The ASCEND Study

A Clinical Evaluation of the UP Drug-Coated Device in Patients with Chronic Rhinosinusitis

Signature Page

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CLINICAL STUDY PROTOCOL

1 TITLE PAGE

Study Title	The ASCEND Study: A Clinical Evaluation of the UP Drug-Coated Device in Patients with Chronic Rhinosinusitis
Protocol Number	P500-0118
Investigational Device	UP Drug-Coated Device (mometasone furoate, 3000 mcg)
Study Design	Prospective, multicenter, clinical trial, enrolling patients into two consecutive cohorts: a PK cohort and a randomized, blinded, intra-patient controlled cohort
Sponsor's Name and Address	Intersect ENT, Inc. 1555 Adams Drive Menlo Park, CA 94025 USA Tel: +1 650-641-2100 Fax: +1 650-641-2053
National Principal Investigator	Boris Karanfilov, MD Director, The Ohio Sinus Institute 5378 Avery Road Dublin, OH 43016 USA Name and address of each participating clinical investigator will be maintained on file by Intersect ENT
Data Management and Study Monitoring	Intersect ENT, Inc.
Biostatistics and Data Analysis	Intersect ENT, Inc.

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 ISO 14155) and other applicable local and federal regulations, including the archiving of essential documents.

Revision History:

Revision	Revision Date	Summary of Changes
1.0	15 Feb 2018	Initial release
2.0	23 Mar 2018	• Renamed pilot to Randomized cohort • Increased sample size of Randomized cohort to 70 subjects and 10 study centers • Added language to allow dilation of the maxillary or sphenoid sinus with the same Sinus Dilation Device after successful dilation of both frontal sinuses, if necessary • Updated sample size justification, analysis of the primary efficacy endpoint, analysis of secondary endpoints, and sensitivity analysis for the primary efficacy endpoint • Added definitions of safety, intent-to-treat, and per-treatment-evaluable populations • Added inclusion criteria to confirm bilateral obstruction of the FSO on endoscopy at baseline • Updated list of compatible devices • Several editorial changes for consistency throughout the protocol
3.0	05 Apr 2018	• Corrected error in the flow diagram – number of subjects changed from N=50 to N=70; pilot cohort corrected to randomized cohort • Removed 'stenosed' in the study objective and design sections
4.0	26 Apr 2018	• Increased the number of enrolling sites for the PK cohort to up to 3 study centers and indicated PK enrollment first • Updated study population to include only patients who had prior endoscopic sinus surgery (> 30 days with a healed mucosa), including ethmoidectomy and uncinectomy • Edited inclusionary criteria to disallow any additional surgical interventions at the baseline balloon dilation procedure • Edited exclusionary criteria to disallow patients with cystic fibrosis • Included assessment of urinary cortisol over 24 hours at baseline (pre-procedure) and 24 hours after the baseline procedure (post-procedure) towards additional safety assessment in the PK cohort • Included descriptive statistics for analysis of safety measures

		• Updated concomitant medications in the synopsis to match the body of the protocol • Updated flow diagram and schedule of assessments table for PK cohort to include urine analysis at baseline and Day 1 post-procedure; separated screening and baseline visits • Deleted reference to investigator brochure for site training (Section 17.2.1)
5.0	21 June 2018	• Added Day 60 follow-up visit to the Randomized cohort and updated relevant sections throughout the protocol to include Day 60 visit • Updated Day 30 visit window from ± 3 days to ± 2 days in the Randomized cohort • Modified inclusionary criteria to allow CT scan confirming bilateral frontal disease within 30 days prior to randomization in the Randomized cohort instead of 30 days prior to enrollment • Updated compatible accessory devices and baseline procedure steps to include an optional use of sinus guide catheter handle • Updated baseline procedure steps to align with the IFU • Removed IFU as an appendix to the ASCEND protocol • Updated reference to “guidewire” to “lightwire” throughout protocol • Updated baseline procedure description to allow for dilation of the maxillary and/or sphenoid sinus, if clinical necessary in the Randomized cohort, with a commercially available balloon sinuplasty device prior to randomization
6.0	22 October 2018	• Updated the name of the investigational device to UP Drug-Coated Device and the name of the control device to the ‘UP Control Device’ • Changed the timepoint of the primary efficacy endpoint in the randomized cohort from Day 30 to Day 14 • Added video-endoscopy grading by an independent reviewer at Day 14 • Updated exclusion criteria (a) to exclude patients with ethmoid polyposis of grade ≥ 2 • Removed the assessment of estimated FSO diameter post-dilation following the baseline procedure • Added a 14-day restriction for use of oral steroids, budesonide or other steroid irrigations/rinses or drops, and nebulized

		steroids administered nasally, prior to the baseline procedure in the randomized cohort • Updated required use of saline sprays/rinses/irrigations starting on Day 2 in all subjects in the randomized cohort • Updated allowance of intranasal corticosteroid sprays after Day 14 if medically necessary in the randomized cohort • Updated Day 60 visit window from ± 3 days to ± 7 days in the randomized cohort • Modified inclusion criteria (f) to allow dilation of the maxillary and/or sphenoid sinus with a commercially available sinus dilation device, if clinically necessary, prior to randomization in the randomized cohort. • Modified inclusion criteria (k) to include optional use of a frontal sinus seeker to assess feasibility of balloon dilation of the FSO • Added a section to describe the personnel and measures to achieve blinding in the randomized cohort • Increased the number of enrolling sites for the randomized cohort to up to 12 study centers
7.0	12 November 2018	• Changed the timepoint of the primary efficacy endpoint in the randomized cohort from Day 14 to Day 30 • Added definition of acute rhinosinusitis to Section 3: Definition of terms • Clarified the use of corticosteroid-eluting implants (including PROPEL®, PROPEL® Mini, PROPEL® Contour and SINUVA® Sinus Implant) is prohibited 14 days prior to baseline
8.0	04 April 2019	• Increased the number of enrolling sites for the randomized cohort to include up to 15 study centers • Modified inclusion criterion (k) to confirm access of each FSO with a light-assisted or image-guided instrument such as a frontal sinus seeker • Modified exclusion criterion (p) to disallow patients who have glaucoma with intraocular pressure > 21 mm Hg even with pressure lowering medication

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2 LIST OF ABBREVIATIONS

Abbreviations	Expansion
ADE	adverse device effect
AE	adverse event
AERD	aspirin exacerbated respiratory disease
ARS	acute rhinosinusitis
ASADE	anticipated serious adverse device effect
BSD	balloon sinus dilation
CFR	Code of Federal Regulations
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRA	clinical research associate
CRF	case report form
CRS	chronic rhinosinusitis
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
FSO	frontal sinus ostium/ostia
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'
IFU	instructions for use
INCS	intranasal corticosteroids
IRB	institutional review board
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous
LLOQ	lower limit of quantification
MF	mometasone furoate
PTE	per-treatment-evaluable
RESS	repeat endoscopic sinus surgery
SAE	serious adverse event
SADE	serious adverse device effect
SNOT-22	Sino-Nasal Outcome Test
UADE	unanticipated adverse device effect
USADE	unanticipated serious adverse device effect

3 DEFINITIONS OF TERMS

Term	Definition
Adverse device effect (ADE)	Adverse event related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. [BS EN ISO 14155]
Adverse event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device [BS EN ISO 14155]
Adhesion/scarring grading scale for the ethmoid sinus	Adhesion/scarring severity in the ethmoid sinus 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
Adhesion/scarring grading scale for the FSO	Adhesion/scarring in the frontal sinus ostium/ostia (FSO) assessed on a 4-point scale as follows: 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)
Acute rhinosinusitis (ARS)	Per the 2016 "International Consensus Statement on Allergy and Rhinology" definition, patient must have ≤ 4 weeks of symptomatic inflammation of the paranasal sinuses and nasal cavity.
Aspirin exacerbated respiratory disease (AERD)	Aspirin exacerbated respiratory disease, also known as Samter's Triad, is a chronic medical condition that consists of three clinical features: asthma, sinus disease with recurrent nasal polyps, and sensitivity to aspirin and other non-steroidal anti-inflammatory drugs.
Case report form (CRF)	Standardized forms designed to capture study data as required by the protocol.
Chronic rhinosinusitis (CRS)	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 Nasal discharge (anterior/posterior) o Nasal blockage/obstruction/congestion

Term	Definition
	○ Reduction/loss 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
Device malfunction	Investigational device: Failure to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical investigation plan. [BS EN ISO 14155] Compatible accessory devices: Failure 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. [21 CFR 803]
Enrolled	Subjects are considered enrolled upon signing the informed consent form.
Estimated FSO diameter	Smallest and largest diameters of the FSO are estimated endoscopically by probing with a 3-mm olive-shaped frontal sinus suction tip and reported in mm.
Inflammation score	For the purpose of the endoscopic scoring method in this study, the term inflammation is a global descriptor defined to include mucosal edema, erythema hypertrophy and/or polypoid changes. The inflammation present in the frontal recess/FSO is estimated visually based on the endoscopic examination on a scale ranging from 0 (no visible inflammation) to 100 (severe inflammation) involving extensive erythema, edema, or polyposis.
Intent-to-treat population	Consists of all subjects in whom a sinus dilation was attempted. An attempt occurs when the physician introduces the delivery system into the subject's nostril with the intent of dilation.
Patency grading scale for the FSO	Patency of the FSO assessed endoscopically by probing with a 3-mm olive-shaped frontal sinus suction tip ("suction tip") and graded on a 5-point scale as follows: 0: Occluded (no opening visible) 1: Significantly stenosed (not occluded, but unable to pass the 3-mm suction tip) 2: Moderately stenosed (able to easily pass the 3-mm suction tip with no additional space around it) 3: Minimally stenosed (able to easily pass the 3-mm suction tip with additional 1-2 mm space around it) 4: Completely patent (able to easily pass the 3-mm suction tip with additional > 2 mm space around it)
Per-treatment-evaluable (PTE) population	Consists of all randomized patients who have received the assigned study device in the target sinus, who have no major procedural protocol deviations and for whom follow-up data are available.

Term	Definition
Polyp grading scale for the ethmoid sinus	Polyps originating from the ethmoid sinus assessed endoscopically and graded on an 8-point scale ranging from 0 to 4 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 completely obstructing the nasal cavity
Polypoid edema grading scale for the FSO	Polypoid edema in the frontal recess/FSO is assessed on a 4-point scale as follows: 0: Normal mucosa, no visible polyps/mucosal edema 1: Minimal amount of polyps/mucosal edema 2: Moderate amount of polyps/polypoid edema 3: Expanded amount of polyps/polypoid edema
Safety population	Consists of all subjects exposed to investigational device with successful dilation of at least one FSO
Serious adverse event (SAE)	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 illness or injury; or • Permanent impairment of a body structure or a body function; or • Inpatient hospitalization or prolongation of existing hospitalization; or • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function; or • Fetal distress, fetal death, 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. [BS EN ISO 14155]
Serious adverse device effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. Anticipated serious adverse

Term	Definition
	device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Sino-Nasal Outcome Test (SNOT-22)	Validated, disease-specific, symptom-scoring instrument consisting of 22 questions, each scored by patient on a 6-point scale 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 The maximum total score for all symptoms is equal to 110.
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 documents containing source data.
Subject	An individual who participates in a clinical investigation.
Successful dilation of the FSO	Insertion of the UP Device into the targeted FSO followed by 2 consecutive complete inflations of the balloon.
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. [21 CFR 812]
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. [BS EN ISO 14155; 21 CFR 812]
Use error	Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user NOTE: Use error includes slips, lapses, and mistakes. An unexpected physiological response of the subject does not in itself constitute a use error. [BS EN ISO 14155]

4 PROTOCOL SUMMARY

Study Title	The ASCEND Study: A Clinical Evaluation of the UP Drug-Coated Device in Patients with Chronic Rhinosinusitis
Objective	To assess the safety, performance, and efficacy of the UP Drug-Coated Device when used in chronic rhinosinusitis (CRS) patients undergoing balloon dilation of frontal sinus ostia (FSO)
Investigational Device	UP Drug-Coated Device (mometasone furoate, 3000 mcg) and UP Control Device (together referred to as "UP Device") are balloon dilation devices intended to dilate the peripheral sinus ostia. The UP Drug-Coated Device is intended to dilate and locally deliver steroids to the frontal sinus ostia to maintain patency in patients ≥ 18 years of age.
Study Design	Prospective, multicenter, clinical trial enrolling and treating a total of **75** subjects in two cohorts: • *PK cohort* (N=5): A non-randomized cohort to assess the systemic safety and performance of the UP Drug-Coated Device for in-office bilateral dilation of the FSO (2 inflations in each FSO for a total of 4 inflations per device). Subsequently, the UP Drug-Coated Device may be used to dilate any sphenoid or maxillary sinuses. • *Randomized cohort* (N=70): A randomized, intra-patient controlled, blinded cohort of 70 subjects to assess the safety and efficacy of the UP Drug-Coated Device used for in-office dilation of the FSO. The FSO randomized to the treatment (Treatment) will undergo dilation using the UP Drug-Coated Device (2 inflations per device) while the contralateral FSO (Control) will be dilated with a UP Control Device (2 inflations per device).
Subject Enrollment	*PK cohort*: 5 subjects at up to 3 study centers. *Randomized cohort:* 70 subjects at up to 15 study centers across the U.S. The PK cohort will enroll first.
Study Population	Patients ≥ 18 years of age with chronic rhinosinusitis (CRS) who had prior endoscopic sinus surgery (ESS) including ethmoidectomy and uncinectomy and are candidates for balloon dilation because they present with bilateral stenosis of the frontal recess/FSO due to scarring or polypoid edema, confirmed on endoscopy.

Eligibility Criteria	**Key inclusion criteria:**
	• Confirmed diagnosis of CRS per the 2016, "International Consensus Statement on Allergy and Rhinology" definition. Patient must have ≥ 12 weeks of:
	  ○ Two or more of the following symptoms:
	  ▪ nasal discharge (anterior/posterior)
	  ▪ nasal blockage/obstruction/congestion

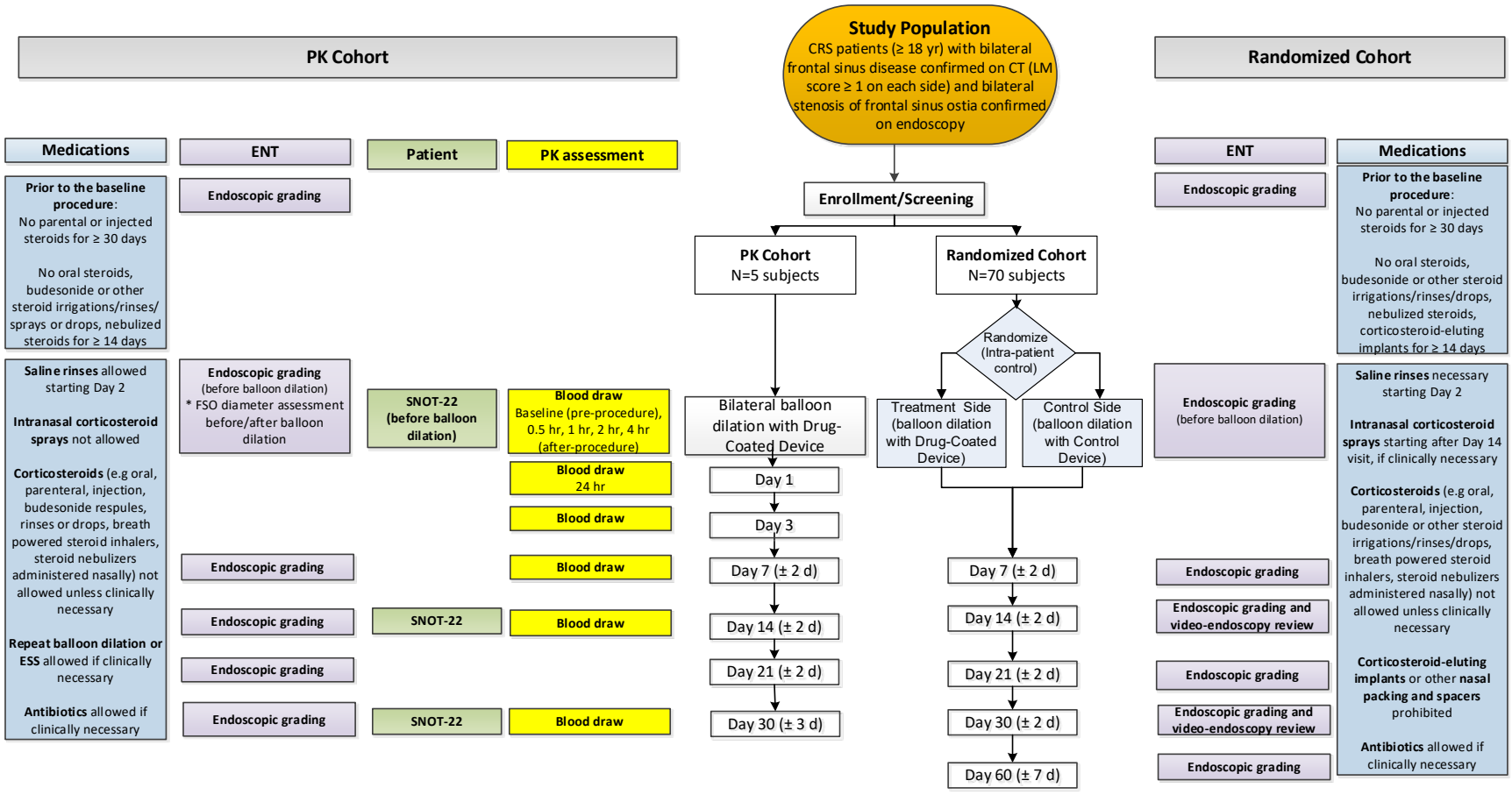
	▪ reduction/loss sense of smell ▪ Facial pressure/pain o And one or more of the following findings: ▪ Evidence of inflammation on paranasal sinus examination or computed tomography (CT) ▪ Evidence of purulence coming from paranasal sinuses or ostiomeatal complex • Bilateral disease in the frontal sinuses (Lund-Mackay score ≥ 1 on each side) on CT scan within 30 days prior to enrollment in the PK cohort and prior to randomization in the randomized cohort. • Patient has bilateral obstruction of the frontal recess/FSO due to scarring and/or polypoid edema confirmed on endoscopy (patency grade of 0 or 1 for each FSO). • Balloon dilation of the FSO judged to be feasible (use light-assisted or image-guided instrument such as a frontal sinus seeker tip to confirm access of each FSO) and medically appropriate. • Patient has had prior ESS (> 30 days with a healed mucosa) including bilateral ethmoidectomy (anterior or total) and uncinectomy for better visualization of the FSO. Note: No additional surgical interventions will be allowed at baseline/procedure. Dilation of the maxillary and/or sphenoid sinus can be performed with a commercially available sinus dilation device, if clinically necessary, prior to randomization in the randomized cohort. **Key exclusion criteria:** • Expanded amount of ethmoid polyposis (grade > 2 PK cohort, grade ≥ 2 randomized cohort) • Complications from prior ESS or balloon dilation procedure (e.g., cerebrospinal fluid leak or injury to the skull base) • History of aspirin exacerbated respiratory disease (AERD) • Patient is a current smoker • History of allergy or intolerance to mometasone furoate • Oral-steroid dependent condition • Evidence of acute rhinosinusitis, invasive fungal sinusitis or another disease or condition expected to compromise survival or ability to complete assessments during the 30-day follow-up period in the PK cohort and during the 60-day follow-up period in the randomized cohort • Use of parenteral and injected steroids (e.g., Kenalog) 30 days prior to the baseline procedure • Use of oral steroids, budesonide or other sinus steroid irrigations/rinses or drops, nebulized steroids administered nasally 14 days prior to screening in the PK cohort and prior to baseline in the randomized cohort
Primary Endpoints	*PK cohort*: Successful dilation of attempted FSO using the UP Drug-Coated Device with no unanticipated serious adverse device effects (USADE)

	Randomized cohort: Difference in the patency grade of the FSO between treatment sides at Day 30, as determined by an independent, blinded sinus surgeon based on the centralized video-endoscopy review
Secondary Endpoints	**Endoscopic endpoints in the FSO by clinical investigators** at specified timepoints through Day 30 in the PK cohort and through Day 60 in the randomized cohort: • Estimated diameter, smallest and largest (mm) • Frequency and grade of patency (5-point categorical scale) • Inflammation (0-100 scale) • Frequency and severity of adhesion/scarring (4-point categorical scale) • Frequency and grade of polypoid edema (4-point categorical scale) • Need for and frequency of post-dilation interventions (e.g., medical, repeat dilation, surgical) **Endoscopic endpoints in the FSO by independent reviewer** in the randomized cohort: • Estimated diameter, smallest and largest (mm) at Day 14 and Day 30 • Frequency and grade of patency at Day 14 and frequency of patency at Day 30 (5-point categorical scale) • Inflammation (0-100 scale) at Day 14 and Day 30 • Frequency and severity of adhesion/scarring (4-point categorical scale) at Day 14 and Day 30 • Frequency and grade of polypoid edema (4-point categorical scale) at Day 14 and Day 30 • Need for and frequency of post-dilation interventions (e.g., medical, repeat dilation, surgical) at Day 14 and Day 30 **Patient-reported outcomes (PK cohort only):** • Change from baseline to Day 14 and Day 30 in Sino-Nasal Outcome Test (SNOT-22) scores
Safety Evaluation	*PK cohort*: • Measurement of plasma concentrations of MF and cortisol at baseline before the baseline procedure (dilation) and at 0.5, 1, 2, 4, and 24 hours after dilation, and again in the morning of Days 3, 7, 14 and 30 o A validated bioanalytical method for human plasma MF with a lower limit of quantification (LLOQ) of 0.25 pg/mL o A validated bioanalytical method for cortisol with a LLOQ of 1.00 ng/mL • Measurement of urinary cortisol excretion for 24 hours prior to the baseline procedure and for 24 hours after the baseline procedure o A validated bioanalytical method for human urinary cortisol with a LLOQ of 1.00 ng/mL

	All adverse events reported by subjects between enrollment and Day 30 (end of study) will be tabulated. *Randomized cohort*: All adverse events reported by subjects between enrollment and Day 60 (end of study) will be tabulated.
Concomitant Medications	• Leading up to the baseline procedure, there is a 30-day restriction for **use of parenteral and injected steroids** (e.g., Kenalog). • Leading up to the baseline procedure, a 14-day restriction for **use of oral steroids, budesonide or other sinus steroid irrigations/rinses or drops, nebulized steroids** administered nasally. • After the baseline procedure, subjects will be allowed in the PK cohort and required in the randomized cohort to use **saline sprays/rinses/irrigations** starting from Day 2. • If infection is suspected at any time during the study, treatment with **antibiotics** will be permitted. • Use of **intranasal corticosteroid** (INCS) sprays will be allowed starting after Day 14 visit in the randomized cohort, if medically necessary, and not allowed throughout the 30-day follow-up duration in the PK cohort. • Use of **other corticosteroids** (e.g., oral, parenteral, injections, budesonide or other sinus steroid irrigations/rinses or drops, breath powered steroid delivery [e.g. XHANCE™, fluticasone proprionate], nebulized steroids administered nasally) will not be permitted during the study follow-up unless clinically necessary. • Use of **orally-inhaled steroids** for control of asthma will be permitted, if already on such medications. • Use of **corticosteroid-eluting sinus implants** (PROPEL®, PROPEL® Mini, PROPEL® Contour, SINUVA® Sinus Implant) or other **nasal packing and spacers** is prohibited 14 days prior to baseline and during the baseline procedure and through Day 30 in the PK cohort and through Day 60 in the randomized cohort. • To the extent possible, subjects will be maintained on stable regimens of leukotriene inhibitors and/or **immunotherapy** for allergies, if currently on such regimens.
Follow-up	*PK cohort*: Each subject will return for 6 follow-up visits at Days 1 (24 hr collection), 3, 7, 14, 21 and 30. All blood draws during follow-up should occur in the morning. *Randomized cohort:* Each subject will return for 5 follow-up visits at Days 7, 14, 21, 30 and 60. Subjects in both cohorts 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, and/or sinus-related adverse events requiring medical evaluation.

Duration of Study Period	For a given subject in the PK cohort: Approximately 32 days = screening visit (1 day) + baseline/procedure (1 day) + follow-up (30 days) For a given subject in the randomized cohort: Approximately 62 days = screening visit (1 day) + baseline/procedure (1 day) + follow-up (60 days) Overall: Approximately 8 months = 6-month enrollment phase + 2-month follow-up.

5 STUDY FLOW DIAGRAM



Abbreviations: CT, computed tomography; FSO, frontal sinus ostia; LM, Lund-Mackay score; SNOT-22, Sino-nasal Outcome Test

6 SCHEDULE OF ASSESSMENTS

6.1 PK Cohort

Assessment	**Screening**	**Baseline/ Procedure**	**Day 1**	**Day 3**	**Day 7** (±2 d)	**Day 14** (±2 d)	**Day 21** (±2 d)	**Day 30** (±3 d)
Informed consent	**X**							
Medical/surgical history	**X**							
CT scan (≤ 30 days prior to enrollment)	**X**							
Blood sample collection (~11 ml)		**X**[a]	**X**[b]	**X**[b]	**X**[b]	**X**[b]		**X**[b]
24-hour urine collection		**X**[c]	**X**[c]					
In-office bilateral FSO dilation		**X**						
Endoscopic grading and recording	**X**	**X**[d]			**X**	**X**	**X**	**X**
Sino-Nasal Outcome Test (SNOT-22)		**X**[d]				**X**		**X**
Concomitant medications	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse event reporting	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Urine pregnancy test (female subjects of childbearing potential)	**X**[e,f]	**X**[e,f]						
Documented birth control (female subjects)			**X**	**X**	**X**	**X**	**X**	**X**

Abbreviations: CT, computed tomography; d, days; FSO, frontal sinus ostium/ostia; min, minutes; ml, milliliter.

a. Blood draws to occur at baseline, before balloon dilation procedure and again at Hour 0.5 (±5 min), 1 (±5 min), 2 (±10 min), and 4 (±15 min) after the end of baseline procedure
b. All blood draws should occur in the morning and at approximately the same time of the day during the follow-up visits. Day 1 blood draw to occur 24 hours (±3 hours) after the baseline procedure. Day 3 blood draw to occur 72 hours (±3 hours) after the baseline procedure
c. Urine samples will be collected for a 24-hour duration prior to the baseline visit (pre-procedure) and for a 24-hour duration following the baseline procedure (post-procedure)
d. All endoscopic assessments and SNOT-22 performed prior to the baseline procedure, except for the FSO diameter, which must be performed before and after the balloon dilation procedure.
e. Female subjects with reproductive potential are required to undergo a urine pregnancy test at screening and prior to the baseline procedure.
f. Female subjects are required to confirm their nursing status at screening and baseline

6.2 Randomized Cohort

Assessment	**Screening**	**Baseline/ Procedure**	**Day 7** (±2 d)	**Day 14** (±2 d)	**Day 21** (±2 d)	**Day 30** (±2 d)	**Day 60** (±7 d)
Informed consent	**X**						
Medical/surgical history	**X**						
CT scan (≤ 30 days prior to randomization)		**X**					
In-office bilateral FSO dilation		**X**					
Endoscopic grading and recording	**X**	**X**[a]	**X**	**X**	**X**	**X**	**X**
Video-endoscopy grading (independent reviewer)				**X**		**X**	
Concomitant medications	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse events reporting	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Urine pregnancy test (female subjects of childbearing potential)	**X**[b,c]	**X**[b,c]					
Documented birth control (female subjects)			**X**	**X**	**X**	**X**	**X**

Abbreviations: CT, computed tomography; d, day; FSO, frontal sinus ostium/ostia.

[a] All endoscopic assessments performed prior to baseline procedure.

[b] Female subjects with reproductive potential are required to undergo a urine pregnancy test at screening and prior to the baseline procedure.

[c] Female subjects are required to confirm their nursing status at screening and baseline.

7 BACKGROUND INFORMATION

7.1 Chronic Rhinosinusitis, Treatment Options and Unmet Clinical Need

Chronic rhinosinusitis (CRS) is defind as sinonasal inflammation persisting for more than 12 weeks. Sinusitis is one of the most prevalent chronic diseases, affecting about 12% of the adult population (Blackwell 2014). It causes a significant burden to the society at large (Rudmik 2014), as well as to the patient in terms of economics (Bhattacharyya 2011; Caulley 2015) and quality of life (Soler 2011). The cardinal symptoms of CRS include nasal congestion, nasal drainage (mucopurulence draining anteriorly or posteriorly), facial pain or pressure, and decrease or loss of sense of smell (Orlandi 2016). Addressing the underlying causes of CRS and controlling the symptoms caused by the inflammatory process have been the focus of medical therapy. Medical management of CRS includes intranasal corticosteroids, supplemented with a combination of antihistamines, antibiotics and/or oral steroids (Orlandi 2016). Patients who fail to respond to medical therapy may be referred for endoscopic sinus surgery (ESS) to improve ventilation and mucociliary clearance through the natural ostia (Fokkens 2012).

ESS has been demonstrated to improve patient-reported symptoms and quality of life in select patients with CRS who have persistent symptoms despite appropriate medical therapy. Longer-term success rates for primary ESS are as high as 98% (Ramadan 1999; Senior 1998). However, the surgical outcomes are compromised by incomplete surgery, postoperative inflammation and adhesions, and recurrence of polyposis, which often require meticulous postoperative debridement and effective medical management (Bhattacharyya 2004; Senior 1998). While ESS with traditional instrumentation has been effective at enlarging the ostia, balloon dilation is increasingly used as either a stand-alone procedure or as part of a hybrid surgery with traditional methods (Chaaban 2017; Svider 2017). This is particularly true when treating the frontal sinus where stenosis of the neo-ostium is a common sequela.

Fueled by the need for minimally invasive, mucosa-sparing techniques, a catheter-based approach was introduced to reduce mucosal trauma, prevent scarring, bleeding and associated sequelae. Balloon sinus dilation (BSD) is a minimally invasive sinus surgery procedure to mechanically dilate the obstructed sinus ostia by inflating the balloon in the target sinus ostia. BSD displaces and compresses mucosa and causes microfracture of the underlying circumferential bone, enlarging the sinus ostia and improving drainage. Patients treated with BSD have been shown to have faster recovery, have less postoperative pain, and require fewer debridements than those undergoing traditional ESS (Catalano and Payne 2009; Chandra 2016; Levine 2008).

The safety and effectiveness of BSD in the paranasal sinuses have been evaluated in several clinical studies in treatment of stenosed peripheral sinuses in CRS patients (Achar 2012; Bikhazi 2014; Bolger 2007; Cutler 2013; Friedman 2008; Koskinen 2017; Kuhn 2008; Levine 2008; Plaza 2011; Weiss 2008). While the device is low risk with no major intraoperative complications (Koskinen 2017; Levine 2008), a known response to the dilation itself is periosteal mucosal edema and ostial narrowing post-dilation (Bolger 2007).

Intersect ENT has developed the UP Drug-Coated Device which is a drug coated sinus dilation device intended to dilate and locally deliver drug to the treated sinus ostia in CRS patients. The

device is coated with 3000 mcg of the corticosteroid (MF), to help minimize edema/inflammation following the sinus dilation procedure.

7.2 Investigational Device

Intended use

The UP Drug-Coated Device is intended to dilate and locally deliver steroids to the frontal sinus ostia to maintain patency in patients ≥ 18 years of age.

Device description

The UP Drug-Coated Device and the UP Control Device (hereafter referred to as "UP Device") are over-the-wire sinus balloon catheters with a balloon at the distal end (with or without MF-coating). **Figure 1** depicts a schematic representation of the UP Device. On the proximal end of the device, there are two primary ports: the first port is compatible with an inflation device that is used to inflate the balloon with saline for sinus dilation; and the second port is intended to be used with a compatible lightwire and guide catheter to confirm access into the target sinus. The usable working length is 207 mm.

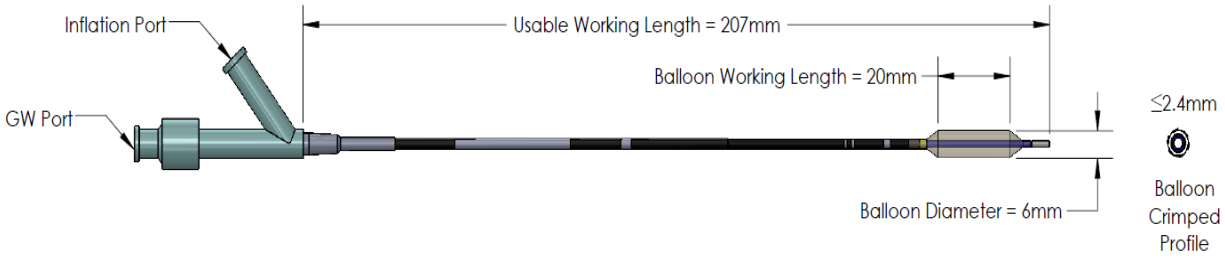


Figure 1: Schematic of the UP Device

Balloon catheter

The UP balloon catheter is shown in **Figure 2** and comprises a nylon balloon and distal shaft with markers to denote balloon distance from the guide catheter. The shaft markers on the distal end of the catheter aid in proper placement. The yellow marker denotes the proximal end of the balloon and the white markers are spaced 1 cm (single band) and 2 cm (double band) away from the proximal end of the balloon. The UP Device has a soft atraumatic distal tip. The balloon diameter is 6 mm in diameter and the 20 mm of working length when inflated to a pressure of 12 atmospheres (atm).

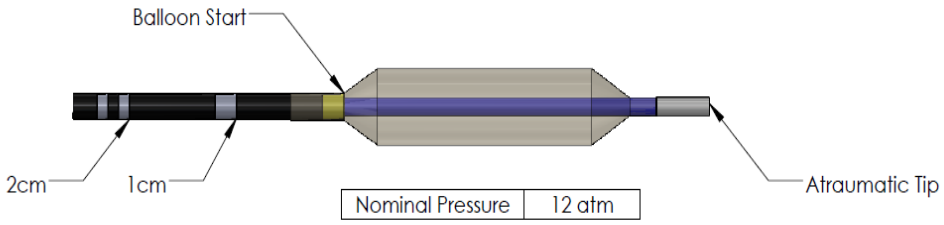


Figure 2: Schematic of the UP Balloon Catheter

Balloon coating

UP Drug-Coated Device: The coating on the balloon of the UP Drug-Coated Device contains 3000 mcg of mometasone furoate (the active ingredient) in a polymer matrix of polyethylene glycol and polysorbate (inactive ingredients). The coating on the balloon is hydrophilic and designed to provide immediate release of MF during dilation into the apposing sinus mucosa. The device locally delivers drug to the treated sinus ostia to reduce edema/inflammation following sinus dilation.

UP Control Device: Similar to the UP Drug-Coated Device, the UP Control Device is an over-the-wire sinus balloon catheter. The UP Control Device does not contain drug and is identical to the UP Drug-Coated Device with respect to dimensions of the balloon.

No changes in the investigational device are anticipated during the study. Any changes in the investigational device during the conduct of the study will be documented and maintained by Intersect ENT.

Compatible accessory devices

The UP Device is intended to be used with 0.035" compatible lightwire (e.g., Relieva Luma® Sentry Sinus Illumination System), 70° sinus guide catheters (e.g. Relieva Flex™ Sinus Guide Catheter Tip, F-70 C), compatible inflation device (e.g., Acclarent® SE Inflation Device) and the sinus guide catheter handle (e.g., Relieva Sidekick Sinus Guide Catheter Handle (Low Profile) [Sidekick LP]).

7.3 Summary of Preclinical Testing

Preclinical testing conducted on the investigational device included bench studies (mechanical and analytical), simulated use testing in a sinus model, shelf-life studies, biocompatibility, packaging and sterilization studies. These studies demonstrated that the investigational device meets its specifications and the safety and performance requirements for use in humans.

Additionally, Intersect ENT conducted a series of preclinical studies using the sheep model to ascertain preliminary safety and feasibility of delivering MF to the sinus ostia. Plasma MF concentrations were maximum at 1-hour post-dilation. The localized release of MF from the UP Drug-Coated Device inflated once in both left and right FSO resulted in transient low systemic exposure to the drug. Systemic MF exposure peaked at 104 pg/mL (C_{max}) by 1 hour (T_{max}) but declined rapidly over 72 hours to negligible or below LLOQ of 20 pg/mL based on assays validated for sheep plasma.

Sinus tissue MF exposure in animal studies demonstrated that tissue healing was not impaired by the UP Drug-Coated Device. Based on visual assessment, no gross adverse tissue responses of edema or erythema and no clinical signs of infection were observed at any time point through 30 days following dilation.

7.4 Summary of Prior Clinical Experience

The ASCEND study is the first human study with the investigational device.

The safety and efficacy of delivering MF locally to the sinus ostia via bioabsorbable implants have been extensively studied in several randomized controlled trials. The PROPEL® Family of Sinus Implants was studied in 6 clinical trials in the U.S., totaling over 350 patients. All 6 studies were designated as non-significant risk (NSR) studies. The PROPEL Family of Sinus Implants is coated with the same corticosteroid, MF, and have demonstrated adequate safety. The PROPEL sinus implant is intended for use in patients ≥ 18 years of age following ethmoid sinus surgery to maintain patency, thereby reducing the need for post-operative intervention such as surgical adhesion lysis and/or use of oral steroids. The PROPEL sinus implant separates mucosal tissues, provides stabilization of the middle turbinate, prevents obstruction by adhesions, and reduces edema. Since commercialization of the PROPEL sinus implant in 2011, the PROPEL Family of Sinus Implants have been used in treatment of over 200,000 patients.

In order to support the safety of the UP Drug-Coated Device with 3000 mcg of MF, a pharmacokinetic (PK) simulation was performed using published human plasma MF PK concentrations, following an intravenous (IV) administration of 400 mcg of MF and a simulated absorption process from the sinus following nasal administration of MF. Available human PK data for the approved MF products (specifically a dry-powder inhalation [DPI] administration of Asmanex®) and supportive data from MF plasma concentration-time profiles generated with the UP Drug-Coated Device were used for comparison. Predicted AUC values with MF from the UP Drug-Coated Device (459-1376 pg.hr/ml) were similar to those reported for the approved daily doses of up to 880 mcg of MF administered as DPI and metered dose inhalation (MDI) (93-1383 pg.hr/ml). Predicted C_{max} ranges for the UP Drug-Coated Device (105-315 pg/ml) overlapped with the C_{max} ranges reported for approved doses of DPI and MDI (35.2-189 pg/ml) but were higher for those simulations which assumed a higher fraction of dose delivered (90%) or at higher (2%) bioavailability than observed for approved products. The predicted MF exposures (AUC and C_{max}) from the 3000 mcg UP Drug-Coated Device are comparable to observed MF exposures described in publicly available documentation at doses up to 1600 mcg/day (*Data on file at Intersect ENT*).

8 STUDY OBJECTIVE

To assess the safety, performance, and efficacy of the UP Drug-Coated Device when used in CRS patients undergoing balloon dilation of FSO.

9 STUDY DESIGN AND ENDPOINTS

9.1 Study Design

This is a prospective, multicenter clinical trial designed to evaluate the safety, performance, and efficacy of the UP Drug-Coated Device in CRS patients who are candidates for in-office balloon dilation of the frontal recess/FSO.

The trial consists of 2 cohorts:

PK cohort: A non-randomized cohort of 5 subjects who are scheduled to undergo bilateral balloon dilation of the FSO. The UP Drug-Coated Device will be used to perform balloon dilation in the FSO (2 inflations in each FSO for a total of 4 inflations per device).

Randomized cohort: A randomized, intra-patient controlled, blinded cohort of 70 subjects who are scheduled to undergo bilateral balloon dilation of the FSO. Subjects will be randomized to undergo balloon dilation with the UP Drug-Coated Device (2 inflations per device) in one FSO (Treatment) while the contralateral side will undergo balloon dilation with the UP Control Device (Control).

The PK cohort will enroll first. Subjects in the PK cohort will be followed for 30 days (± 3 d) post-procedure and subjects in the randomized cohort will be followed for 60 days (± 7 d) post-procedure.

9.2 Study Endpoints

9.2.1 Primary Endpoints

PK cohort: Successful balloon dilation of attempted FSO using the UP Drug-Coated Device with no unanticipated serious adverse device effects (USADE). Successful dilation is defined as insertion of the UP Drug-Coated Device into the targeted FSO followed by 2 consecutive complete inflations of the balloon.

Randomized cohort: Difference in patency grade of the FSO between treatment sides at Day 30 as determined by an independent, blinded sinus surgeon based on the centralized, video-endoscopy review.

- Patency of the FSO is assessed endoscopically by probing with a 3-mm olive-shaped frontal sinus suction tip (“suction tip”) and graded on a 5-point scale.

9.2.2 Secondary Endpoints

Endoscopic measures in the FSO by clinical investigators at specified timepoints through Day 30 in the PK cohort and through Day 60 in the randomized cohort:

- Estimated FSO diameter, smallest and largest (mm)
- Frequency and grade of patency (5-point categorical scale)
- Inflammation (0-100 scale)
- Frequency and severity of adhesion/scarring (4-point categorical scale)
- Frequency and grade of polypoid edema (4-point categorical scale)
  Need for and frequency of post-dilation interventions (e.g., medical, repeat dilation, surgical)

Endoscopic endpoints in the FSO by independent reviewer in the randomized cohort:

- Estimated diameter, smallest and largest (mm) at Day 14 and Day 30
- Frequency and grade of patency at Day 14 and frequency of patency at Day 30 (5-point categorical scale)
- Inflammation (0-100 scale) at Day 14 and Day 30
- Frequency and severity of adhesion/scarring (4-point categorical scale) at Day 14 and Day 30
- Frequency and grade of polypoid edema (4-point categorical scale) at Day 14 and Day 30
- Need for and frequency of post-dilation interventions (e.g., medical, repeat dilation, surgical) at Day 14 and Day 30

Patient-reported outcomes (PK cohort only):

- Change from baseline to Day 14 and Day 30 in Sino-Nasal Outcome Test (SNOT-22) scores

See **Section 3 Definitions of Terms**.

9.2.3 Safety Evaluation

In the PK cohort, systemic safety will be evaluated via measurements of plasma MF and cortisol concentrations and 24-hour urinary cortisol excretion. Morning plasma MF and cortisol concentrations before the baseline procedure (dilation) and at 0.5, 1, 2, 4, and 24 hours after dilation, and again in the morning of Day 3, 7, 14 and 30 will be analyzed. The MF concentrations will be determined using a validated bioanalytical method a lower limit of quantification (LLOQ) of 0.25 pg/mL. Plasma cortisol will be determined using a validated bioanalytical method with a LLOQ of 1.00 ng/mL. Measurement of urinary cortisol excretion for 24 hours prior to the baseline procedure and for 24 hours after the baseline procedure will be analyzed using a validated bioanalytical method with a LLOQ of 1.00 ng/mL.

In both cohorts, all adverse events (AE) reported by subjects between enrollment (i.e., consent date) and the Day 30 follow-up visit in the PK cohort and the Day 60 follow-up visit in the randomized cohort (end of study) will be tabulated. Each AE will be evaluated by clinical investigators in terms of seriousness, severity (i.e., mild, moderate, severe) and strength of

relationship (i.e., not related, unlikely related, probably related, definitely related) to study drug, study investigational device, study accessory device, and dilation procedure.

Device malfunctions and use errors will be reportable as applicable for both the investigational and the accessory devices.

10 SUBJECT SELECTION AND WITHDRAWAL

10.1 Study Population

The study population will consist of patients ≥ 18 years of age with CRS who had prior ESS, including ethmoidectomy and uncinectomy, and are candidates for balloon dilation because they present with bilateral stenosis of the frontal recess/FSO due to scarring or polypoid edema, confirmed on endoscopy.

10.2 Eligibility Criteria

Subjects are eligible for treatment (PK and randomized cohort) after they 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 CRS, as defined in the 2016 "International Consensus Statement on Allergy and Rhinology".
e. Patient has bilateral disease in the frontal sinuses (Lund-Mackay score ≥ 1 on each side) on CT scan within 30 days prior to enrollment in the PK cohort and prior to randomization in the randomized cohort.
f. Patient has had prior ESS (> 30 days with a healed mucosa), including bilateral ethmoidectomy (anterior or total) and uncinectomy for better visualization of the FSO. Note: No additional surgical interventions will be allowed at baseline/procedure. Dilation of the maxillary and/or sphenoid sinus can be performed with a commercially available sinus dilation device, if clinically necessary, prior to randomization in the randomized cohort.
g. Patient is able to tolerate topical/local anesthesia.
h. Female patients of reproductive potential must not be pregnant or nursing and must agree to not become pregnant during their participation in the study.
i. Female patients of childbearing potential must agree to use consistent and acceptable method(s) of birth control during their participation in the study.
j. Patient has bilateral obstruction of the frontal recess/FSO due to scarring and/or polypoid edema confirmed on endoscopy (patency grade of 0 or 1 for each FSO).

k. Balloon dilation of the FSO with a 6 mm balloon is judged to be feasible (use light-assisted or image-guided instrument such as a frontal sinus seeker tip to confirm access of each FSO) and medically appropriate.

Exclusion criteria

a. Patient has expanded amount of ethmoid polyposis (grade > 2 in the PK cohort, and grade ≥ 2 in the randomized cohort).
b. Complications from prior ESS or balloon dilation procedure (e.g., cerebrospinal fluid leak or injury to the skull base).
c. History of aspirin exacerbated respiratory disease (AERD).
d. Patient is a current smoker.
e. Patient has known history of allergy or intolerance to MF.
f. Patient has used parenteral or injected steroids (e.g., Kenalog) during 30 days prior to the baseline procedure.
g. Patient has clinical evidence of acute rhinosinusitis, as defined in the 2016 "International Consensus Statement on Allergy and Rhinology".
h. Patient has oral-steroid dependent condition such as chronic obstructive pulmonary disease (COPD) or asthma.
i. Patient has used oral steroids, budesonide or other sinus steroid irrigations/rinses or drops, nebulized steroids administered nasally during 14 days prior to the screening in the PK cohort and prior to baseline procedure in the randomized cohort
j. Patient has clinical evidence or suspicion of invasive fungal sinusitis (e.g., bone erosion on prior CT scan, necrotic sinus tissue).
k. Patient has known history of human immunodeficiency virus (HIV), immunoglobulin G or A subclass deficiency or cystic fibrosis.
l. Patient has evidence of severe concomitant disease or condition expected to compromise survival or ability to complete assessments during the 30-day study follow-up period in the PK cohort and during the 60-day study follow-up period in the randomized cohort (e.g., cancer).
m. Patient is currently participating in another clinical study.
n. Patient has known dehiscence of the lamina papyracea.
o. Patient has evidence of active tuberculosis or active viral illness (e.g., ocular herpes simplex, chickenpox, and measles).
p. Patient has glaucoma (prior ocular exam with intraocular pressure of > 21 mm Hg 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 pre-existing disease or condition that precludes subject's participation.
- Subject voluntarily chooses not to participate further in the study.
- Subject's non-compliance with study procedures.
- Lost to follow-up: the subject has missed 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 clinical investigator's opinion, a significant safety concern arises that requires subject discontinuation.
- In the clinical investigator's opinion, it is not in the best interest of the subject to continue study participation.
- In the sponsor's or IRB's opinion, it is not in the best interest of subject to continue the study.

If a subject decides to withdraw from the study, clinical investigator should follow patients with ongoing AEs till resolution according to the standard of care. 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, clinical 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, enrollment, and screening

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.

Clinical investigators or designees will approach the patient to obtain written informed consent. The background of the proposed study, the dilation procedure, the follow-up schedule and all potential risks and benefits will be carefully explained to each patient. The clinical 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 Institutional Review Board (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 the Electronic Data Capture (EDC) system and entered into the study database. Upon enrollment, subjects will have a screening assessment.

The screening assessment for both cohorts will include:

- CT scan (must be performed within 30 days prior to enrollment in the PK cohort and prior to randomization in the randomized cohort),
- Endoscopic examination, grading and video recording,
- Female subjects of reproductive potential must confirm their nursing status, undergo a urine pregnancy test, and be informed about acceptable birth control methods as part of the screening assessment and again at baseline.

PK cohort subjects who pass the screening assessment will be asked to collect urine samples for a 24-hour duration prior to the baseline visit.

For the randomized cohort subjects, if the screening visit occurs on the same day as the baseline/procedure visit, all assessments will be recorded in the baseline visit forms. See **Section 5 Study Flow Diagram** and **Section 6 Schedule of Assessments**. All subjects who do not pass the screening assessment, including inability to confirm access to each FSO, will be considered as screen failures and will be terminated from the study. The reason for ineligibility will be recorded in the EDC system.

11.2 Baseline/Procedure Phase

Baseline assessment

Upon meeting eligibility requirements, subjects in both cohorts will undergo a baseline endoscopic examination, including 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 implantable hormonal contraceptives;

- Double-barrier methods (i.e., intra-uterine devices) and barrier contraceptives (i.e., 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 endoscopic assessment and pregnancy testing must be performed before the dilation procedure.

PK cohort: Baseline assessment will also include:

- SNOT-22 questionnaire.
- A blood sample collection prior to the baseline procedure.
- Instructions for urine sample collection through 24 hours after the baseline procedure
    - Urine collection starting with the void after the procedure through 24 hours on following day.

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

All UP Devices will be provided by the study sponsor and must be used according to the instructions for use (IFU). Subjects will undergo bilateral in-office dilation of the FSO with the study UP Device.

Prior to the baseline sinus dilation procedure, the FSO will be assessed under endoscopic visualization and the assessment will be recorded on the Endoscopic Scoring Form. Using a 3-mm olive-shaped frontal sinus suction tip, the patency and FSO diameter assessments will be performed. Final subject eligibility will be confirmed based on bilateral stenosis of the FSO on endoscopic assessment. NOTE: Physician may use light-assisted or image-guided instrument such as a smaller diameter frontal sinus seeker tip to confirm access of each FSO and if the sinus is amenable to balloon insertion.

No other devices, spacer, or packing (with or without steroid) may be used during or after the baseline dilation procedure. Aggressive suction and irrigations of the treated site should be avoided, as much as possible.

In subjects in the PK cohort, dilation of the maxillary and/or sphenoid sinus with the same UP Device may be performed, if clinically necessary, after the index dilation procedure. In subjects in the randomized cohort, dilation of the maxillary and/or sphenoid sinus with a commercially available balloon sinuplasty device may be performed, if clinically necessary, prior to randomization. No other surgical procedures at baseline will be allowed.

The steps to be followed for the in-office dilation procedure for this study are as follows:

1. Insert a compatible lightwire through the proximal end of the UP Device.
2. Insert the UP Device into the compatible sinus guide catheter.
   a. If desired, attach the compatible sinus guide catheter handle to the sinus guide catheter before insertion of the UP Device.
3. Insert the sinus guide catheter into the FSO and position the sinus guide catheter tip opening toward the FSO (See **Section 7.2 Investigational Device** for compatible accessory devices).
4. Confirm that the lightwire is in the sinus, then advance the UP Device through the guide catheter and position it in the targeted FSO. Note: Under endoscopic visualization, ensure that the proximal end of the balloon (yellow single-band marker) is visible outside of the frontal sinus ostium.
5. Inflate the balloon of the UP Device with the compatible inflation device to 12 atmospheres (atm).
6. Hold the inflated balloon at 12 atm for a minimum of ~10 s and maximum of ~30 s.
7. Deflate the balloon.
8. Reposition the balloon distal to the first inflation site such that the proximal half of the balloon is in contact with sinus mucosa, adjacent to the first inflation site.
9. Repeat steps 5 and 6 to dilate the sinus ostium for a total of 2 inflations in each sinus ostium.
10. Retract the deflated balloon into the guide catheter before removing the dilation system out of the nostril (Note: Do not retract the tip of the UP Device beyond the blue tip marker on the guide catheter to prevent loss of the drug).

PK cohort: Subjects will undergo in-office bilateral sinus dilation with the UP Drug-Coated Device in the frontal sinuses with 2 inflations per sinus (total of 4 inflations per Device).

- Repeat steps 1 through 10 for each FSO with the same UP Drug-Coated Device. Note: Dilation of the maxillary and/or sphenoid sinus with the same UP Device may be performed, if clinically necessary. However, dilation of the maxillary and/or sphenoid sinuses must be performed only after dilation of the frontal sinuses.
- On the day of the baseline procedure, 4 additional blood draws (~ 11 ml at each timepoint) will be performed at 0.5 (± 5 min), 1 (± 5 min), 2 (± 10 min) and 4 (± 15 min)

hours following the end of the baseline procedure, defined as removal of UP Device from the nostril after successful dilation of both FSO in each subject.

Randomized cohort: Subjects will undergo an in-office sinus dilation with the UP Drug-Coated Device of the FSO randomized to treatment (2 inflations per device) while the contralateral FSO will serve as control and undergo sinus dilation with a UP Control Device (2 inflations per device).

- Steps 1 through 10 will be followed with each frontal side dilated with the assigned UP Device.

Postoperative care

PK cohort subjects will be required to collect urine samples for 24 hours following the baseline procedure.

After the baseline procedure, subjects in the PK cohort will be allowed and subjects in the randomized cohort will be required to use saline sprays/rinses/irrigations starting Day 2.

PK cohort subjects will not be allowed to use INCS sprays throughout the 30 days follow-up duration. Randomized cohort subjects will be allowed to use INCS sprays starting after the scheduled Day 14 study visit, if medically necessary.

Device disposal

The investigational and compatible accessory devices must be disposed per standard institutional practices for biohazard waste. If the UP Device or other compatible accessory devices are associated with a device-related AE, malfunction, or failure, all the components should be returned to the sponsor for evaluation, as much as possible. For the return of biohazard product, the sponsor must be contacted prior to product return for handling instructions.

Device malfunction and use error

All potential and suspected device malfunctions and use errors of the investigational device will be reported to and reviewed by the sponsor. Any AEs associated with the investigational device and/or compatible accessory devices will be recorded in the corresponding CRFs in the EDC system.

11.3 Follow-Up Phase

The follow-up period begins immediately post-procedure (once the subject exits the clinic).

PK cohort

Each subject will return for up to 6 follow-up visits (see **Section 5 Study Flow Diagram** and **Section 6 Schedule of Assessments**).

- Day 1 (24 hours ± 3 hours after the baseline procedure)

- Day 3 (72 hours ± 3 hours after the baseline procedure)
- Day 7 ± 2 days
- Day 14 ± 2 days
- Day 21 ± 2 days
- Day 30 ± 3 days

The protocol-required follow-up assessments through Day 30 will consist of:

- SNOT-22 questionnaire (at Days 14 and 30)
- Endoscopic examination, grading and video recording (at Days 7, 14, 21 and 30)
- Blood sample collection of 11 ml (at Days 1, 3, 7, 14, and 30)
    - All blood draws must occur in the morning and at approximately the same time of the day during the follow-up visits.

Randomized cohort

Each subject will return for up to 5 follow-up visits for endoscopic grading and video recording (see **Section 5 Study Flow Diagram** and **Section 6 Schedule of Assessments**).

- Day 7 ± 2 days
- Day 14 ± 2 days
- Day 21 ± 2 days
- Day 30 ± 2 days
- Day 60 ± 7 days

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, and/or
- Sinus-related adverse events requiring medical evaluation.

The assessment at an unscheduled visit will consist of:

- SNOT-22 questionnaire (PK cohort only), and,
- Endoscopic examination, 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).

- Leading up to the baseline procedure, a 14-day restriction for use of oral steroids, budesonide or other sinus steroid irrigations/rinses or drops, and nebulized steroids administered nasally.
- After the baseline procedure, subjects will be allowed in the PK cohort and required in the randomized cohort to use saline sprays/rinses/irrigations starting at Day 2.
- If infection is suspected at any time during the study, treatment with antibiotics will be permitted.
- Use of intranasal corticosteroid (INCS) sprays is allowed starting after Day 14 visit in the randomized cohort, if clinically necessary, and not allowed throughout the 30-day follow-up period in the PK cohort.
- Use of other corticosteroids (e.g., oral, parenteral, injections, budesonide or other sinus steroid irrigations/rinses or drops, breath powered steroid delivery [e.g. XHANCE™, fluticasone proprionate] nebulized steroids administered nasally) will not be permitted during the study follow-up unless clinically necessary (see **Section 13 Medical and Surgical Interventions**).
- If already on such medications, use of orally-inhaled steroids for control of asthma will be permitted.
- Use of corticosteroid-eluting sinus implants (PROPEL®, PROPEL® Mini, PROPEL® Contour, SINUVA®) or other nasal packing and spacers is prohibited 14 days prior to baseline, during the baseline procedure and through Day 30 in the PK cohort and through Day 60 in the randomized cohort.
- To the extent possible, subjects will be maintained on stable regimens of leukotriene inhibitors and/or immunotherapy (e.g., Montelukast, Zafirleukast, Zileuton) for allergies throughout the follow-up duration, if currently on such regimens.

All sinus-related medications will be recorded in the EDC system including their full brand/trade or generic names (whichever prescribed), dose, frequency, indication, start and end dates are coded using the World Health Organization drug dictionary.

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, INCS sprays will be allowed starting after Day 14 visit, if clinically necessary, for subjects in the randomized cohort and not allowed throughout the 30-day follow-up period for subjects in the PK cohort.

Other corticosteroids (e.g., oral, parenteral, injection, budesonide or other sinus steroid irrigations, rinses or drops, nebulized steroids administered nasally) will not be permitted unless

there is a clinically significant increase or persistence in frontal sinus inflammation occurs, coupled with subject complaint of sinusitis symptoms that cause subject to request medical intervention.

13.2 Surgical Intervention

Surgical intervention (e.g., repeat balloon dilation or sinus surgery, in-office polypectomy) may be required in cases where a clinically significant increase or persistence in frontal sinus inflammation occurs, coupled with complaints of sinusitis symptoms that cause subject to prefer a surgical intervention (e.g. sinus surgery).

All oral steroid and surgical intervention will be noted on the concomitant medication and follow up CRFs (see **Section 16.6 Handling Steroid or Surgical Interventions**).

14 ASSESSMENT OF SAFETY

14.1 Specifications of Safety Parameters

Pharmacokinetic analyses

Plasma concentrations of MF and cortisol at specified time points will be performed. Samples will be analyzed with a validated bioanalytical method for both human plasma MF with a lower limit of quantification (LLOQ) of 0.25 pg/mL and for cortisol with an LLOQ of 1.00 ng/mL. Additionally, measurement of urinary cortisol excretion 24 hours prior to the baseline procedure and 24 hours after the baseline procedure will be analyzed using a validated bioanalytical method with a LLOQ of 1.00 ng/mL.

Adverse event assessment

Adverse events (AE) for each subject from the time the subject gives informed consent through Day 30 in the PK cohort and through Day 60 in the randomized cohort (end of study) will be recorded in the EDC system and monitored. Each AE will be evaluated by clinical investigators in terms of strength of relationship (i.e., not related, unlikely related, probably related, definitely related) to study drug, study device, and dilation 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 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 in-office balloon dilation. These may include symptoms such as pain and discomfort, headache, decreased sense of smell, crusting, epistaxis, and other symptoms. Patients healing appropriately after in-office procedure may suffer from acute infections and/or inflammatory exacerbations unrelated to the procedure due to the natural course of their CRS. Therefore, clinical investigators will evaluate the occurrence of AEs excluding usual post-operative recovery signs and symptoms experienced by study subjects, unless corroborated by objective findings and/or requiring specific medical or therapeutic interventions (e.g., antibiotics, repeat ESS, etc.).

Note: The need for medical or surgical intervention in the FSO post-dilation that is captured on the endoscopic scoring CRF, will not be considered an AE. Likewise, other endoscopic findings such as adhesion/scarring, polyp formation and restenosis of the FSO will not be considered AE.

14.2 Classification of Adverse Events

All adverse events will be reported from the time of consent through study exit. The relationship of all AEs to the investigational device will be categorized into:

- *Definitely related:* There is a clear-cut temporal association, and no other possible cause.
- *Probably related:* There is a clear-cut temporal association, and a potential alternative etiology is not apparent.
- *Unlikely related:* The AE does not follow a reasonable temporal association; or causal relationship with the drug, device, or procedure involved in the research is unlikely but cannot be completely ruled out.
- *Not related:* The AE is completely independent of study product 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 related (definitely related, probably related) to the study drug, investigational device, accessory device or dilation procedure will be categorized as device-related.

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

14.3 Guidelines for Reporting of Adverse Events

All AEs, regardless of seriousness or relationship to the investigational device and compatible accessory devices, will be recorded in the EDC system and will include event description, date of onset, investigator's assessment of severity, relationship to investigational device, 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 pre-existing medical condition that is present at the time of screening will not be reported as an AE. The occurrence of 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 the investigational or accessory device, 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 investigational or accessory device.

The investigator should take appropriate measures to follow all AEs until resolution or until progression has been stabilized, or until study exit, to ensure the safety of the subjects. If the AE continues beyond the last planned visit per protocol and/or the subject withdraws from the study, clinical investigators should follow the subjects according to standard of care.

If a subject decides to withdraw from the study, clinical investigator should follow patients with ongoing AEs till resolution according to the standard of care.

All AEs must be reported to the sponsor based on the following timeline:

Type of Report	Reporting Schedule to the Sponsor
Investigational or accessory 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/SADE/UADE/USADE	Verbal report within 24 hours followed by a written report within 5 working days

Device malfunctions, device deficiencies and use errors must be reported to the sponsor promptly.

The investigator will report the above to the reviewing IRB per the IRB's guidelines. The study sponsor will be responsible for reporting safety events to the FDA as required per 21 CFR 812.

All SAEs (SAE/SADE/UADE/USADE) will be followed until satisfactory resolution; until the investigator deems the event to be chronic or the adherence to be stable or until the subject exits the study. Other supporting documentation of the event may be requested by the sponsor and should be provided as soon as possible.

All device deficiencies including malfunctions, use errors, and inadequate labeling, will be reported to appropriate regulatory bodies and Institutional Review Boards (IRBs)/Ethics Committees (ECs) as applicable.

Each AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and presented based on the system organ class and preferred term.

15 RISK/BENEFIT ASSESSMENT

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

15.1 Potential Risks

Risks associated with the use of the UP Drug-Coated Device are anticipated to be similar to those experienced by patients who undergo balloon dilation of the sinuses with a non-drug coated balloon.

Consequently, the risks potentially associated with the use of the UP Device may include but are not limited to the following:

- Epistaxis
- Cerebrospinal fluid leak
- Pneumocephalus
- Damage of the orbital wall or other ocular structures
- Impaired or loss of vision
- Impaired tearing
- Periorbital cellulitis/edema
- Infection
- Facial/nasal pain
- Facial/nasal discomfort
- Headache

Risks or side effects associated with intranasal mometasone furoate are:

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

Risks associated with steroids in general are:

- Alteration of the hypothalamic-pituitary-adrenal axis including growth suppression
- Immunosuppression
- Hypersensitivity reactions
- Headache
- Epistaxis
- Coughing
- Vomiting
- Candidiasis
- Glaucoma/elevation of intraocular pressure
- Cataracts/change in lens opacities
- Arthralgia
- Myalgia

Inhaled and intranasal MF is generally well tolerated in clinical trials and any AE are mild and generally of short duration with similar incidence to placebo. The proportion of patients discontinuing as a result of AEs related to treatment is very low and generally < 2-5% in most trials (Asmanex 2005; Dulera 2010; Nasonex 2005).

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. Local mycotic infections and septal perforations with prolonged use of nasal corticosteroids are extremely rare and have not been reported for mometasone furoate. These findings may be related to the more rapid clearance of the topical corticosteroid by the ciliated nasal epithelium (Kyrmizakis 2000; Van Cauwenberge 2005; Vogt 1979).

The MF and polyethlene glycol material constituting the balloon-coating has been used extensively in the manufacture of the PROPEL Family of Sinus Implants. The polysorbate material consistuting the balloon-coating has extensive history of use in medical devices such as vascular drug-coated balloons. Either material is not expected to present any new risks.

Risks associated with blood sample collection may include fainting, redness, pain, bruising, and swelling at the site of venipuncture.

15.2 Minimization of Potential Risks

Risks associated with the UP Device are minimized via:

- The use of medical grade materials that have a long history of use and have been characterized and tested to assure biocompatibility
- Pre-clinical evaluation including bench testing, analytical testing, and animal studies
- IFU that detail appropriate device preparation and dilation
- Selection of investigators with adequate experience and qualifications in the treatment of CRS
- Training of the investigators on proper use of the UP Device, the study protocol, investigator responsibilities, and human subjects' protection. Routine subject follow-up that includes direct endoscopic visualization of the dilated sinus and surrounding tissue.

Additionally, risks will also be minimized by including clinical investigators experienced in performing balloon dilation procedures and nasal endoscopy.

15.3 Potential Risks to Study 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 electronic 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 Intersect ENT that inadvertently contains it.

15.4 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 CRS, which may provide some indirect health benefits.

Subjects who receive the UP Drug-Coated Device may benefit from dilation and local delivery of the drug that is intended to reduce post-dilation inflammation/edema. Subjects who receive UP Control Device may benefit from dilation of sinuses.

15.5 Risk/Benefit Conclusion

Based upon the Risk assessment performed by Intersect ENT, the risk profile is considered appropriate and acceptable given the phase of development of the device. Potential benefits associated with the UP Device are expected to outweigh the identified potential risks to the patient.

16 STATISTICAL CONSIDERATIONS

A formal Statistical Analysis Plan will be prepared prior to the study database lock and formal data analysis from the randomized study. Data collected from the PK and randomized cohorts will be analyzed separately. Following is a summary of the intended analyses.

16.1 Randomization Scheme

Randomized cohort

The ratio of left to right sinus assignments will be 1:1. Eligible subjects will be randomized to receive the UP Drug-Coated Device in one FSO (Treatment) while the contralateral side will receive the UP Control Device (Control). Randomization will be stratified by site and will be implemented using the envelope method. The randomization scheme will be generated by an independent biostatistician.

16.2 Sample Size Calculation

PK cohort

The sample size for this cohort was selected without regard for statistical considerations. The sample of 5 treated subjects was deemed adequate to assess whether there will be any quantifiable systemic exposure to mometasone furoate when delivered via this route of administration.

Randomized cohort

The sample size calculation is based on the primary efficacy endpoint – the difference in the patency grade at Day 30 between the treatment and control sides, as determined by a blinded, independent sinus surgeon based on the centralized video-endoscopy review.

The relevant null and alternative hypotheses are:

H_0: $\mu = 0$
H_1: $\mu \neq 0$

where μ is the mean difference in the FSO patency grade at Day 30 between treatment and control sides. The study will be considered successful if there is a statistically significant difference in mean patency grade in favor of the UP Drug-Coated Device.

The sample size for this cohort is calculated based on the following assumptions:

- Expected mean difference of 0.5 between the treatment and control sides in patency grade
- A standard deviation (SD) of 1.1 for side-to-side difference in the mean patency grade
- Target power of ≥ 90%
- Type I error rate: $\alpha = 0.05$, 2-sided

A mean difference of 0.5 between the treatment and control sides in the patency grade is considered clinically meaningful. Based on standard formulas for a 1-sided t-test, a sample size of 53 subjects provides at least 90% power to detect a difference of 0.5 in mean patency grade. Assuming 25% subjects with non-evaluable data on one or both sides, an additional 17 subjects will be enrolled for a total of 70 subjects in the randomized cohort.

16.3 Analysis of Primary Endpoints

PK cohort

The primary efficacy endpoint is the number of successful balloon dilations, which will be reported with descriptive statistics. The left and right sides of each subject will be considered independent, and each subject is expected to contribute up to 2 observations. The study will be considered successful if ≥ 80% of attempted FSO are dilated successfully with no USADE related to the investigation device. A successful FSO dilation is one in which the physician has inserted the UP Drug-Coated Device into the targeted FSO, followed by 2 consecutive, complete inflations of the balloon.

Continuous data from the plasma MF, plasma cortisol and 24-hour urinary cortisol concentrations will be expressed using descriptive statistics, including but not limited to, means, standard deviations, medians, ranges and, where appropriate, coefficient of variation (%).

Randomized cohort

The primary efficacy endpoint is the difference in the patency grade between treatment sides at Day 30 as determined by an independent, blinded sinus surgeon based on the centralized video-endoscopy review.

The primary efficacy endpoint will be analyzed using the paired t-test.

16.4 Analysis of Secondary Endpoints

Endoscopic and patient-reported outcome measures and change from baseline in these measures (PK cohort only) will be summarized. Continuous data will be expressed as means, standard deviations, medians, ranges and, where appropriate, 95% confidence intervals (CI) for the mean assuming a normal distribution. The paired t-test will be conducted to assess side-to-side differences. Categorical data will be expressed as counts and percentages and, where appropriate, 95% CI. To compare the need for post-dilation medical or surgical interventions (paired binary outcomes) at each timepoint, McNemar's test will be used. Analyses will be presented for each time point.

To support potential product labeling claims, a subset of secondary endpoints will be identified and analyzed using appropriate methods for controlling for family-wise type-1 error rate. This will be detailed in the statistical analysis plan prior to database lock for the randomized cohort.

16.5 Analysis of Safety Measures

The incidence of AEs and SAEs– including investigational device-related AEs, USADE – will be tabulated for the PK (through Day 30) and randomized cohorts (through Day 60) separately.

16.6 Handling Steroid or Surgical Interventions

Use of clinically necessary corticosteroids (e.g., oral, parenteral, injection, budesonide or other sinus steroid irrigations/rinses or drops, nebulized steroids administered nasally) or surgical intervention (including repeat balloon dilation for the FSO) during the study will be recorded and tabulated.

16.7 Sensitivity Analysis for the Primary Efficacy Endpoints

Since the primary efficacy endpoint in the randomized cohort 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 efficacy conclusion to actual interventions given. In this analysis, data imputations will be performed as follows:

- If prior to Day 30, a clinical investigator indicates on the Endoscopic Scoring Form that either frontal recess/FSO required oral steroids or surgical intervention, and such 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 visit preceding such intervention.

- 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 (prior to Day 30).

Additional sensitivity analysis may be performed to assess the sensitivity of the primary efficacy conclusion to patterns of missing data. This will be detailed in the statistical analysis plan.

16.8 Analysis Populations

PK cohort: The PK population will consist of all subjects in the safety population with at least one non-missing and eligible plasma concentration value.

Safety population will consist of all subjects and sinuses exposed to investigational device with successful dilation of at least one FSO.

Randomized cohort: All primary analyses will be conducted on the intent-to-treat population. Additional analyses may be performed on the per-treatment-evaluable population.

- *Intent-to-Treat* (ITT) population will consist of all subjects and sinuses where a sinus dilation was attempted. An attempt occurs when the physician introduces the UP Device into the subject's nostril with the intent of dilation. Subjects and sinuses will be analyzed according to randomization assignment.

- *Per-Treatment-Evaluable* (PTE) population will consist of all randomized patients and sinuses which have received the assigned study device in the target sinus, who have no major procedural protocol deviations, and for whom follow-up data are available.

If a subject decides to discontinue from the study, every attempt will be made to continue to collect the safety and efficacy data according to the protocol procedures.

17 STUDY MANAGEMENT

17.1 Ethical Considerations

The rights, safety and well-being of subjects shall be protected in accordance with the ethical principles based in the Declaration of Helsinki and consistent with ISO14155, 21 CFR Parts 11, 50, 54, 56, and 812 Good Clinical Practice, all IRB requirements and all applicable local laws and requirements. 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 (E6), Clinical investigation of medical devices for human subjects – Good clinical practice (BS EN ISO 14155) and other applicable local and federal (e.g., 21 CFR Parts 11, 50, 54, 56, and 812) regulations, including the archiving of essential documents. A list of the names, locations, and chairpersons of all IRBs (including actions taken by each IRB on the protocol) that have been or will be asked to review the protocol will be kept on file. Qualified personnel who participate in the conduct of this clinical trial will be qualified by education and/or experience and trained 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 clinical investigators with training on use of the UP Device 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 and Human Subjects Protection
- Instructions for use
- Investigator responsibilities, including reporting requirements
- Monitoring and auditing
- CRF completion guidelines
- EDC system
- Electronic recordkeeping
- Endoscopic grading scales, recording and video uploading
- Investigational device accountability procedures
- Protection of subject confidentiality

New members of the investigation site team may be added from time to time at new or existing sites. New personnel should only start their assignment after receiving adequate training in the clinical investigation requirements and this training shall be documented. The names, initials, signatures, functions, and designated authorizations of new site personnel shall be documented.

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 (IRB) 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 device 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 trained and qualified Clinical Research Associates (CRAs) from the sponsor and contract CRAs who will be trained and qualified by the sponsor. Study sites will be visited regularly to ensure that the study is conducted in compliance with 21 CFR Parts 11, 50, 54, 56, 812, ISO 14155, the study protocol and other applicable regulations. Study monitors will also ensure that the data reported in the 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. A detailed monitoring plan will be developed and maintained by the sponsor.

17.2.4 Data Management Responsibilities

Data management will be performed by the sponsor.

Electronic data capture

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'. The EDC will be validated and verified prior to use, and validation and verification and release documentation will be maintained on file by the study sponsor. 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 Device Accountability

An appropriate number of the investigational devices, the UP Drug-Coated Device and UP Control Device, will be provided to the study sites. The sites maintain the investigational devices in a locked, secure location. Only clinical investigators participating in the study will have access to the investigational device. Dispensing of investigational device will be documented by authorized personnel. Each batch of the investigational device will be assigned a serial/lot number for tracking purposes.

Investigational devices received by the clinical site will be logged in by the site personnel on inventory logs and/or the EDC system. Final reconciliation will be completed at each site before or during site closure. Any unused inventory of the investigational device will be returned to the sponsor at the direction of the sponsor or at the close of the study. At the end of the study, overall study final device reconciliation will be completed internally by the sponsor.

17.3 Blinding

17.3.1 Randomization

Randomization assignment will be stratified by site, will follow a blocked scheme with blocks of varying sizes, and will be performed using the envelope method. After subjects meet the study entry criteria, have been anesthetized, and final eligibility confirmed, site personnel will open the assigned randomization envelope for that particular subject.

17.3.2 Blinding

The treatment and control devices are randomly designated with a device code (e.g.: Device C and Device D) and do not contain any identifying information regarding the treatment or control device. The information inside the randomization envelope will indicate which frontal sinus side receives which device code (e.g.: C or D). After the first side is treated with the assigned device, that device will be discarded before opening the device assigned to the contralateral side, so that no side-by-side comparison of the two devices is made by the clinical investigators or clinical staff.

Hence, the following personnel will be blinded to treatment assignment:

- Research coordinators at the site who have various responsibilities in conducting the study including assisting in baseline dilation procedure, handling randomization assignment, maintaining investigational product accountability records, and complete AE reports.
- Sponsor representatives who serve as a resource and provide guidance for clinical investigators and clinical staff on procedure with the investigational devices or during patient follow-up.
- Clinical Research Associates from Intersect ENT and its sub-contractors (as needed), who perform routine monitoring activities.
- The independent reviewer who will grade the Day 14 and Day 30 videoendoscopies.

17.4 Investigator Responsibilities

General responsibilities

- Each investigator is responsible for ensuring that an investigation is conducted per the signed investigator statement (Investigator Agreement/Commitment), the study protocol, and applicable regulations; for protecting the rights, safety, and welfare of study subjects under the investigator's care and for the control of drugs/devices under investigation.
- The investigator shall assure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the CRFs and in all required reports.
- Each investigator shall obtain informed consent of each patient to whom the treatment is administered in accordance with provisions of 21 CFR Part 50 and ISO14155.
- Each investigator (designee) is responsible for all applicable IRB requirements under 21 CFR Part 56 and ISO14155.
- Each investigator is responsible for disclosure of financial obligations/conflict of interest to the sponsor in accordance with provisions of 21 CFR Part 54.
- The study will be conducted under 21 CFR 11, 50, 54, 56, 812 and ISO14155. Investigators will be trained on their responsibilities.
- To ensure proper execution of the study protocol, each investigator will identify a study coordinator(s) for this study. Working with and under the oversight of the principal investigator, the study coordinator(s) ensures that all study requirements are fulfilled.
- Each investigator will allow monitoring and auditing of their clinical investigation procedure(s) by the sponsor or designee.

Control and disposition of the investigational device

An investigator shall administer the investigational device only to subjects under the clinical investigator's personal supervision. The investigator shall not supply the investigational device to any person not authorized to receive it. An investigator (or designee) is required to maintain adequate records of the disposition of the investigational devices, including dates, quantity, and use by subjects. All unopened unused devices must be returned to the 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) per 21 CFR 812. 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, and investigational device malfunctions and deficiencies, use errors (as applicable) 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 applicable/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, baseline 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 device 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. 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, the 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 subjects study records, or if the records are moved to be under the oversight of a different sponsor-approved investigator or 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)
- Investigator agreement/commitment for the participating investigator(s)
- 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 the sponsor, a site initiation visit has been performed, and the sponsor has provided written approval to begin enrollment.

17.5 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 the 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.

Clinical investigators will maintain confidential study subject lists identifying all enrolled subjects. The clinical 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.

17.6 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/device presents an unreasonable and significant risk to subjects (the sponsor may terminate the study immediately)

- Persistent non-compliance with the study protocol
- Persistent non-compliance with the applicable ethics committee or regulatory requirements
- Sponsor decision to terminate study

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.

17.7 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.

17.8 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. The 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. A justification of the non-significant risk determination of the study and any supporting information, as necessary, will be provided to the IRB under 21 CFR 812.2(b). Clinical investigators must also obtain renewal of IRB approval throughout the duration of the study. Clinical investigators are responsible for fulfilling any conditions of approval imposed by the reviewing IRB, such as regular reporting, study timing, etc. Clinical investigators will provide the study sponsor with copies of such approvals and reports.

Other investigator reports

Clinical investigators are responsible for notifying the sponsor of the following:

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 becoming aware

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

17.9 Final Clinical Study Report

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

17.10 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. Co-authorship will be granted to the national investigator and to principle investigators from each study site based on enrollment contribution.

18 APPENDIX 1: LIST OF CORTICOSTEROID MEDICATIONS

Trade Name (alphabetical order)	**Generic Name**	**Route of Administration**
Budesonide Pulmicort Respules	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 Intranasal sprays
Kenalog	Triamcinolone Triamcinolone Acetonide	Intramuscular Subcutaneous Submucosal
Mometasone	Mometasone furoate	Nasal irrigations Intranasal sprays
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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