STATISTICAL ANALYSIS PLAN

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
Sponsor's Name and Address	Intersect ENT, Inc. 1555 Adams Drive Menlo Park, CA 94025 Tel: +1 650-641-2100 Fax: +1 650-641-2053
Investigational Device	UP Drug-Coated Device (mometasone furoate, 3000 mcg)

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APPROVAL SIGNATURES

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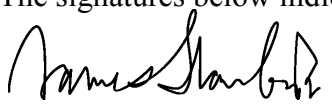

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Revision History:

Version	Date	Summary of Changes
1.0	29 November 2018	Document created

3 INTRODUCTION

This document outlines the statistical analysis plan (SAP) for the ASCEND Study conducted by Intersect ENT under protocol P500-0118 entitled "A Clinical Evaluation of the UP Drug-Coated Device in Patients with Chronic Rhinosinusitis." Preparation of this SAP was based on the ASCEND study protocol version 7.0 dated November 12, 2018. The SAP specifies the data listings, tabular summaries, and analyses to be performed.

4 STUDY OBJECTIVE

The objective of the study is to assess the safety, performance, and efficacy of the UP Drug-Coated Device when used in chronic rhinosinusitis (CRS) patients undergoing balloon dilation of the frontal sinus ostia (FSO).

5 STUDY DESIGN

This is a prospective, multicenter clinical trial enrolling and treating a total of 75 subjects in two consecutive 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. Subsequently, the UP Drug-Coated Device may be used to dilate any sphenoid or maxillary sinuses, if clinically necessary. Subjects in the PK cohort will return for 6 follow-up visits at Day 1, 3, 7, 14, 21 and 30. Follow-up evaluations will include endoscopic examination, endoscopic grading, and patient-reported outcomes.
- 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 side) will undergo dilation using the UP Drug-Coated Device while the contralateral FSO (control side) will be dilated with the UP Control Device without any coating and with identical dimensions of the balloon to that of the UP Drug-Coated Device. Subjects in the randomized cohort will return for 5 follow-up visits at Days 7, 14, 21, 30 and 60. Follow-up evaluation will include recorded endoscopic examination and endoscopic grading.

See Appendix A for Schedule of Assessments for both cohorts.

6 STUDY ENDPOINTS

6.1 Primary Endpoints

PK Cohort: The primary endpoint in the PK cohort is the successful balloon dilation of attempted FSO using the UP Drug-Coated Device with no unanticipated serious adverse device effects (USADE).

- Successful dilation of the FSO 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: The primary efficacy endpoint for the randomized cohort is the 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.

- 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.

6.2 Secondary Endpoints

The secondary endpoints for each cohort are listed below

6.2.1 PK Cohort

Endoscopic endpoints in the FSO by clinical investigators at specified timepoints through Day 30:

- 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)

Patient-reported outcomes:

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

6.2.2 Randomized Cohort

Endoscopic endpoints in the FSO by independent reviewer:

- 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

Endoscopic endpoints in the FSO by clinical investigators at specified timepoints through Day 60:

- 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)

6.3 Safety Evaluation

6.3.1 PK Cohort

Systemic Safety: In the PK cohort, systemic safety will be evaluated via measurements of plasma mometasone furoate (MF) and cortisol concentrations and 24-hour urinary cortisol excretion.

- Morning plasma MF and cortisol concentrations before the baseline procedure and at 0.5, 1, 2, 4, and 24 hours after dilation, and again in the mornings of Day 3, 7, 14 and 30 will be tabulated.
    - A validated bioanalytical method for human plasma MF with a lower limit of quantification (LLOQ) of 0.25 pg/mL.

    - A validated bioanalytical method for human plasma 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
    - A validated bioanalytical method for human urinary cortisol with a LLOQ of 1.00 ng/mL

AEs reported by subjects between enrollment (i.e., consent date) through Day 30 follow-up visit 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 device, accessory devices, and baseline procedure.

6.3.2 Randomized Cohort

All AEs reported by subjects between enrollment (i.e., consent date) and Day 60 follow-up visit (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.

7 ANALYSIS COHORTS

7.1 PK Cohort

7.1.1 Safety Population

The safety population will consist of all subjects and sinuses exposed to the investigational device with successful dilation of at least one FSO. All primary and secondary endpoint analyses will be performed on the safety population for the PK cohort.

7.2 Randomized Cohort

7.2.1 Intent-to-Treat Population

The intent-to-treat (ITT) population will consist of all subjects in whom the UP Drug-Coated Device or the UP Control Device was attempted. An attempt occurs when the surgeon introduces the UP Drug-Coated Device into the subject's nostril on the treatment side or the UP Control Device on the control side. Sinus sides will be analyzed according to their randomization assignment.

The ITT population is considered the principal analysis population. All primary and secondary efficacy endpoint analyses will be performed using the ITT population. Summaries for demographics, baseline clinical characteristics, procedure characteristics, procedure success, concomitant medication use, adverse events (AE), and study visit compliance will be carried out using the ITT population.

7.2.2 Per-Treatment Evaluable Population

The per-treatment evaluable (PTE) population will consist of all subjects and sinuses that were successfully treated with the UP Drug-Coated Device on the treatment side and with the UP Control Device on the control side, have had no major procedural protocol deviations (i.e., if a study subject was treated before signing an ICF, or sinuses received a treatment not consistent with the randomization assignment), and have follow-up data available. Reasons for exclusion from PTE will be provided in data listings.

8 GENERAL DATA DERIVATIONS

8.1 Study Day Calculation

Study day 0 is the day of the baseline balloon dilation procedure. Study day is calculated relative to baseline procedure (Study day 0) and will appear in the listings where applicable.

If the date of event is on or after the date of the baseline procedure, study day will be calculated as:

Study day = date of event – date of procedure

8.2 Baseline

The baseline is defined as the last observation recorded prior to the initiation of the baseline procedure.

8.3 Study Visits

Subjects in the PK cohort will return for 6 follow-up visits at Day 1 (24-hour following the baseline procedure), 3, 7, 14, 21, and 30. Subjects in the randomized cohort will return for 5 follow-up visits at Days 7, 14, 21, 30 and 60 (end of study).

Subjects in both PK and randomized cohorts may come in for additional unscheduled office visits, if clinically necessary. Data from the unscheduled visits in the randomized cohort will be handled as described in Section 9.2.

8.4 Role of the Independent Reviewer

Video-endoscopies of the FSO at Day 14 and Day 30 from all subjects in the randomized cohort will be provided to an independent sinus surgeon reviewer for grading and determination of the primary and secondary efficacy endpoints. The reviewer will be independent from the study (i.e., not enrolling study subjects for the study) and masked to treatment assignment (i.e., not know which sides received the UP Drug-Coated Device and the UP Control Device). To reference the subjects' pre-dilation anatomy as needed, the independent reviewer will have access to the pre-procedure videos.

Video-endoscopies obtained pre-procedure, at Day 14 and at Day 30 will be labeled with subject ID and will be checked to ensure no subject-identifying information (e.g., images of subjects' face) is included before being providing to the independent reviewer.

9 STATISTICAL METHODS

9.1 Randomization

Eligible subjects in the randomized cohort will have their sinus sides randomly assigned to receive the UP Drug-Coated Device in one FSO (treatment side) while the contralateral FSO (control side)

will receive the UP Control Device. The ratio of left to right FSO assignments will be 1:1. The randomization scheme will be generated by a biostatistician consultant and the randomization envelopes will be assembled by an in-house clinical research associate. The randomization scheme will be stratified by each clinical center. To maintain blinding of study personnel to the treatment assignment, the treatment and control devices will be designated with a letter such as Device C and Device D. The information inside the randomization envelope will indicate which FSO side receives which device letter with no information regarding the treatment or control device (e.g., Device C – LEFT, Device D – RIGHT).

9.2 General Statistical Considerations

The primary endpoint, all secondary efficacy endpoints, and safety evaluations will be analyzed for each study cohort separately. The analysis of each cohort will stand on its own; achieving the primary objective in one cohort is considered sufficient for outcomes in that cohort, regardless of the results in the other cohort.

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

9.3 General Statistical Procedures

Statistical summaries, confidence intervals (CI), and p-values will be generated using SAS® software. Descriptive statistics will consist of means, standard deviations (SD), median, and ranges for continuous data; and counts and percentages for categorical data. Data from the protocol-specified visits (i.e., as reported in the case report form, CRF) will be used in the summary tables and data listings.

9.3.1 PK Cohort

Data from the pharmacokinetic (PK) assessments of plasma MF, plasma cortisol, and 24-hour urinary cortisol concentrations, endoscopic and SNOT-22 scores will be expressed using descriptive statistics, including but not limited to, means, SD, medians, ranges and, where appropriate, coefficient of variation (%). The PK and cortisol parameters, C_{max}, C_{24}, T_{max}, and AUC_{0-24} will be calculated by non-compartmental methods according to the definitions below. Nominal sample times will be used in the calculation of all parameters.

C_{max}	Maximal concentration after the baseline procedure.
T_{max}	Time at which maximal concentration after the baseline procedure
C_{24}	PK and cortisol concentration 24 hours after the baseline procedure.
AUC_{0-24}	Area under the concentration-time curve from time 0 to 24 hours. The linear/log trapezoidal rule will be used.

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.

A_e	The amount of cortisol excreted in urine, will be calculated by multiplying the volume of urine collected over the 24-hour period by the concentration of cortisol measured in the urine sample.
ΔA_e	The change in cortisol urine exposure following administration- calculated as A_e for the 24 hours after baseline procedure minus A_e for the 24 hours prior to the baseline procedure.

The 24-hour urinary cortisol data will be tabulated for each subject for whom amounts are quantifiable.

9.3.2 Randomized Cohort

The primary and secondary efficacy endpoints that are continuous variables will be analyzed using paired t-test. All statistical tests will be two-sided and interpreted at a 5% significance level. A

p-value < 0.05 will be considered statistically significant. Unless stated otherwise, a two-sided 95% CI will be calculated and presented.

Categorical variables will be analyzed using McNemar's test for correlated proportions. In this intra-patient control study design, only discordant pairs of observations contribute to evidence of treatment effect. The appropriate test is an exact binomial calculation, using a 2-sided alpha of 0.05 or a 1-sided alpha of 0.025. In addition, frequency distributions showing findings by treatment side will be presented with counts, percentages and, where appropriate, exact 95% CI using the Clopper and Pearson method.

All available data at each time point will be presented. No imputations for missing data are planned, unless indicated otherwise. For the primary efficacy endpoint, if missing values exceed 10%, sensitivity analyses with imputations will be conducted. (see Section 10.3.2.2).

9.3.3 Relative Difference Calculation

Relative side-to-side difference at any timepoint will be calculated as:

$$[\text{Value}_{(\text{treatment side})} - \text{Value}_{(\text{control side})} / \text{Value}_{(\text{control side})}] \times 100$$

A negative relative difference reflects a decrease in a given parameter on the treatment side compared to control, while a positive relative difference reflects an increase in the parameter on the treatment side compared to control.

9.4 Determination of Sample Size

9.4.1 PK Cohort

The sample size for the PK cohort was selected without regard for statistical considerations. The sample of 5 treated subjects was deemed adequate to assess the quantifiable systemic exposure to MF when delivered from a UP Drug-Coated Device.

9.4.2 Randomized Cohort

The sample size was calculated based on the difference in the patency grade at Day 30 between the treatment and control sides with the following assumptions:

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

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

9.5 Interim Analysis

There is no interim analysis planned for this study.

9.6 Coding Dictionaries

AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 21.0 or later). Concomitant medications, will be coded using the March 2018 or later version of the World Health Organization (WHO) Drug Global dictionary.

10 STATISTICAL ANALYSES

10.1 Subject Disposition

The number and percentage of sinuses in which dilation with the UP Drug-Coated Device or UP Control Device was attempted, and those in which the dilation was successful will be summarized in each cohort. The primary reason for subject discontinuation will be summarized. Major protocol deviations will be incorporated into the subject disposition outputs. Screen failures will be reported in the data listings and not presented in the summary table. Data for subject disposition, including termination date and reason, will be listed.

10.2 Demographics and Baseline Clinical Characteristics

Demographic data (i.e., age, gender, race, ethnicity) and baseline clinical characteristics (i.e., number and extent of prior endoscopic sinus surgery (ESS), symptoms that have been present for ≥ 12 weeks prior to baseline, current status of asthma and allergic rhinitis diagnosed by physician, aspirin intolerance or allergy, any allergies, and history of smoking), history of repeated courses of corticosteroids and history of epistaxis will be presented for all subjects in each cohort. Lund-Mackay score, baseline patency and polypoid edema grades of the FSO will be summarized per treatment side.

10.3 Primary Endpoints

10.3.1 PK Cohort – Primary Endpoint

The primary endpoint is the number of successful sinus dilations of all attempted FSO using the UP Drug-Coated Device. 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 UP Drug-Coated Device. A successful FSO dilation is defined as insertion of the UP Drug-Coated Device into the targeted FSO followed by 2 consecutive complete inflations.

10.3.2 Randomized Cohort – Primary Efficacy Endpoint

The primary efficacy endpoint is the difference in patency grade of the FSO between the treatment and control sides at Day 30 as determined by an independent, blinded sinus surgeon based on the centralized video-endoscopy review. Patency of the FSO will be assessed endoscopically by probing with a 3-mm olive-shaped frontal sinus suction tip (“suction tip”) and will be analyzed using the paired t-test.

For each subject, the difference in patency grade of the FSO between the treatment and control sides will be calculated and then averaged across all subjects. The difference in patency grade for a given subject will be set as missing if one of the FSO is unable to be viewed or graded.

The primary efficacy hypothesis is that mometasone furoate (MF) from the UP Drug-Coated Device will significantly increase the patency grade on the treatment side compared to control. The statistical test will be paired t-test where the difference in patency grade between treatment and control sides is determined.

The relevant null and alternative hypotheses for this primary efficacy endpoint are:

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

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

Although the alternative hypothesis is specified as two-sided, only a statistically significant difference in patency grade favoring treatment sides will constitute evidence of effectiveness. The two-sided α for this test is 0.05 (or one-sided α of 0.025).

10.3.2.1 Sensitivity Analysis for Steroid and Surgical Interventions

Because the primary efficacy endpoint for the randomized cohort will be determined by the 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 this outcome. Therefore, a sensitivity analysis will be performed to test the robustness of the efficacy conclusion to actual interventions given. Use of clinically necessary high-dose corticosteroids (e.g., oral, parenteral, injection, budesonide or other sinus steroid irrigations/rinses or drops, nebulized steroids administered nasally) or surgical intervention (e.g., repeat balloon dilation or sinus surgery involving dissection of the FSO) during the study will be tabulated.

In this analysis, data imputations will be performed as follows:

- If at Day 7, 14 or Day 21, a clinical investigator indicates on the Endoscopic Scoring Form that the frontal recess/FSO required oral steroids or surgical intervention, and that intervention was actually given, then the grades given by the independent reviewer at Day 30 will be

replaced by the grades given by the clinical investigator at the visit preceding commencement of oral steroids.

- If oral steroids were actually prescribed for reasons other than frontal sinus obstruction, then the grades given by the independent reviewer at Day 30 will be replaced by the grades given by the clinical investigator at the visit preceding commencement of oral steroids.

10.3.2.2 Sensitivity Analyses for Missing Data

Subjects with missed visit, lost to follow-up or patency grade 'unable to view' by the independent reviewer will be considered as missing data. If more than 10% of the primary efficacy data are missing, the following imputation analyses will be performed to assess the sensitivity of conclusions to missing data from the independent reviewer:

- Impute '4', for all missing values on the control sides and '0' on the treatment sides; this is a worst-case imputation.
- Impute '0', for all missing values on the control sides and '4' on the treatment sides; this is a best-case imputation.
- A "tipping point" analysis in which all missing observations on the control side will systematically be assigned a 0, 1, 2, 3 or 4, and all missing observations on the treatment side will separately be assigned a 0, 1, 2, 3, or 4, for a total of 5×5 = 25 analyses.
- Impute patency grades at Day 30 by clinical investigators in subjects missing values on the control or treatment sides.

10.4 Secondary Endpoints

10.4.1 PK Cohort

10.4.1.1 Endoscopic Outcomes Assessed by Clinical Investigators

Categorical measures will be analyzed as counts, proportions and frequencies and, where appropriate, 95% CI will be computed using exact methods.

The counts, proportion and frequency of the following outcomes will be presented per sinus side:

- Patency grade: sinuses with clinically significant stenosis/occlusion in the FSO (patency grade 0 or 1).

- Adhesion/scarring grade: sinuses with clinically significant amount of adhesion/scarring in the frontal recess/FSO (adhesion/scarring grade 2 or 3)
- Polypoid edema grade: sinuses with clinically significant amount of polypoid edema in the frontal recess/FSO (polypoid edema grade 2 or 3)
- Need for post-dilation intervention: proportion of sinuses that need post-dilation interventions in the frontal recess/FSO (e.g., steroid, surgical, repeat balloon dilation).

  Post-dilation intervention is a composite endpoint that includes:

  - Surgical interventions required to debride obstructive adhesions or scar tissue formation in the FSO (adhesion/scarring grade 2 or 3), and/or
  - Oral steroid interventions warranted to resolve recurrent inflammation or polypoid edema in the frontal recess/FSO, and/or
  - Repeat balloon dilation warranted to resolve clinically significant stenosis/occlusion of the FSO (patency grade 0 or 1)

Additional grouping for the above variables will also be analyzed.

Continuous measures will be analyzed using descriptive statistics such as means, SD, and, where appropriate, 95% CI, assuming a normal distribution for each timepoint. A change from baseline in patency, estimated FSO diameter, polypoid edema and inflammation score will be computed for each treated sinus.

10.4.1.2 Patient Reported Outcomes

The total SNOT-22 scores and individual domain scores will be computed. The total score is calculated as the sum of all 22 items, and ranges from 0 to 110, with the higher scores being worse outcome. The following table lists items and ranges for each symptom domain score.

SNOT-22 Domains	**Survey Items**	**Score Range**
Rhinologic Symptoms	#1, #2, #3, #6, #21, #22	0–30
Extra-Nasal Rhinologic Symptoms	#4, #5, #6	0–15
Ear/Facial Symptoms	#2, #7, #8, #9, #10	0–25

SNOT-22 Domains	Survey Items	Score Range
Psychological Dysfunction	#14, #15, #16, #17, #18, #19, #20	0–35
Sleep Dysfunction	#11, #12, #13, #14, #15	0–25

10.4.2 Randomized Cohort

10.4.2.1 Endoscopic Outcomes Assessed by Independent Reviewer

Descriptive statistics such as means, SD, median and, where appropriate, 95% CI will be computed for all continuous measures. Paired t-test will be used to assess side-to-side differences between treatment sides.

Descriptive statistics and side-to-side differences between treatment and control sides will be analyzed for the following outcomes:

- Patency grade of the FSO at Day 14
- Polypoid edema grade of the FSO at Day 14 and Day 30
- Estimated largest diameter of the FSO at Day 14 and Day 30
- Inflammation in the frontal recess/FSO at Day 14 and Day 30

Categorical measures will be analyzed as counts, proportions and frequencies and, where appropriate, 95% CI will be computed. Categorical data that can be localized to the treatment or control side will be analyzed using McNemar's test for correlated proportions. An exact version of McNemar's test will be performed for correlated proportions.

Counts, proportions and frequencies and side-to-side differences between treatment sides will be analyzed for the following categorical measures by independent reviewer at Day 14 and Day 30:

- Patency grade: sinuses with clinically significant stenosis/occlusion in the FSO (patency grade 0 or 1).
- Adhesion/scarring grade: sinuses with clinically significant amount of adhesion/scarring in the frontal recess/FSO (adhesion/scarring grade 2 or 3)
- Polypoid edema grade: sinuses with clinically significant amount of polypoid edema in the frontal recess/FSO (polypoid edema grade 2 or 3)

- Need for post-dilation intervention: proportion of sinuses that need post-dilation interventions in the frontal recess/FSO (e.g., steroid, surgical, repeat balloon dilation).

Additional grouping for the above variables will also be analyzed.

10.4.2.2 Endoscopic outcomes assessed by clinical investigators

Descriptive statistics such as means, SD, median and, where appropriate, 95% CI will be computed for all continuous measures. A paired t-test will be used to assess side-to-side differences between treatment and control sides. Descriptive statistics and side-to-side differences between treatment sides through Day 60 will be analyzed for the following:

- Patency grade of the FSO
- Polypoid edema grade of the frontal recess/FSO
- Estimated largest diameter of the FSO
- Inflammation in the frontal recess/FSO

Categorical measures will be analyzed as counts, proportions and frequencies and, where appropriate, 95% CI will be computed. Categorical data that can be localized to the treatment or control side will be analyzed using McNemar's test for correlated proportions. An exact version of McNemar's test will be performed for correlated proportions.

Counts, proportions and frequencies and side-to-side differences between treatment sides will be analyzed for the following categorical measures by clinical investigators through Day 60:

- Patency grade: sinuses with clinically significant stenosis/occlusion in the FSO (patency grade 0 or 1).
- Adhesion/scarring grade: sinuses with clinically significant amount of adhesion/scarring in the frontal recess/FSO (adhesion/scarring grade 2 or 3)
- Polypoid edema grade: sinuses with clinically significant amount of polypoid edema in the frontal recess/FSO (polypoid edema grade 2 or 3)
- Need for post-dilation intervention: proportion of sinuses that need post-dilation interventions in the frontal recess/FSO (e.g., steroid, surgical, repeat balloon dilation).

Additional grouping for the above variables will also be analyzed.

10.5 Consistency Across Study Centers

The consistency of device performance across the study centers will be investigated. A one-way analysis of variance (ANOVA) will be used to test whether the mean difference in patency grade between treatment and control sides differs by site. If a statistically significant site effect is not found ($p > 0.05$), results will be considered poolable across sites. If a statistically significant site is found ($p < 0.05$), exploratory analyses will be conducted to investigate the issue. This may include regression adjustment for baseline clinical characteristics; the set of baseline characteristics to be considered include those that significantly differ across sites, or significantly predict the difference in patency grade between the treatment sides. If regression adjustment causes the site term to become non-significant, results will be considered poolable across sites, and covariate-adjusted estimates of the treatment effect will be reported. If regression adjustment does not explain the site heterogeneity, further summaries (separating sites or excluding sites) will be explored.

10.6 Multiplicity Adjustment for Secondary Efficacy Endpoint Analyses

The company intends to present inferential statistical results in the clinical summary section of the instructions for use for 4 secondary endpoints. This section describes the methods that will be used to control the familywise type 1 error rate (FWER) among the tests of these 4 secondary endpoints.

If and only if the primary efficacy objective of the randomized cohort is met, Holm's step-down procedure will be used to control the FWER at a one-sided significance level of 0.025 for the following 4 secondary endpoints:

- Difference in the mean polypoid edema grade of the frontal recess/FSO between the treatment and control sides at Day 14 by independent reviewer
    - Test: H_0: $\mu_T = \mu_C$ *vs* H_A: $\mu_T < \mu_C$, by paired t-test
- Difference in mean estimated largest diameter of the FSO between the treatment and control sides at Day 30 by independent reviewer
    - Test: H_0: $\mu_T = \mu_C$ *vs* H_A: $\mu_T > \mu_C$, by paired t-test

- Difference in the proportion of clinically significant amount of stenosis/occlusion in the FSO (grade 0 or 1) between the treatment and control sides at Day 30 by independent reviewer
    - Test: H_0: $P_T = P_C$ *vs* H_A: $P_T < P_C$, by McNemar's test (exact version)
- Difference in the mean estimated largest diameter of the FSO between the treatment and control sides at Day 60 by clinical investigators
    - Test: H_0: $\mu_T = \mu_C$ *vs* H_A: $\mu_T > \mu_C$, by paired t-test

Let $p_{(1)} \leq p_{(2)} \leq \ldots \leq p_{(m)}$ be the m=4 p-values resulting from the above 4 tests, after being placed in ascending order. Adjusted p-values $\tilde{p}_{(1)}, \ldots, \tilde{p}_{(m)}$ from Holm's step-down procedure will be calculated as follows:

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

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

If any adjusted p-value exceeds 1, it is set to 1. Using this procedure, any adjusted one-sided p-value that is < 0.025 is statistically significant and supports a claim for the corresponding endpoint, while any adjusted p-value ≥ 0.025 is not statistically significant. Both adjusted and unadjusted p-values will be reported. (Cook 1998)

10.7 Safety Measures

In the PK cohort, 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, mean, SD, medians, ranges and, where appropriate, coefficient of variation as described in Section 9.3.1.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Where possible, and if applicable, AE will be localized to a sinus type and side. If a subject reports the same AE more than once or experiences the same AE on multiple occasions, the maximum severity grade and relationship to the study drug, study device, accessory devices, and/or dilation procedure will be presented.

The incidence and percentages of AE and serious adverse events (SAE) through Day 30 in the PK cohort and through Day 60 in the randomized cohort, including adverse device effects and USADE, will be presented by MedDRA system organ class (SOC) and preferred term (PT). Complete subject listings of all AE will be provided. For each AE, the following will be specified:

- Start and stop dates, and event onset (study day)
- The affected side (right or left) if available
- Seriousness
- Severity
- Strength of relationship
- Action taken
- Outcome

10.8 Concomitant Medications

Prior and concomitant medications will be coded to therapeutic class and PT using the WHO Drug Global dictionary. All concomitant medications will be listed and summarized in a table.

11 REFERENCES

Cook, R. and Dunnett, C. (1998). Multiple Comparison. Encyclopedia of Biostatistics. Armitage, P. and Chichester, C. Wiley**:** 2739.

12 APPENDICES

Appendix A: Schedule of Assessments

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

Randomized Cohort

Assessment	Screening	Baseline/ Procedure	Day 7 (±2 d)	Day 14 (±2 d)	Day 21 (±2 d)	Day 30 (±2 d)	Day 60 (±3 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

Appendix B: Table Mock-Ups for PK Cohort

Appendix C: Listing Mock-Ups for PK Cohort

Appendix D: Table Mock-Ups for Randomized Cohort

Appendix E: Listing Mock-Ups for Randomized Cohort