assessments must be recorded on the baseline visit forms.

a. Repeat implant placement will be performed at Day 90 in each ethmoid sinus with polyp grade ≥ 1 (See Section 11.3 *Repeat Implant Placement Procedure*).

b. Female subjects with reproductive potential are required to undergo a urine pregnancy test at screening and prior to the baseline procedure. If the screening and baseline/procedure visits occur on the same day, only one urine pregnancy test is required prior to the baseline procedure. The pregnancy test must be repeated at Day 90 prior to repeat implant placement procedure.

c. Female subjects are required to confirm their nursing status at baseline.

7 BACKGROUND INFORMATION

7.1 Chronic Sinusitis, Treatment Options and Unmet Clinical Need

Chronic sinusitis (CS) is a prevalent disease process affecting 32 million Americans, corresponding to 13% of the adult population (Blackwell 2014). CS results in 18 to 22 million U.S. physician office visits annually, representing considerable health care expenditures (Bhattacharyya 2011, Caulley 2015). Patients with CS with nasal polyps have a higher burden of symptoms, revision sinus surgery, and greater use of medications. The presence of polyps negatively affects the ability of the otolaryngologists to treat patients and patients are subject to frequent relapses.

The myriad of clinical management options demonstrates the lack of long-term effectiveness of any single treatment option for CS with nasal polyps (Joe 2008). This is best explained by the multi-factorial pathophysiology of CS with nasal polyps (Han 2013). Medical management with topical and possibly systemic corticosteroids are considered the initial treatment strategy of choice, with endoscopic sinus surgery (ESS) reserved for patients whose CS with nasal polyps fail to improve. Surgical treatment with polypectomy temporarily relieves ostiomeatal complex blockage and improves ventilation but is not curative (Fokkens 2012, Manes 2013). Nasal polyps have a strong tendency to recur in up to 40% of patients within 1.5 years after surgery (DeConde 2016) and 60% within 3 years (Wynn 2004) even when aeration is improved. Furthermore, about 20% of patients undergo revision surgery within 5 years after initial surgery (Philpott 2015, Wu 2014).

Systemic corticosteroids have been shown to enhance the efficacy of surgical approaches but result in numerous adverse events such as gastrointestinal symptoms, adrenal suppression, insomnia, increased bone turnover, and epistaxis (Orlandi 2016, Poetker 2013). The development of corticosteroids that are delivered directly to the nasal mucosa has addressed much of the concern about the systemic adverse effects associated with systemic corticosteroid therapy (Fandino 2013, Sastre 2012, Wei 2013). However, intranasal topical preparations often fail because of limited penetration to the target sinus anatomy due to blockage of ostiomeatal complex by polyposis, crusting, secretions, and/or edema which limit delivery of an adequate amount of drug to the sinuses. Moreover, patient compliance with daily dosing of topical preparations and proper head position may compromise drug delivery and reduce efficacy (Sanan 2017).

Current therapies for CS with nasal polyps have been tailored to improving postoperative aeration and minimizing sinonasal inflammation in hopes of decreasing polypoid regrowth (Santarelli 2016). Intersect ENT has developed the S8 Sinus Implant to provide an in-office option, independent of patient compliance, for treating recurrent CS with nasal polyps after ESS.

The efficacy and safety of a single-use bilateral placement of the S8 Sinus Implant was studied as part of the S8 clinical program. This Phase IIIb study is designed to assess the safety of repeat placement of the S8 Sinus Implant when used in chronic sinusitis (CS) patients with recurrent nasal polyps.

7.2 Investigational Product - S8 Sinus Implant

Intended use

The S8 Sinus Implant is indicated for the treatment of nasal polyps in patients ≥ 18 years of age who have had ethmoid sinus surgery.

Description

The S8 Sinus Implant is designed to accommodate the size and variability of a previously operated ethmoid sinus cavity. Once inserted under endoscopic visualization, the S8 Sinus Implant is designed to be self-retaining within the cavity. The S8 Sinus Implant is intended to provide an immediate onset of action by mechanical dilation of the middle meatus and ethmoid sinus with concurrent restoration of ventilation and drainage by decreasing nasal obstruction/congestion, inflammation and polyposis through local steroid delivery. Therefore, the S8 Sinus Implant combines a device mode of action (mechanical opening) with a drug mode of action (reduced inflammation).

Figures 1a-b depict the structure of the S8 Sinus Implant. The structural design features are the rounded cap at the leading end and the arched components that expand after placement to create an opening within ethmoid cavity. The arched components run through the cap to provide the shape of the implant. The resulting self-expanding nature of the implant provides an outward force against the mucosal surfaces. The alternating lengths of the implant legs are 25 and 20 mm. This feature assists with retention of the implant within the sinus. When expanded to the dimensions of a typical operated ethmoid sinus cavity, the S8 Sinus Implant is approximately 20 mm in nominal length and can expand to a nominal diameter of 34 mm. **Figure 2a** shows an ethmoid cavity obstructed by scarring and polyps; **Figure 2b** shows the S8 Sinus Implant immediately after placement, dilating the obstructed by polyps ethmoid sinus seen in **Figure 2a** to create an opening that permits ventilation and drainage to occur.

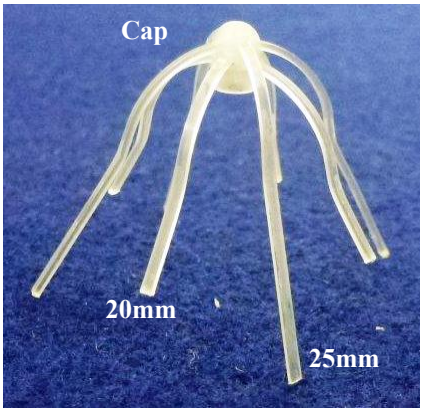


Figure 1a. S8 Sinus Implant in an expanded state

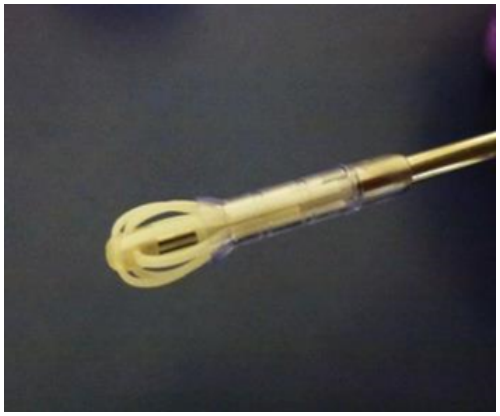


Figure 1b. S8 Sinus Implant in a crimped state loaded onto the delivery system

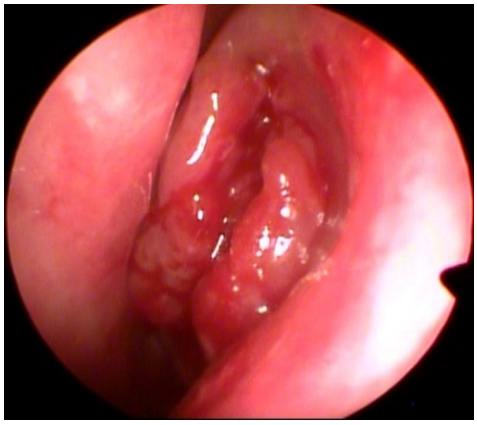


Figure 2a. Endoscopic view of the ethmoid cavity obstructed by scarring and polyposis before placement of the S8 Sinus Implant

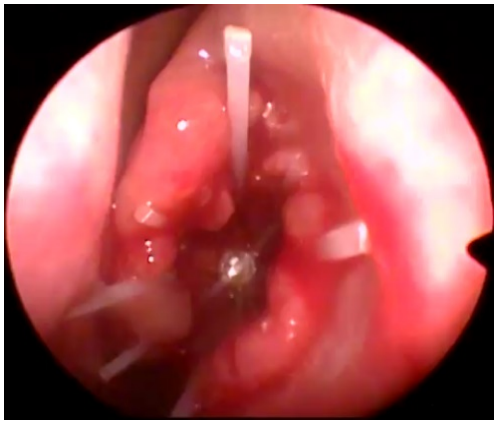


Figure 2b. Endoscopic view of the ethmoid cavity depicted in 2a after placement of the S8 Sinus Implant. Note dilation effect and creation of opening

Composition

The S8 Sinus Implant is composed of a blend of two different ratios of a synthetic bioabsorbable co-polymer, poly(L-lactide-co-glycolide) with different lactide/glycolide ratios. The implant has a coating containing mometasone furoate (active ingredient), a synthetic corticosteroid with anti-inflammatory activity. The chemical name is 9α, 21-dichloro-11β,17α -dihydroxy-16α -methylpregna-1,4-diene-3,20-dione 17-(2-furoate), with the empirical formula $C_{27}H_{30}Cl_2O_6$, and a molecular weight of 521.43 g/mol. The drug is embedded in a bioabsorbable polymer matrix containing poly-(DL-lactide-co-glycolide) and polyethylene glycol (inactive ingredients) which provides for gradual release of the drug. This top coating is designed to provide a controlled release of mometasone furoate over the course of 90 days.

Crimper and delivery system

The implant comes pre-assembled in a crimper. The crimper holds the implant during shipping and works in concert with the delivery system to crimp and load the implant. The delivery system is designed to be single-handed, allowing the physician to place the implant under endoscopic guidance.

The delivery system is designed to provide access to the ethmoid sinus and controlled accurate deployment of the implant. The delivery system comprises the thumb and finger rests, the seeker and a cup (**Figure 3**). The seeker is extended by pushing with the thumb rest to load the implant onto the delivery system. The tip of the delivery system has a curvature of 10° to facilitate endoscopic placement.

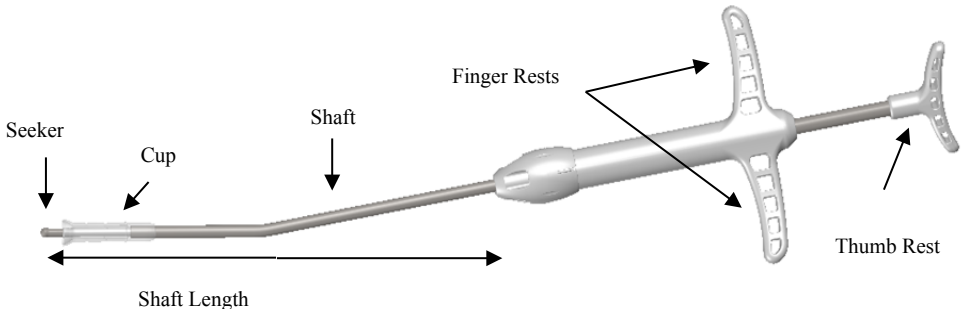


Figure 3. Delivery system

General instructions for placement

The S8 Sinus Implant must be placed according to the prescribing information. To summarize, the S8 Sinus Implant is crimped and loaded by introducing the delivery system's seeker tip into the center of the implant, depressing the finger rests to extend the seeker and allowing the cup to capture all legs of the implant. For endoscopic placement, the thumb rest is pressed again to release the implant from the distal tip of the seeker into the ethmoid cavity. Upon release, the S8 Sinus Implant expands radially to conform to and dilate the sinus tissue. The delivery system is then retracted out of the patient. Final placement is confirmed by endoscopic visualization. The position of the S8 Sinus Implant can be adjusted after placement using the seeker on the delivery system.

7.3 Overview of Prior Clinical Studies

The safety and efficacy of the S8 Sinus Implant have been evaluated in four US clinical studies: two controlled and two uncontrolled, totaling 417 CS with nasal polyps patients.

Controlled studies

The two randomized, sham-controlled, parallel group, single-blind, multicenter studies were P500-1113 RESOLVE II (N = 300) and P500-1012 RESOLVE (N = 100). The RESOLVE II study was a Phase III clinical trial designed to demonstrate the efficacy and safety of the S8 Sinus Implant by evaluating the patient-reported symptoms of nasal obstruction and congestion and the objective endoscopic measure of bilateral polyp grade as co-primary efficacy endpoints. RESOLVE II also included a prespecified plan to test five secondary efficacy endpoints, which are clinically relevant for this patient population.

Uncontrolled studies

The two uncontrolled studies were P500-0911 *S8* Pilot (N = 12) and P500-0513 S8 PK (N = 5). The S8 Pilot assessed and demonstrated the feasibility and safety of implant placement and its initial signals of efficacy (Lavigne 2014). The S8 PK study assessed implant delivery to the ethmoid sinus and systemic exposure to mometasone furoate by measuring plasma mometasone furoate concentrations through 30 days post-procedure (Ow 2014).

Overall efficacy and safety conclusions

The efficacy results from RESOLVE II and RESOLVE in 400 subjects demonstrated that bilateral placement of the S8 Sinus Implant provides compelling benefits consisting of early onset of symptomatic relief and endoscopic improvements in CS with nasal polyps patients who had undergone previous ESS but still presented with symptoms refractory to medical therapy and were candidates for RESS. Treatment effects were maintained long term (6 months).

The safety results from the four clinical studies with 417 subjects supported favorable safety profile, including high patient acceptance, negligible systemic exposure, negligible ocular risk, and overall low implant-related adverse events, making it an appealing, minimally invasive topical therapy strategy for patients with CS with nasal polyps.

8 STUDY OBJECTIVE

To assess the safety of repeat placement of the S8 Sinus Implant when used in CS patients with recurrent nasal polyps.

9 STUDY DESIGN AND ENDPOINTS

9.1 Study Design

This is a prospective, non-randomized, open-label, multicenter clinical trial. A total of 50 subjects will be treated at up to 10 study centers across the U.S. with a maximum of 15 subjects treated at a single center.

The study will consist of three phases: screening, baseline/procedure and follow-up. The total duration of an individual subject's study participation will be approximately 367 days.

9.2 Study Endpoints

9.2.1 Safety Evaluation

All AE reported by subjects between consent and the Day 365 follow-up visit (end of study) will be tabulated.

Each AE will be evaluated by investigators in terms of seriousness, severity (i.e., mild, moderate, severe) and strength of relationship (i.e., not related, unlikely related, possibly related, related) to study drug, study device, and implant procedure.

9.2.2 Efficacy Endpoints

Efficacy endpoints will consist of both patient-reported and endoscopic outcomes through Day 180 follow-up visit.

Patient-reported endpoints

- Change from baseline to each time-point (Days 30, 60, 90, 120, 150, 180) in the mean nasal obstruction/congestion score (scale 0 to 3)
- Change from baseline to each time-point (Days 30, 60, 90, 120, 150, 180) in SNOT-22 total score (scale 0 to 110), domain scores and individual symptom scores (scale 0 to 5)

Subjects will assess their CS sinus symptoms during each visit using paper questionnaires.

See Section 3 *Definitions of Terms* and Section 6 *Schedule of Assessments* for details on scoring scales and timing of assessments.

Endoscopic endpoints

- Change from baseline to each time-point (Days 30, 60, 90, 120, 150, 180) in bilateral polyp grade (scale 0 to 8)
- Change from baseline to each time-point (Days 30, 60, 90, 120, 150, 180) in ethmoid sinus obstruction (scale 0% to 100%)

Investigators will perform endoscopic evaluation with real-time grading and video recording. When grading polyps for this study, investigators will be instructed to consider only polyps originating from the ethmoid sinus/middle meatus and focus within the anatomical boundaries of the ethmoid sinus. Grading should not include polyps medial to the middle turbinate, polyps originating from the maxillary sinus, or polyps within the sphenoethmoid recess. Investigators will also be instructed to consider and account for polypoid edema if present in an expanded amount in the ethmoid sinus and middle meatus.

See Section 3 *Definitions of Terms* and Section 6 *Schedule of Assessments* for details on endoscopic grading scales and timing of assessments.

9.3 Other Endpoints

Implant delivery success rate

Proportion of successful deployments of the S8 Sinus Implant to the target site per total number of sinuses attempted including the baseline and repeat placement procedures.

Interventions received

Proportion of subjects who received interventions (i.e., sinus-related medications, systemic steroid interventions, surgical interventions) through Day 365.

10 SUBJECT SELECTION AND WITHDRAWAL

10.1 Study Population

The study population will consist of adult patients (≥ 18 years of age) with CS who have undergone prior ESS including bilateral total ethmoidectomy and present with bilateral ethmoid polyposis, and in whom bilateral placement of the S8 Sinus Implant is both feasible and medically appropriate.

10.2 Eligibility Criteria

To be enrolled in the study, patients must meet all of the following inclusion criteria and none of the following exclusion criteria.

Inclusion criteria

a. Patient has provided written informed consent using a form approved by the reviewing institutional review board (IRB) and sponsor.
b. Patient is ≥ 18 years of age.
c. Patient is willing and able to comply with protocol requirements.
d. Patient has a confirmed diagnosis of CS with nasal polyps, as defined in the 2016 "International Consensus Statement on Allergy and Rhinology".
e. Patient has undergone prior ESS including bilateral total ethmoidectomy at least 90 days prior to screening.
f. Patient has evidence of bilateral ethmoid sinus obstruction due to polyposis warranting intervention (polyp grade ≥ 2 on each side).
g. Patient is able to tolerate daily use of Mometasone Furoate Nasal Spray (MFNS).
h. Patient is able to tolerate topical/local anesthesia.
i. In the opinion of the investigator, patient's ethmoid sinus anatomy is amenable to in-office bilateral placement of the S8 Sinus Implant (i.e., able to pass into the middle meatus on both sides the S8 Sinus Implant with 20 mm in nominal length and 7 mm in compressed diameter).
j. Female patients of reproductive potential must not be pregnant or nursing and must agree to not become pregnant during their participation in the study.
k. Female patients of childbearing potential must agree to use consistent and acceptable method(s) of birth control during their participation in the study.

Exclusion criteria

a. Patient has extensive ethmoid sinus polyp grade (grade 4 on at least one side).
b. Patient has extensive adhesions/synechiae (grade 3 or 4).

c. Patient has used parenteral and injected steroids (e.g., Kenalog injection) during 30 days prior to the baseline procedure.

d. Patient has used oral steroids, budesonide or other sinus steroid irrigations/rinses, nebulized steroids administered nasally or budesonide drops during 14 days prior to the baseline procedure.

e. Patient has oral-steroid dependent condition such as chronic obstructive pulmonary disease (COPD) or asthma.

f. Patient has known history of allergy or intolerance to corticosteroids or mometasone furoate.

g. Patient has used monoclonal antibodies for asthma, allergies or nasal polyps (e.g., Dupixent, Nucala, Xolair) during 30 days prior to the baseline procedure.

h. Patient requires monoclonal antibodies for asthma, allergies or nasal polyps during the duration of the study.

i. Patient has presence of physical obstruction that would preclude access and placement of the S8 Sinus Implant in the middle meatus (e.g., severe septal deviation, septal spur, very small middle meatus, total obstruction of the sinonasal passage with severe adhesion, scarring, polypoid edema or polyps).

j. Patient has known history of human immunodeficiency virus (HIV) or immunoglobulin G or A subclass deficiency.

k. Patient has clinical evidence of acute sinusitis (AS), as defined in the 2016 “International Consensus Statement on Allergy and Rhinology”.

l. Patient has clinical evidence or suspicion of invasive fungal sinusitis (e.g., bone erosion on prior computed tomography (CT) scan, necrotic sinus tissue).

m. Patient has evidence of severe concomitant disease or condition expected to compromise survival or ability to complete assessments during the 365-day study follow-up period (e.g., cancer).

n. Patient is currently participating in another clinical study.

o. Patient has previously undergone ESS and experienced a cerebrospinal fluid (CSF) leak or has residual compromised vision as a result of a complication in a prior ESS procedure.

p. Patient has known dehiscence of the lamina papyracea.

q. Patient has evidence of active tuberculosis or active viral illness (e.g., ocular herpes simplex, chickenpox, measles).

r. Patient has known history or diagnosis of glaucoma or ocular hypertension (prior ocular exam with intraocular pressure of >21 mmHg and pressure lowering medication given) or posterior subcapsular cataract.

10.3 Subject Withdrawal

Study subject may be withdrawn or terminated for the following reasons:

- Subject death
- Concomitant disease or any disease or condition that makes further study participation impossible (but without relationship to the investigational product).
- Subject voluntarily chooses not to participate further in the study. If withdrawal takes place after baseline procedure, the implants will be removed, if still present.
- Subject's non-compliance with study procedures.
- Lost to follow-up: the subject is more than 30 days late to a study visit and three documented attempts to contact the subject are unsuccessful. A subject who misses a study visit should be contacted by site personnel to determine the reason for the missed visit, which should be documented in the subject's study records. Note: A subject who misses a study visit but attends a subsequent visit will no longer be considered lost to follow-up.
- In the investigators's opinion, a significant safety concern arises that requires subject discontinuation.
- In the investigators's opinion, it is not in the best interest of the subject to continue study participation. The implants will be removed, if still present.

If a subject decides to withdraw from the study, every attempt should be made to continue to collect safety data in the patient's medical records. Data collected up to the point of subject withdrawal or termination will be maintained in the study database and included in analyses as appropriate.

All enrolled subjects, including those withdrawn or lost to follow-up, will be accounted for and documented.

11 SUBJECT TREATMENT AND STUDY PROCEDURES

11.1 Screening Phase

Pre-screening

During the pre-screening phase, investigators or designees 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, medical history, sinus endoscopies, sinus surgery).

Consent, screening and enrollment

If the patient appears to be a potential candidate for the study based upon 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.

Investigators or designees 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 risks and benefits will be carefully explained to each 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, and
- Provide ample time for the patient to consider participation.

Each patient must sign and date the informed consent form (ICF) approved by an appropriate IRB and the sponsor. Patients are considered enrolled in the study upon signing the IRB-approved ICF. Enrolled subjects will be assigned unique identifying codes by an Electronic Data Capture (EDC) system and entered into the study database.

The screening assessment will include an endoscopic examination, which will be recorded (see Section 5 *Study Flow Diagram* and Section 6 *Schedule of Assessments*). In addition, female subjects of reproductive potential must confirm their nursing status and undergo a urine pregnancy test and be informed about acceptable birth control methods. If the screening visit occurs on the same day as the baseline/procedure visit, all assessments will be recorded in the baseline visit forms.

All subjects who do not pass the screening assessment will be considered as screen failures and will be terminated from the study. The reason for ineligibility will be recorded in the EDC.

11.2 Baseline/Procedure Phase

Baseline assessment

Upon meeting eligibility requirements, subjects will come in for an in-office baseline assessment, consisting of:

- Nasal obstruction/congestion questionnaire,
- SNOT-22 questionnaire, and
- Endoscopic grading and video recording.

Female subjects of childbearing potential will undergo a urine pregnancy test prior to the baseline procedure and be required to use acceptable contraceptive method(s) during the entire duration of the study follow-up. Acceptable methods of contraception may include:

- Established use of oral, injection or implantables hormonal contraceptives;
- Double-barrier methods (i.e., intra-uterine devices) and barrier contraceptives (e.g., condom, diaphragm or cervical/vault caps) used with spermicide (foam, gel, film, cream or suppository);
- Female sterilization (e.g., tubal occlusion, hysterectomy or bilateral salpingectomy); or
- Vasectomized male partner, if the sole partner for the subject.

Note: The baseline assessment of symptoms and pregnancy testing must be performed before implant procedure.

Subject preparation for baseline procedure

Subjects will be prepared for the baseline procedure per investigator's standard protocol used for nasal endoscopy. The topical anesthesia regimen may consist of:

- Spraying the nasal cavity with 4% lidocaine (or equivalent, such as pontocaine) with oxymetazoline (or equivalent) nasal decongestant spray;
- Placing cotton pledgets soaked in lidocaine (or equivalent) and oxymetazoline (or equivalent) solution against the inferior turbinate, and into the ethmoid sinus (if available in the clinic setting, topical cocaine may be used); and
- Injecting into the sinus tissue and/or polypoid tissue with lidocaine (or equivalent) as necessary.

The anesthesia period should be as long as necessary to ensure complete numbness of the subject's septum and middle turbinate. Once properly anesthetized, subjects may undergo the baseline procedure.

Baseline procedure

Subjects will undergo in-office bilateral placement of the S8 Sinus Implant in the ethmoid sinuses (total of two implants). The S8 Sinus Implant will be provided by sponsor and must be placed according to the prescribing information.

No other procedures (e.g. polypectomy or balloon sinuplasty) are allowed at the time of the baseline procedure.

Implant disposal

The crimper and delivery system must be disposed per standard institutional practices for biohazard waste. If the S8 Sinus Implant, delivery system or other system components are associated with a device-related adverse event (AE), malfunction or failure, all the components should be returned to sponsor for evaluation, when possible. For the return of biohazard product, sponsor must be contacted prior to product return for handling instructions.

Implant removal

The S8 Sinus Implant is made from bioabsorable polymers designed to gradually soften over time. The implant may be left in the sinus to gradually release the corticosteroid over approximately 90 days. It must be removed by 90 days or may be removed earlier at the investigator's discretion, using standard surgical instruments. As the implant softens over time and the polyps decrease, the implant may expel out of the nose on its own or with actions such as sneezing or forceful nose blowing.

Implant malfunction

All potential implant malfunctions and any associated AEs will be recorded in the corresponding CRFs in the EDC system. All instances of suspected implant malfunction will be reviewed by the sponsor.

11.3 Follow-Up Phase

The follow-up period begins immediately post-procedure (once the patient exits the clinic). Each subject will return for up to 7 follow-up visits (s*ee* Section 5 *Study Flow Diagram* and Section 6 *Schedule of Assessments*).

- Day 30 (± 7 days)
- Day 60 (± 7 days)
- Day 90 (± 7 days) – implant removal & repeat implant placement
- Day 120 (± 7 days)
- Day 150 (± 7 days)
- Day 180 (± 14 days) – implant removal, as applicable
- Day 365 (± 14 days)

The protocol-required follow-up assessment at each visit through Day 180 will consist of:

- Nasal obstruction/congestion questionnaire,
- SNOT-22 questionnaire, and
- Endoscopic grading and video recording.

Repeat implant placement procedure at Day 90

At the Day 90 follow-up visit, subjects with ethmoid sinuses with polyps (grade ≥1) will undergo repeat implant placement unilaterally or bilaterally. Repeat implant placement must not be performed in the ethmoid sinuses with no nasal polyps (grade <1). All implants placed at Day 90 must be removed at Day 180 or may be removed earlier at the investigator's discretion.

If polypectomy is performed at the Day 90 follow-up visit, polyp grading must be done after polypectomy to qualify a given subject for repeat placement of the S8 Sinus Implant.

Note: The assessment of symptoms and pregnancy testing must be performed before repeat implant placement procedure.

Unscheduled visits

Subjects may come in for additional unscheduled office visits if necessary. Circumstances that may warrant additional visits include but are not limited to:

- Worsening of sinus symptoms,
- Sinus-related adverse events requiring medical evaluation, and/or
- Implant migration

The assessment at an unscheduled visit will consist of:

- Nasal obstruction/congestion questionnaire,
- SNOT-22 questionnaire, and
- Endoscopic grading and video recording.

12 CONCOMITANT MEDICATION

The study standardized medication regimen will be as follows:

- Leading up to the baseline procedure, there is a 30-day restriction for use of parenteral and injected steroids (e.g., Kenalog injection), and monoclonal antibodies (e.g., Dupixent, Nucala, Xolair) 1
- Leading up to the baseline procedure, a 14-day restriction for use of oral steroids, budesonide or other sinus steroid irrigations/rinses, nebulized steroids administered nasally or budesonide drops.
- After the baseline procedure, subjects will be encouraged to use saline rinses regularly through Day 365.
- After the baseline procedure, subjects will be required to use MFNS 200 mcg (two sprays in each nostril) once daily throughout the entire duration of the follow-up, unless the use of MFNS is not warranted clinically. Both the generic version of MFNS by Apotex or Novartis and the brand-name version by Merck (Nasonex) can be used.
- High-dose steroids (e.g., oral, parenteral, injections, budesonide or other sinus steroid irrigations, rinses or drops, nebulized steroids administered nasally) will be allowed during the study follow-up only if clinically necessary (see Section 13 *Medical and Surgical Interventions*).
- Orally-inhaled steroids for control of asthma will be permitted.
- If infection is suspected at any time during the study, treatment with antibiotics will be permitted.

- Use of monoclonal antibodies is prohibited during the 365-day follow-up period.
- To the extent possible, subjects will be maintained on stable regimens of leukotriene inhibitors and/or immunotherapy (e.g., Montelukast, Zafirleukast, Zileuton) for allergies through Day 365, if currently on such regimens; however, use of breath-powered or other methods of intranasal steroid delivery for allergies is not permitted during the study.
- Use of drug-eluting implants (PROPEL®, PROPEL® Mini, PROPEL® Contour) is prohibited during the baseline procedure and throughout the 365-day follow-up period, unless placed immediately following RESS performed in the operating room setting.

All sinus-related and AE-related medications will be recorded in EDC, including their full brand/trade or generic names (whichever prescribed), dose, frequency, indication, start and end dates. Each AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and presented based on the system organ class (SOC) and preferred term.

13 MEDICAL AND SURGICAL INTERVENTIONS

Subsections below describe the rescue treatments consisting of medical and surgical interventions that will be allowed during the study follow-up based upon subject's symptomatic and endoscopic outcomes.

13.1 Medical Intervention

During study follow-up, high-dose steroids (e.g., oral, parenteral, injection, budesonide or other sinus steroid irrigations, rinses or drops, nebulized steroids administered nasally) may be used as a medical intervention in cases where a clinically significant increase or persistence in ethmoid sinus polyposis occurs, coupled with subject complaint of sinusitis symptoms that cause subject to request intervention.

If oral steroids are required for reasons other than, and not including, ethmoid sinus polyposis, a regimen is allowed. In either case, oral steroid intervention will be noted on the medication and follow up CRFs (see Section 16.5 *Handling Steroid or Surgical Interventions*).

13.2 Surgical Intervention

During study follow-up, surgical intervention (e.g., in-office polypectomy, RESS) may be required in cases where a clinically significant increase or persistence in ethmoid sinus polyposis occurs, coupled with subject complaints of sinusitis symptoms that cause subject to prefer sinus surgery.

Note: Subjects requiring medical or surgical interventions will be followed through the end of the study.

14 ASSESSMENT OF SAFETY

14.1 Specifications of Safety Parameters

Adverse events for each subject from the time the subject gives informed consent through Day 365 (end of study) will be recorded in EDC and monitored. Each AE will be evaluated by investigators in terms of seriousness, severity (i.e., mild, moderate, severe) and strength of relationship (i.e., not related, unlikely related, possibly related, related) to study drug, study device, and implant procedure. Each AE will be reviewed by sponsor personnel or contractors. The study sponsor is responsible for ensuring that all AEs are appropriately recorded and, when applicable, reported to the government(s), ethics committee(s) and other study centers per applicable regulations.

Subjects may experience a persisting set of symptoms associated with CS with nasal polyps and continue to present with symptoms during the timeframe after the baseline procedure. These may include symptoms such as facial pain or discomfort, headache, return of sense of smell, crusting, or epistaxis. Subjects with CS may also suffer from acute infectious and/or inflammatory exacerbations unrelated to the implant due to the natural course of their chronic sinusitis. Therefore, investigators should evaluate the occurrence of adverse events in this population with CS with the natural course of the disease in mind. Findings such as crusting, polyp persistence/formation or middle turbinate lateralization will not be considered as AEs since they are captured on the endoscopic grading forms.

14.2 Classification of Adverse Events

Severity of event

Sponsor will be responsible for determining whether an AE is expected or unexpected based on the nature, severity, or frequency of the event as previously described in the risk management documents for the investigational product. TEAE, SAE, SAR, SUSAR, UADE and USADEs are defined in *Section 3 Definitions of Terms.*

Relationship of adverse event

An adverse event related to the use of study implant, which includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This also includes any event resulting from user error or from intentional misuse of the implant. [BS EN ISO 14155]

Based on the 21 CFR 312 and BS EN ISO 14155, the relationship of all AEs to the implant will be categorized into:

- *Related*: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to

withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.

- *Possibly-related:* There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and be updated, as appropriate.
- *Unlikely-related:* A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- *Not-related*: The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the investigator.

Any AE that is determined by a participating investigator to be directly related (related and possibly-related) to the implant-procedure, device, or drug will be categorized as implant-related.

For implant-related AE (anticipated or unexpected/unanticipated), sponsor may request source documentation to confirm the relationship of the AE/SAR to the implant and may review such AE with an independent otolaryngologist, as needed.

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 implant-related.

Severity of adverse event

Severity of AEs will be graded per 21 CFR 312 as follows:

- *Mild*: If an AE requires minimal or no treatment and does not interfere with the participant's daily activities.
- *Moderate*: If an AE results in a low level of inconvenience or concern with the therapeutic measures. Moderate AEs may cause some interference with functioning.
- *Severe*: If an AE interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe AEs are usually potentially life-threatening or incapacitating.

14.3 Guidelines for Reporting of Adverse Events

Adverse event reporting

All AEs, regardless of seriousness or relationship to the implant, will be recorded in EDC and will include event description, date of onset, investigator's assessment of severity, relationship to investigational product, and date of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed through end of the study.

Any preexisting medical condition that is present at the time of screening will not be reported as an AE. The occurrence of a diagnostic or elective surgical procedures for a pre-existing condition will not be recorded as an AE, unless the condition become more severe or results in an AE

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The investigator should specify the date of onset, severity, action taken with respect to implant, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the implant.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The investigator should take appropriate measures to follow all AEs until resolution or until progression has been stabilized, to ensure the safety of the subjects. If the AE continues beyond the last planned visit per protocol, investigators should follow the subjects until AE resolution; stabilization and safety data will be recorded in the patient medical records.

When subject participation is prematurely discontinued, every attempt should be made to continue to collect safety data in the patient's medical records.

Serious adverse event reporting

All AEs that meet the criteria of an SAE must be reported to the sponsor based on the following timeline:

Type of Report	**Reporting Schedule**
Serious adverse event or Serious Suspected Adverse Reaction	Within 24 hours after becoming aware

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

All SAEs will be followed until satisfactory resolution; until the investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the sponsor and should be provided as soon as possible.

Drug and device serious adverse event reporting

The study sponsor is responsible for conducting an evaluation of all ADE/SAR throughout the study duration. Since S8 Sinus Implant is a single-entity combination product, the sponsor shall report to the FDA all device-related UADE within 10 working days and all SAE and SUSAR within 15 calendar days after the sponsor deems the adverse event to be reportable. Sponsor is also responsible to notify all reviewing IRBs and participating investigators within 10 days after such determination is made. Thereafter the sponsor shall submit any additional reports concerning the effect as FDA requests. The sponsor will notify FDA of any unexpected fatal or life-threatening AE/SAR as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

15 SAFETY INSTRUCTIONS

15.1 Contraindications

The S8 Sinus Implant is contraindicated in patients with:

- Suspected or confirmed intolerance to mometasone furoate.
- Known hypersensitivity to lactide, glycolide, or caprolactone copolymers

15.2 Warnings and Precautions

Refer to Section 5 of the S8 Sinus Implant Package Insert.

15.3 Adverse Reactions

Adverse reactions from placement of the S8 Sinus Implant may include:

- Epistaxis
- Nasal discomfort
- Facial pain
- Headache
- Parosmia
- Nasal odour
- Eye irritation
- Dizziness
- Rhinalgia

- Presyncope
- Nasal congestion

Refer to Section 6.2 of the S8 Sinus Implant Package Insert for additional potential risks or adverse events.

Risks relating to the insertion and removal procedure

Risks associated with the insertion and removal of the S8 Sinus Implant are similar to those associated with other endoscopic sinus procedures. These potential risks include:

- Facial pain, nasal pain or discomfort related to the use of topical or local anesthetic medications
- Vasovagal reaction associated with the application of topical or local anesthetic medications
- Facial pain, nasal discomfort or pain, minor oozing or bleeding related to suctioning, manipulation of polyps, lysis of adhesions related to insertion or removal of the implant
- Injury to the middle turbinate or other structures of the middle meatus or ethmoid sinus
- Injury to nerves or blood vessels
- Infection at the insertion site
- Implant migration from its intended location in the sinus in which it was placed

15.4 Patient Counseling

For best results, subjects will be advised as follows:

- To use nasal saline sprays or irrigations
- That the implant is bioabsorbable and intended to soften over time. As the implant softens and polyps decrease, the implant may be expelled out of the nose on its own or with actions such as sneezing or forceful nose blowing.
- To call the study investigator immediately if they experience any of the following:
- Excessive nasal bleeding or symptoms of infection, such as excessive pain or discomfort, persistent headache, increased sinus discharge.
- Symptoms suggesting the implant has migrated posteriorly, such as irritation or choking sensation in the back of the throat.

15.5 Potential Benefits from Study Participation

There may be no direct benefits from participating in the study. However, study patients will undergo an enhanced level of clinical scrutiny compared to routine clinical care for chronic sinusitis, which may provide some indirect health benefits.

When placed in post-ESS patients with symptoms of recurrent nasal obstruction, the implant is intended to provide an immediate onset of action by dilating the sinus tissue, creating an opening in the middle meatus and ethmoid sinus, providing for ventilation, drainage and reducing the perceived sensation of nasal obstruction/congestion. The addition of mometasone furoate to the implant is intended to reduce inflammation and polyps. Patients may benefit from these actions.

16 STATISTICAL CONSIDERATIONS

A formal Statistical Analysis Plan (SAP) will be prepared prior to the study database lock and formal data analysis. Following is a summary of the intended analyses.

16.1 Sample Size Calculation

The 50-patient sample size was selected based on clinical judgment. Based on the RESOLVE II study (data on file at Intersect ENT Inc.), ~90% of sinuses had polyps of grade 1 or higher at Day 90. Based on this data, of the 100 sinuses that undergo implant placement at baseline, greater than 85 sinuses are expected to undergo repeat placements at Day 90. This will provide safety data on up to 185 implant procedures (100 implants at baseline; 85 implants at Day 90), which is deemed to be a large enough sample to detect potential additional implant-related adverse events associated with recurrent use of the implant.

16.2 Analysis of Safety Measures

The incidence of AEs and SAEs through Day 365, including treatment emergent AEs (TEAE), implant-related AEs, UADE/USDAE, and SAR/SUSAR will be presented.

16.3 Analysis of Efficacy Endpoints

Patient-reported outcomes

Symptom scores and change from baseline in symptom scores will be summarized using descriptive statistics. Means, standard deviations (SD), medians, ranges and, where appropriate, 95% CI for the mean assuming a normal distribution will be presented at each timepoint.

Endoscopic outcomes

Endoscopic grades and change from baseline in endoscopic grades will be summarized using descriptive statistics. Means, standard deviations (SD), medians, ranges and, where appropriate, 95% confidence intervals (CI) for the mean assuming a normal distribution will be presented at each timepoint.

16.4 Analysis of Other Endpoints

Implant delivery success rate

Implant delivery success rate will be reported with descriptive statistics. The left and right sides of each patient will be considered independent, and each patient is expected to contribute up to 4 observations: 2 implants at baseline; between 1 and 2 observations during follow-up (maximum of 1 repeat placements in each ethmoid sinus).

Interventions received

All interventions received for ethmoid sinus obstructions will be tabulated and reported with descriptive statistics.

16.5 Handling Steroid or Surgical Interventions

Use of high-dose steroids (e.g., oral, parenteral, injection, budesonide or other sinus steroid irrigations or drops, nebulized steroids administered nasally) or surgical intervention during the study will be recorded and tabulated.

Note: Repeat S8 Sinus Implant at the protocol-specified Day 90 visit does not constitute a high dose steroid intervention.

16.6 Analysis Populations

All analyses will be conducted using the safety population defined as all subjects and sinuses that actually received the S8 Sinus Implant in a target sinus at baseline.

17 STUDY MANAGEMENT

17.1 Ethical Considerations

The rights, safety and well-being of subjects shall be protected in accordance with the ethical principles described in the Declaration of Helsinki. All parties are responsible for ethical conduct of the study in accordance with their respective roles in the investigation. The sponsor and the investigator(s) shall avoid improper influence or inducement of the study subject, monitor, the clinical investigator(s) or other parties participating in or contributing to the clinical investigation.

17.2 Sponsor Responsibilities

Intersect ENT, as the study sponsor, has the overall responsibility for the conduct of the study and will ensure that the study is conducted under the guidance of ICH Good Clinical Practice, Clinical investigation of medical devices for human subjects – Good clinical practice (BS EN ISO 14155: 2011) and other applicable local and federal (e.g., 21 CFR Parts 11, 50, 56, 312 and 812) regulations, including the archiving of essential documents. Qualified personnel who participate in the conduct of this clinical trial will be qualified by education and/or experience to

perform their tasks. Intersect ENT will not use, in any capacity, the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this clinical study.

17.2.1 **Training**

Sponsor personnel or designee will provide all investigators and sub-investigators with training on use of the S8 Sinus Implant prior to their participation in the clinical study.

The study center staff involved will undergo site initiation and training which will include:

- Study protocol
- Consenting procedures
- Package Insert
- Investigator responsibilities, including reporting requirements
- CRF completion guidelines
- EDC system
- Endoscopic grading scales, recording and video uploading.
- Investigational product accountability procedures
- Protection of subject confidentiality

17.2.2 **Protocol Deviation**

Any deviation from the requirements outlined in this protocol will be considered a protocol deviation. A protocol deviation that may affect the scientific soundness of the protocol or the rights, safety, or welfare of the patients should be reported to the sponsor and the Institutional Review Board or Ethics Committee as soon as possible. Other deviations are those that occur in direct association with a specific study patient. These include, but are not limited to, deviations from the informed consent process, inclusion/exclusion criteria, protocol-specified procedures and assessments, and investigational product handling and usage. All efforts should be made to avoid any protocol deviation.

17.2.3 **Monitor Responsibilities**

Study site monitoring will be performed by Clinical Research Associates (CRAs) from sponsor and contract CRAs who will be trained by sponsor. Study sites will be visited regularly to ensure that the study is conducted in compliance with 21 CFR Parts 50, 56, 312, 812, the study protocol and other applicable regulations. Study monitors will also ensure that the data reported in the Electronic Data Capture (EDC) system is consistent with the information found in the subject'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.

17.2.4 **Data Management Responsibilities**

Data management will be performed by sponsor.

Electronic data capture (EDC)

An EDC system will be utilized to capture study data and compliant with 21 CFR Part 11 and under the guidance of 'FDA Guidance for Industry: Computerized Systems Used in Clinical Investigations'. Data entry will be performed by site personnel after completing an appropriate training. Modifications to the EDC will be made if deemed necessary by the study sponsor.

Data cleaning

The database will be subject to initial inspection 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.

Data back-up, confidentiality and security

Incremental data back-up will be performed on a regular basis by the EDC system vendor. All media will be stored in a secure location. Passwords will be issued to appropriate personnel to ensure confidentiality and protection of data.

17.2.5 **Investigational Product Accountability**

An appropriate number of the investigational product, S8 Sinus 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 investigational product. 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 sponsor at the direction of the sponsor or at the close of the study.

17.3 Investigator Responsibilities

General responsibilities

- Each investigator is responsible for ensuring that an investigation is conducted per the signed investigator statement (form FDA1572), the study protocol, and applicable

regulations; for protecting the rights, safety, and welfare of study participants under the investigator's care; and for the control of drugs under investigation.

- Each investigator shall, obtain informed consent of each patient to whom the treatment is administered in accordance with provisions of 21 CFR part 50.
- Each investigator is responsible for all applicable IRB requirements under 21 CFR part 56.
- Each investigator and sub-investigators are responsible for disclosure of financial obligations to the sponsor.
- To ensure proper execution of the study protocol, each investigator will 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.
- Each investigator will allow auditing of their clinical investigation procedure(s) by the sponsor or designee.

Control and disposition of the investigational product

An investigator shall administer the product only to patients under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator. The investigator shall not supply the investigational product to any person not authorized to receive it. An investigator is required to maintain adequate records of the disposition of the product, including dates, quantity, and use by patients. All unused product must be returned to sponsor.

Maintenance of study records

Each investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each subject participating in the investigational plan (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 records such as x-rays, CT scans and video-endoscopies and associated reports (hard copy and digital copy of images, as available)
- Notes of phone calls and/or correspondence indicating study center's attempts to follow study patients at the required follow-up visits until their participation in the study is complete or terminated

- Records relating to subject deaths (e.g., death certificate, autopsy report)
- Printouts of source data generated by technical equipment (e.g., CT, endoscopy, MRIs) must be filed with the subject's records.
- Video of endoscopic procedures (screening, treatment and follow up assessments).

An investigator shall retain records required to be maintained for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed, records shall be retained for two years after the investigation is discontinued and FDA is notified. 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, sponsor should be contacted if the investigator plans to leave the study center, so that arrangements can be made for the handling or transfer of study records, or if the records are moved to an off-site location.

Required documents from study centers

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

- IRB study approval letter
- IRB approved informed consent
- fully executed clinical trial agreement (CTA)
- signed statement of investigator (form FDA 1572)
- financial disclosure form for the participating investigator(s)
- curriculum vitae (CV) for the participating investigator(s)
- current medical license for the participating investigator(s)
- principal investigator protocol acknowledgement form

A site may not begin active enrollment of patients until the documentation for the site principal investigator has been provided to sponsor and an initiation visit has been performed.

17.4 Protection of Subject 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 CRFs or other study related documentation to be provided to the study sponsor. It is the sponsor's policy to redact any subject's personally identifying information from any documentation sent to Sponsor that inadvertently contains it.

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 subject shall be preserved in the reports and in any publication. Each subject participating in this study will be assigned a unique identifier. All database forms and

source documents sent to the sponsor will be tracked, evaluated, and stored using only this unique identifier.

Investigators will maintain confidential study subject lists identifying all enrolled subjects. The investigators bear responsibility for keeping these lists current and confidential. These lists will not be provided to the study sponsor.

Monitors and auditors will have access to the study screening and enrollment logs and other personally identifying information of study subjects to ensure that data reported in the EDC corresponds to the person who signed the ICF and the information contained in the original source documents. Such personal identifying information may include, the subject's name, address, date of birth, gender, race and medical record number.

The subject'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 include age, race and gender.

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

17.5 Study Suspension or Early Termination

The study can be discontinued at the discretion of the investigator or study sponsor for reasons including the following:

- Occurrence of AE unknown to date in respect to their nature, severity, or duration, or the unexpected incidence of known AE
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Insufficient recruitment of subjects
- Investigational drug presents an unreasonable and significant risk to subjects (sponsor may terminate the study immediately)
- Persistent non-compliance with the study protocol
- Persistent non-compliance with the applicable ethics committee or regulatory requirements

If the study is discontinued or suspended prematurely, the sponsor shall promptly inform all clinical investigators and study centers of the termination or suspension and the reason(s) for termination. 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 and/or investigation centers. Regulatory authorities and the subject's physicians may also need to be informed, if deemed necessary.

17.6 Site Closeout

At the time of the site close-out visit, the monitor will have ensured all outstanding study documents are reconciled, the investigator's files are accurate and complete, have reviewed record retention requirements with the investigator, made a final accounting of all study supplies, and ensured 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.

17.7 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 subject'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 subject confidentiality.

The study centers are 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 sites any patterns of non-compliance. The sponsor will work with the sites to determine any necessary corrective action, as applicable. The sponsor will continue to monitor sites until compliance has been secured. If the site continues to display non-compliance, more serious action may be taken by the sponsor. The study protocol, data-recording procedures, data handling and study reports are subject to an independent clinical Quality Assurance audit by sponsor, its designee, or health authorities.

Approved informed consent form: protection of study subjects

An IRB must review and approve an ICF specific to this study. Sponsor 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 sponsor. 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 subject should be maintained by the site for monitoring.

Subjects will be informed both verbally and in writing (i.e., ICF) about the nature of the study, the anticipated risks and benefits involved and the discomfort to which they will be exposed. They will be instructed about their right to discontinue their participation at any time without prejudice or jeopardy to future medical care. They must confirm consent in writing prior to any screening procedures. A copy of the informed consent form will be provided to the subject.

Institutional review board approval

IRB approval of study protocol and ICF is required prior to study commencement under 21 CFR Part 56. Investigators must also obtain renewal of IRB approval throughout the duration of the study. Investigators are responsible for fulfilling any conditions of approval imposed by the

reviewing IRB, such as regular reporting, study timing, etc. Investigators will provide the study sponsor with copies of such approvals and reports.

Other investigator reports

Investigators are responsible for notifying the sponsor of the following:

Type of Notification	Timeline
Withdrawal of IRB Approval	Within 24 hours of becoming aware
Informed Consent not Obtained	Within 24 hours of becoming aware

Notifications must identify subjects using the unique study identifier to protect subject's confidentiality.

17.8 Final Clinical Study Report

A final clinical study report (CSR) will be prepared by the study sponsor and provided to the regulatory agency.

17.9 Publication Policy

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

18 APPENDIX

Appendix A. List of medications considered as high-dose steroids

Trade Name (alphabetic order)	**Generic Name**	**Route of Administration**
Budesonide Pulmicort Respules	Prednisone (Budesonide) Budesonide	Nasal (e.g., irrigations, rinses)
Dexamethasone	Dexamethasone	Intramuscular Oral
Decadron Dexamethasone	Dexamethasone	Intravenous or oral Nasal irrigations/rinses
Depo Medrol Medrol Medrol Dosepak Methylprednisolone	Methylprednisolone Methylprednisolone Acetate	Oral Parenteral routes (e.g., intra-articular, intra-cervical)
Fluticasone	Fluticasone Propionate Fluticasone Propionate w/Salmeterol	Nasal irrigations
Kenalog	Triamcinolone Triamcinolone Acetonide	Intramuscular Subcutaneous Submucosal
Prednisone	Prednisone	Intramuscular Oral

Note for CRAs, data managers, biostatisticians: The above table is for reference purposes only and not a comprehensive list. Any questionable cases should be reviewed individually.

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