STATISTICAL ANALYSIS PLAN

1 TITLE PAGE

Study Title	The EXPAND Study: A Clinical Evaluation of PROPEL® Contour Placement Following In-Office Frontal Sinus Balloon Dilation
Protocol Number	P500-1220
ClinicalTrials.gov ID	NCT04858802
Study Devices	PROPEL Contour (mometasone furoate, 370 mcg) VenSure™ Nav Balloon Device Cube Navigation System
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
Biostatistics and Data Analysis	Intersect ENT, Inc.

Statistical considerations addressing the impact of COVID-19 on the primary and key secondary endpoints are detailed in Section **10**.

TABLE OF CONTENTS

LIST OF TABLES

2 REVISION HISTORY

Revision	Revision Date	Summary of Changes
1.0	29-NOV-2021	Initial release
2.0	20-MAY-2022	• Replaced all instances of FSO maximum diameter with FSO minimum diameter • Tables 1 and 2 reorganized based on type of analysis (primary and key secondary; secondary and exploratory) instead of timepoint (Day 45; Day 90 and 180) • Sec. 4.5 specified major procedural protocol deviations and updated analysis populations for primary and secondary analyses • Sec. 6.1 and 9.8 specified the type of data collected and analyses to be performed for endpoints and economic measures • Sec. 9.2 updated the definition of primary efficacy endpoint and implant success rate per updated study protocol (CP-00030 Rev 5.0) • Sec. 9.4 replaced key secondary endpoint of polypoid edema in the frontal recess/FSO with FSO minimum diameter at Day 45 on CT by an independent, blinded reviewer • Added CP-00030, CP-00038, and R 28020 to references • Made minor clarifications, edits, and editorial changes throughout

3 LIST OF ABBREVIATIONS

Abbreviation	Expansion
ADE	adverse device effect
AE	adverse event
BSD	balloon sinus dilation
CIP	clinical investigational plan
CRF	case report form
CRS	chronic rhinosinusitis
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
FSOT	frontal sinus outflow tract
GCP	good clinical practice
ICH	International Council on Harmonization
i.e.	'id est' in Latin, meaning 'that is'
INCS	intranasal corticosteroids
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
OS	frontal sinus outflow narrowest diameter
PTE	per-treatment evaluable
RSI	Rhinosinusitis Symptom Inventory
SADE	serious adverse device effect

SAE	serious adverse event
SAP	statistical analysis plan
SNOT	Sino-Nasal Outcome Test
SOP	standard operating procedure
UADE	unanticipated adverse device effect
USADE	unanticipated serious adverse device effect
WHO	World Health Organization

4 INTRODUCTION

This document outlines the statistical analysis plan (SAP) for the EXPAND Study conducted by Intersect ENT under protocol P500-1220 entitled "The EXPAND Study: A Clinical Evaluation of PROPEL® Contour Placement Following In-office Frontal Sinus Balloon Dilation". Preparation of this SAP was based on the EXPAND study protocol version 5.0 dated 20 May 2022. The SAP specifies the data listings, tabular summaries, and analyses to be performed.

4.1 Study Objective

The objective of the EXPAND study is to evaluate the efficacy of PROPEL Contour placement in the frontal sinus ostium (FSO) following in-office frontal sinus balloon dilation (SBD) in patients with chronic rhinosinusitis (CRS).

4.2 Study Design

This is a post-market, randomized, intra-patient controlled, blinded, multicenter trial enrolling up to 80 randomized subjects from up to 20 US sites. Study subjects will be randomized following a successful in-office bilateral frontal BSD to receive 1 PROPEL Contour on 1 FSO side (treatment), and nothing on the contralateral side (the control treatment).

4.3 Study Visits and Assessments

Subjects are expected to return for 4 follow-up visits at Day 21, 45, 90 and 180 (end of study). Each follow-up visit includes endoscopic evaluation with video recording, and computed tomography (CT) scan will be performed at Day 45 and 180 (see **Appendix A**).

4.4 Sample Size and Power

The sample size was calculated based on the mean difference in the cross-sectional area of the FSO by CT at Day 30 between the treatment and control sides from subjects in the PROGRESS study who underwent bilateral frontal BSD followed by unilateral placement of PROPEL Contour with the following assumptions:

- Expected mean difference of 9 mm^2 between the treatment and control sides
- A standard deviation (SD) of 18 mm^2 for side-to-side difference
- Target power of 95%
- Type I error rate of $\alpha = 0.05$, 2-sided

Internal, unpublished data suggest that SD = 18 is a reasonable assumption and that an achievable difference in mean cross-sectional areas of the FSO may be greater than 9 mm^2. The 9 mm^2 is deemed to be a clinically important difference to detect. Based on standard formulas for a t-test, a sample size of 56 subjects provides at least 95% power to detect a difference of 9 mm^2 in mean FSO cross-sectional area between treatment side and control side. Assuming up to 20% of subjects

with non-evaluable data on one or both sides, as it was reported in PROGRESS study report (R 28020), an additional 24 subjects will be enrolled for a total of 80 randomized subjects. Sample size calculations were carried out in PASS 14 (PASS 2015).

4.5 Analysis Populations

The analysis of the primary and key secondary endpoints at Day 45 will be conducted on the intent-to-treat (ITT) population. The secondary endpoint analyses will be performed on the ITT and per-treatment evaluable (PTE) populations through Day 180. The exploratory endpoint analysis will be performed on the PTE population. The safety will be evaluated on the safety population. All analysis populations are defined below:

- *ITT Population*. All randomized subjects and sinuses in whom SBD followed by placement of PROPEL Contour in the target sinus was attempted. An attempt occurs when the physician introduces the delivery system into the subject's nostril with the intent of implant placement. Subjects' sinuses are analyzed in the treatment group to which they are randomized. This is the main analysis population for the primary and key secondary efficacy endpoints.
- *PTE Population*. All randomized subjects who have received PROPEL Contour in the target sinus, who have no major procedural protocol deviations (e.g., underwent study-related prior to informed consent, received treatment other than assigned by randomization), and for whom follow-up data are available. This population will be used for the secondary and exploratory endpoints.
- *Safety Population*. All subjects and sinuses exposed to PROPEL Contour. This population will be used for all summaries of AEs. Any subjects enrolled in the study who are not exposed to PROPEL Contour will be summarized separately.

5 TYPE OF PLANNED ANALYSIS

5.1 Interim Analysis

There is no interim analysis planned for this study.

5.2 Primary Analysis

After the last enrolled and randomized subject has completed all Day 45 assessments or been lost to follow-up, all outstanding data queries related to the primary and key secondary endpoints have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the study blind will be broken, and the primary analysis will be performed. The primary analysis will be performed using ITT population as detailed in **Table 1**.

Table 1: Summary of Primary and Key Secondary Endpoints at Day 45

Endpoint	Display	ITT	PTE	Sensitivity	Subgroup
Primary					
Patency based on cross-sectional area of FSO on CT by an independent, blinded reviewer	T,L	Y	-	Y	Y
Key Secondary Adjusted for Multiplicity					
Cross-sectional area of FSO on CT change from baseline	T,L	Y	-	-	-
FSOT volume on CT	T,L	Y	-	-	-
FSO minimum diameter on CT	T,L	Y	-	-	-
Zinreich's score for frontal sinus	T,L	Y	-	-	
Need for post-op interventions in the frontal recess/FSO	T,L	Y	-	-	-

Abbreviations: CT, computed tomography; FSOT, frontal sinus outflow tract; ITT, intent to treat; L, listing; PTE, per treatment evaluable; T, table; Y, yes.

5.3 Secondary and Exploratory Analyses

The secondary and exploratory analyses through Day 180 (end of study) will be performed after completing primary analysis and after the database is locked, using analysis populations and endpoints detailed in

Table 2.

Table 2: Summary of Secondary and Exploratory Analyses

Endpoint	Display	ITT	PTE
Secondary			
Cross-sectional area of FSO on CT (Day 180)*	T,L	Y	-
FSOT volume on CT (Day 180)*	T,L	Y	-
FSO minimum diameter on CT (Day 180)*	T,L	Y	-
Lund-Mackay score for the frontal sinus (Day 45, 180)*	T,L	Y	-
Zinreich's score for the frontal sinus (Day 180)*	T,L	Y	-
Lund-Mackay score for the frontal sinus (Day 45, 180)**	T,L	Y	-
Need for post-operative interventions in the frontal recess/FSO (Day 21, 90, 180)**	T,L	Y	
Adhesion/scarring grade in the frontal recess/FSO and ethmoid sinus (Day 21, 45, 90, 180)**	T,L	Y	-
Polypoid edema in the frontal recess/FSO (Day 21, 45, 90, 180)**	T,L	Y	-

Endpoint	Display	ITT	PTE
Inflammation score in the frontal recess/FSO (Day 21, 45, 90, 180)**	T,L	Y	-
Polyp grade in the ethmoid sinus (Day 21, 45, 90, 180)**	T,L	Y	-
CRS side-specific score (Day 21, 45, 90, 180)	T,L	-	Y
SNOT-22 score (Day 180)	T,L	-	Y
RSI score (Day 180)	T,L	-	Y
Implant delivery success rate	T,L	Y	-
Exploratory			
Patient satisfaction (Day 90, 180)	T,L	-	Y
Health-economic measures (Day 180)	T,L	-	Y

Abbreviations: CRS, chronic rhinosinusitis; CT, computed tomography; FSO, frontal sinus ostium; FSOT, frontal sinus outflow tract; ITT, intent to treat; L, listing; PTE, per treatment evaluable; RSI, Rhinosinusitis Symptom Inventory; SNOT, Sino-Nasal Outcome Test; T, table; Y, yes.
** By an independent, blinded reviewer.*
*** By clinical investigators.*

6 STATISTICAL METHODS

6.1 General Considerations for Data Analysis

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

Continuous data such as cross-sectional area of FSO, FSO minimum diameter, FSOT volume, inflammation score, CRS side-specific symptom score, SNOT-22 score, and RSI score will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum, and number of observations, unless otherwise stated.

Categorical data such as Lund-Mackay score, Zinreich's modified Lund-Mackay score, adhesion/scarring grade, polypoid edema grade, and polyp grade will be analyzed quantitatively and summarized in terms of the mean, standard deviation (SD), median, minimum, maximum, and number of observations, unless otherwise stated.

Categorical data such as need for post-operative intervention in the frontal recess/FSO, patient satisfaction, implant delivery success rate, and economic measures will be summarized in terms of the number of subjects providing data at the relevant time point, frequency counts and percentages. If not stated otherwise, percentages will be presented with one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. 100% will be presented without decimal places. 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.

P-values greater than or equal to 0.001, in general, will be presented to 3 decimal places. P-values less than 0.001 will be presented as "< 0.001".

95% Confidence intervals (CI) will be presented to 1 more decimal place than the raw data. Unless stated otherwise, a two-sided 95% confidence level will be calculated when confidence interval is presented.

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.

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.

All available data at each time point will be presented. No imputations for missing data are planned, unless indicated otherwise.

6.2 Baseline

The baseline is defined as the last observation recorded prior to the initiation of the study treatment (i.e., PROPEL Contour placement on the treatment site following successful BSD procedure) and referred to as Day 0.

6.2.1 Study Day Calculation

Study day is calculated relative to the date of Day 0 (baseline) and will appear in the listings where applicable. If the date of event is on or after Day 0, study day will be calculated as:

Study day = date of event – date of Day 0

6.3 Randomization

Following frontal BSD, eligible subjects will have their sinus sides randomly assigned to receive the PROPEL Contour (treatment) on one side, and no implant (control) on the contralateral side. The ratio of left to right sinus assignments will be 1:1. The randomization scheme will be generated by an independent statistician, and the randomization envelopes will be assembled by an in-house clinical research associate. The randomization scheme will be stratified by each clinical center, and will use permuted blocks of various sizes.

6.4 Role of the Independent Reviewer

The CT scans at Screening, Day 45 and 180 from all subjects will be evaluated by an independent, blinded reviewer, a role assumed by the centralized imaging core lab, for determination of the

primary and CT-related secondary efficacy endpoints. The reviewer will be independent from the study (i.e., not enrolling study subjects for the study) and blinded to implant treatment assignment (i.e., will not know which side received PROPEL Contour). CT scans will be labeled with subject ID and be provided to the independent reviewer.

The primary efficacy endpoint requires precise measurements of the FSO using reconstructed cone beam images in the axial, coronal and sagittal planes. The image reconstructions and measurements of CT-related endpoints will be performed by board-certified independent radiologists at the centralized imaging core lab in accordance with the standardized protocol (see CP-00038). The reviewers will be blinded to treatment assignment and have no access to any symptomatic or endoscopic outcomes.

6.5 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.

6.6 Missing Dates

In analysis of AEs and medication, a complete date will be established in order to identify AEs or medication as occurring during treatment or not. For handling partially reported onset/start and outcome/end dates for AEs or medication the following algorithms are applied:

- AEs:
  - Missing onset day, but month and year present:
    - If baseline visit occurred in the same month and year as the occurrence of the AE, then the onset day of the event is assigned to the date of baseline visit.
    - Otherwise, the onset day is set to the first day of the month (e.g., XX-Sep-2021 is considered as 01-Sep-2021).
  - Missing onset day and month, but year present:
    - If baseline visit occurred in the same year as the occurrence of the AE, then the onset date of the event is assigned to the date of baseline visit.
    - Otherwise, the onset day and month is set to 01 January (e.g., XX-XXX-2021 is considered as 01-Jan-2021).

- Missing outcome day, but month and year present:
  - The day is set to the last day of the month (e.g., XX-Sep-2021 is considered as 30-Sep-2021).
- Missing outcome day and month, but year present:
  - The outcome day and month is set to 31 December (e.g., XX-XXX-2021 is considered as 31-Dec-2021).

- Medications:
  - Missing start day, but month and year present:
    - If baseline visit occurred in the same month and year as the occurrence of the medication, then the start day of the medication is assigned to the date of baseline visit.
    - Otherwise, the start day is set to the first day of the month (e.g., XX-Sep-2021 is considered as 01-Sep-2021).
  - Missing start day and month, but year present:
    - If baseline visit occurred in the same month in the same year as the occurrence of the medication, then the start date of the medication is assigned to the date of baseline visit.
    - Otherwise, the start day and month is set to 01 January (e.g., XX-XXX-2021 is considered as 01-Jan-2021).
  - Missing stop day, but month and year present:
    - The day is set to the last day of the month (e.g., XX-Sep-2021 is considered as 30-Sep-2021).
  - Missing stop day and month, but year present:
    - The stop day and month is set to 31 December (e.g., XX-XXX-2021 is considered as 31-Dec-2021).

6.7 Missing Data for Efficacy and Safety Endpoints

Missing data for each efficacy endpoint will be handled as described in Sections **9.1** and **9.3.4**.

For continuous endpoints, change from baseline will be set to missing at visits with missing postbaseline values or where data were imputed to missing. Continuous efficacy endpoints will be set to missing for subjects who received any of the following not allowed medication post-baseline procedure:

- Corticosteroids (e.g., oral, parenteral or injection, budesonide or other sinus steroid irrigations/rinses or drops, breath powered Xhance, nebulized steroids administered nasally or other drug eluting stents) through Day 45; or
- Biologics for CRS treatment (e.g., Dupixent).

For binary endpoints, subjects with missing efficacy data, early withdrawals, and/or subjects who received not allowed corticosteroids or biologics for chronic sinusitis condition attributable to the FSO/frontal recess will be imputed as a treatment failure. If a subject initiates high-dose steroid for other reasons not involving FSO/frontal recess, this does not represent treatment failure.

Additional rules for handling of missing data and rescue treatments are detailed below:

- *Missing efficacy data*. Visits with missing data (due to a missed visit or missing component of a composite endpoint) will be set to treatment failure.
- *Early withdrawals*. Only visits following the early withdrawal visit will be set to treatment failure.
- *Rescue treatments*. Subjects who rescue with corticosteroids (before Day 45) or biologics will be set to treatment failure at all subsequent visits and continuous endpoints set to missing.
- *Missing baseline value*. For efficacy endpoints, a missing value at baseline will not be imputed, and the endpoint will be set to missing for all visits.

6.8 Multiple Assessments and Visits

If a variable (e.g., CT) has been assessed multiple times at the same visit, only the last assessment will be used.

Only completed scheduled visits will be included in summary tables (**Appendix B**). Listings will include scheduled and unscheduled visits (**Appendix C**).

6.9 Data Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency and integrity in accordance with the study sponsor's SOPs.

6.10 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 FSO area between treatment and control sides differs by site. If a statistically significant site effect is not found (at the 0.15 significance level, i.e., $p \geq 0.15$), results will be considered poolable across sites. If a statistically significant site effect is found ($p < 0.15$), 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 FSO area 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.

6.11 Coding Dictionaries

Each AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 24.0 or later). Prior and concomitant medications will be coded using the March 2018 or later version of the World Health Organization (WHO) Drug Global dictionary.

7 SUBJECT ENROLLMENT AND DISPOSITION

The number and percentage of subjects in whom the implant procedure was attempted and in whom it was successful will be summarized. The primary reason for subject discontinuation will be summarized. Screen failures will be reported in the data listings and the summary table. Data for subject disposition, including termination date and reason, will be listed. The randomization schedule used for the study will be provided in a listing and as an appendix to CSR.

8 DEMOGRAPHICS AND BASELINE CLINICAL CHARACTERISTICS

Demographic data (i.e., age, gender, race, ethnicity) and baseline clinical characteristics (i.e., CRS diagnosis, CRS symptoms present for at least 12 weeks, number and extent of prior endoscopic sinus surgery, 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. Baseline Lund-Mackay score and endoscopic scorings will be summarized per treatment side.

9 EFFICACY ANALYSES

9.1 General Considerations

Missing data imputation analyses:

- *Observed case (OC).* Missing values remain missing. For the categorical composite endpoints, in the case that some components are missing, the composite endpoint assessment will be derived based on the non-missing components. If non-missing components are not sufficient to determine final composite endpoint, then the composite endpoint will be set as missing. For continuous composite endpoints, if any components are missing, the composite endpoints will be set as missing.
- *Last observation carried forward (LOCF).* Baseline measurements will not be carried forward to post-baseline. Only post-baseline measurements will be LOCF. For the composite

endpoints, the last non-missing post-baseline observation will be carried forward to subsequent visits for each individual component first, and then the composite endpoints using individual components imputed by LOCF will be calculated as described above. If a subject does not have a non-missing observed record for a post-baseline visit, the last post-baseline record prior to the missed visit will be used for this post-baseline visit. If the last non-missing observation prior to the missing visits cannot be determined due to multiple measurements occurring at the same time or the time not available within the same day, the worst outcome will be used for LOCF. If missing components still exist after LOCF, the composite endpoints will be calculated using the same rules as described in OC.

- *Non-responder imputation (NRI).* For all binary response measurements, starting from OC, all missing values will be set as non-responders. If subject only had baseline measurements, LOCF and OC analyses will not include this subject. But this subject will be treated as non-responder in NRI analyses.

9.2 Clinical Variables

9.2.1 CT Endpoints

The independent, blinded reviewer will perform computer assisted measurements in the FSO and frontal sinus outflow tract (FSOT) according to a validated protocol (See CP-00038).

Cross-sectional area of the FSO

The cross-sectional area within the mucosa and the bone at the location of the measured minimum diameter between 5 mm superior and 5 mm inferior to the ostium. It will be reported in mm^2 for the mucosa and bone for the left and right ostia separately. This measurement will be repeated at the location 5 mm superior and 5 mm inferior to the ostium.

FSO minimum diameter

The minimum diameter as output by the segmentation software at the FSO reference plane between the boundaries of the mucosa and bone, representing the pneumatized portion of the ostium (with mucosa as boundaries) or the pneumatized and mucosal portions of the ostium (with bone as boundaries). It will be reported in mm for the left and right ostia separately. This measurement will be repeated at the CT slice corresponding to the location 5 mm superior and 5 mm inferior to the ostium.

FSOT volume

The volume of the patent frontal sinus outflow tract (FSOT) between boundaries of the mucosa located 5 mm superior and 5 mm inferior to the ostium in the 3D volume segmentation of the FSOT. It will be reported in mm^3 and measured separately for the left and right FSOT. This space

corresponds to the implant location. The measurements will be repeated for the volume of mucosal and patent FSOT (i.e., with bone as boundaries).

Zinreich's modified Lund-Mackay score

Each sinus is assigned a score based on the percentage of opacification from mucosal thickening as follows:

0: 0%

1: 1% to 25%

2: 26% to 50%

3: 51% to 75%

4: 76% to 99%

5: 100% or completely occluded

The ostiomeatal complex (OMC) is given a score of 0 if it is completely patent, 1 if it is partially obstructed, or 2 if it is completely obstructed. Similar to the Lund-Mackay system, each side is graded, and their sum is the total score out of maximum of 54.

Lund-Mackay score

For each of the frontal, anterior ethmoid, posterior ethmoid, maxillary, and sphenoid sinus, a value of 0 is assigned if the sinus is totally patent, 1 if it is partially opacified, or 2 if it is completely opacified. The OMC is scored either 0 or 2. The maximum score for each side is thus 12, with a total score determined out of 24 after summing both sides. The Lund-Mackay scores are evaluated by the independent, blinded reviewer and by clinical investigators.

9.2.2 Endoscopic Endpoints

Adhesion/scarring grade in the frontal recess/FSO and ethmoid sinus

Adhesion/scarring severity in the FSO is 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)

Adhesion/scarring severity in the ethmoid sinus graded on a 5-point scale 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

Inflammation score in the frontal recess/FSO

For the purpose of the endoscopic scoring method in this study, the term inflammation is a global descriptor that includes erythema, edema 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.

Polypoid edema in the frontal recess/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

Polyp grade in the ethmoid sinus

Polyps originating from the ethmoid sinus are assessed endoscopically and graded on an 8-point scale 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

9.2.3 Need for Post-operative Intervention

Need for post-operative intervention is determined by clinical investigators at Day 21, 45, 90, and 180 as follows:

- Repeat frontal BSD warranted or performed for restenosis/occlusion in the frontal recess/FSO; or
- Surgical intervention warranted or performed to debride obstructive adhesions/scarring or for restenosis/occlusion in the frontal recess/FSO; or
- Oral steroids warranted or prescribed to resolve recurrent edema in the frontal recess/FSO.

9.2.4 Patient-Reported Outcomes

9.2.4.1 SNOT-22 Questionnaire

The Sino-Nasal Outcome Test (SNOT-22) questionnaire is a 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. 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 3** lists items and ranges for each symptom domain score.

Table 3: SNOT-22 Domain Scoring

SNOT-22 Domain	Survey Item	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
Psychological Dysfunction	14, 15, 16, 17, 18, 19, 20	0–35
Sleep Dysfunction	11, 12, 13, 14, 15	0–25

9.2.4.2 RSI Questionnaire

The Rhinosinusitis Symptom Inventory (RSI) is administered using a paper (reflective) questionnaire to assess the CRS symptoms: 5 key symptoms (facial pain/pressure, facial congestion/ fullness, nasal obstruction/blockage, nasal discharge or post-nasal drip, decreased sense of smell), 7 other symptoms (headache, halitosis, dental pain, cough, ear symptoms, fevers, and fatigue) on a 6-point scale of 0 to 5, as follows:

- 0: Absent
- 1: Very mild
- 2: Mild
- 3: Moderate
- 4: Severe
- 5: Very severe

The total symptom scores and individual domain scores will be computed. The total score is calculated as the sum of all 12 symptom scores. The individual symptom scores are used to calculate 4 domain scores (**Table 4**).

Table 4: RSI Domain Scoring

RSI Domain	Symptom	Score Range
Nasal symptoms	Nasal obstruction Rhinorrea Sense of smell	0–15
Facial symptoms	Facial pain/pressure Facial congestion/fullness Headache	0–15
Otolaryngologeal symptoms	Halitosis Dental pain Cough Ear symptoms	0–20
Systemic	Fevers Fatigue	0–10

9.2.4.3 CRS Side-Specific Questionnaire

The CRS side-specific Questionnaire allows patients to evaluate each of the following 5 cardinal symptoms of CRS on the left and right side:

- Facial pain/pressure

- Facial congestion/fullness
- Nasal obstruction/blockage
- Discolored or pus nasal discharge or post-nasal drip
- Decreased sense of smell

Each side is scored individually on a 6-point scale as follows:

- 0: Absent
- 1: Very mild
- 2: Mild
- 3: Moderate
- 4: Severe
- 5: Very severe

9.2.4.4 Patient Satisfaction Questionnaire

The patient is asked to evaluate how satisfied they are with PROPEL Contour for treatment of CRS using a 5-point Likert scale as follows and whether they would recommend or not PROPEL Contour to a family member or a friend.

- Very dissatisfied
- Somewhat dissatisfied
- Neither satisfied or dissatisfied
- Somewhat satisfied
- Very satisfied

9.2.5 Implant Delivery Success

Implant delivery success is defined as successful access and deployment of the PROPEL Contour Sinus Implant into the FSO. Delivery is considered successful if the procedure concludes with correct implant placement on the intended side, even if a second attempt to place the implant is necessary. An attempted deployment occurs when the investigator introduces the delivery system into the subject's nostril with the intent of placing an implant.

9.3 Primary Efficacy Endpoint

Side-to-side difference in the FSO patency at Day 45 based on cross-sectional area of the FSO by CT measurements by an independent, blinded reviewer.

9.3.1 Definition

The cross-sectional area will be determined by the independent, blinded reviewer on CT at Day 45 within the mucosa at the location of the measured minimum diameter between 5 mm superior and 5 mm inferior to the ostium. It will be reported in mm^2 for the left and right ostia separately.

For each subject, the difference between FSO cross-sectional area at Day 45 in the treatment and control sides will be calculated and then averaged across all subjects in the ITT population. The FSO cross-sectional area will be set as missing if the FSO is unable to be viewed or measured.

9.3.2 Statistical Hypothesis

The primary efficacy hypothesis is that the placement of the PROPEL Contour will significantly increase the FSO cross-sectional area on the treatment side versus the control side. The relevant null and alternative hypotheses for this primary efficacy endpoint are:

H_0: $\mu = 0$

H_1: $\mu \neq 0$

Where μ represents the mean difference between the treatment and control sides in cross-sectional area of the FSO at Day 45.

9.3.3 Primary Analysis

The primary statistical method is a t-test comparing the mean FSO cross-sectional area at Day 45 in the treatment and control sides.

The study will be considered successful if there is a statistically significant difference in mean FSO cross-sectional area in favor of the treatment side. Although the alternative hypothesis is two-sided, only a statistically significant difference in average FSO area favoring the treatment side will constitute evidence of effectiveness.

9.3.4 Sensitivity Analyses

Sensitivity analysis for medical or surgical intervention

Because intervention with oral steroids or surgical intervention may confound the primary efficacy endpoint, the following method will be applied to the analyses in cases where such interventions are performed:

- If a subject initiates oral steroids or undergoes revision ESS for CRS conditions attributable to the FSO/frontal recess before Day 45, this represents treatment failure. If the intervention occurs on the treatment side or both sides, the FSO cross-sectional area of the treatment side will be imputed with the value of the control side (i.e., side-to-side difference in FSO area is

zero). If the intervention occurs on the control side only, the FSO cross-sectional area in the control side will be imputed as zero (i.e., totally occluded).

- If a patient initiates oral steroids for other reasons not involving the FSO/frontal recess before Day 45, this does not represent treatment failure. In this scenario, the side-to-side difference in FSO cross-sectional area for that subject will be imputed as zero.
- No other data imputation rules will be applied in the planned statistical analyses.

Sensitivity analysis for missing data

Subjects with a missed visit, lost to follow-up, or with FSO cross-sectional area 'unable to view' by the independent, blinded 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 test the robustness of the primary efficacy conclusion in order:

- *Worst-case imputation*. The worst case of side-to-side difference in FSO area is zero. If the primary efficacy endpoint passes (p-value < 0.05) using worst-case imputation, then there is no need to do a best-case imputation analysis.
- *Best-case imputation*. The best case of side-to-side difference in FSO area is equal to the average for the treatment site.

9.3.5 Subgroup Analyses

The primary efficacy endpoint will be examined using the following subgroups that are of interest in assessing the treatment effect of PROPEL Contour. The analysis of the primary endpoint may be performed if each subgroup represents at least 10% of the ITT population.

- Age (< 65 vs. ≥ 65)
- Gender (male vs. female)
- Previous frontal BSD (Yes vs. No)
- Ethmoid polyp grade (Yes vs. No)

9.4 Key Secondary Endpoints

- Cross-sectional area of the FSO change from baseline to Day 45 on CT by an independent, blinded reviewer
- FSOT volume at Day 45 on CT by an independent, blinded reviewer
- FSO minimum diameter at Day 45 on CT by an independent, blinded reviewer
- Zinreich's modified Lund-Mackay score for the frontal sinus at Day 45 on CT by an independent, blinded reviewer

- Need for post-operative intervention in the frontal recess/FSO by clinical investigators at Day 45

See Section **9.2.1** for the definitions for these endpoints.

9.4.1 Multiplicity Adjustment for Key Secondary Endpoints

Intersect ENT intends to present inferential statistical results to support product labeling claims for 5 key 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 5 secondary endpoints. All other secondary endpoints will be viewed as exploratory or explanatory in nature.

1. Cross-sectional area of the FSO change from baseline to Day 45 on CT by an independent, blinded reviewer

   Test: H_0: $\mu = 0$ vs $\mu \neq 0$ by t-test

2. FSOT at Day 45 on CT by an independent, blinded reviewer

   Test: H_0: $\mu = 0$ vs $\mu \neq 0$ by t-test

3. FSO minimum diameter at Day 45 on CT by an independent, blinded reviewer

   Test: H_0: $\mu = 0$ vs $\mu \neq 0$ by t-test

4. Zinreich's modified Lund-Mackay score for frontal sinus at Day 45 on CT by an independent, blinded reviewer

   Test: H_0: $\mu = 0$ vs $\mu \neq 0$ by t-test

5. Need for post-operative intervention by clinical investigators at Day 45

   Test: H_0: $p_T = p_C$, where p_T and p_C are the probability of needing post-operative intervention on the treatment and control sides, respectively. Tested by McNemar's test (exact version).

Let $p_{(1)} \leq p_{(2)} \leq \ldots \leq p_{(m)}$ be the m=5 p-values resulting from the above 5 tests, after being placed in ascending order. Adjusted p-values $\tilde{p}_{(1)}, \ldots, \tilde{p}_{(m)}$ from Holm's step-down procedure will be calculated as follows:

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

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

If any adjusted p-value exceeds 1, it is set to 1. Using this procedure, any adjusted p-value that is < 0.05 is statistically significant and supports a claim for the corresponding endpoint, while any

adjusted p-value ≥ 0.05 is not statistically significant. Both adjusted and unadjusted p-values will be reported.

9.5 Secondary Endpoint Analysis

Secondary endpoints to be collected and analyzed are listed below alongside references to the sections in which they are defined:

CT grading by an independent, blinded reviewer (see Section **9.2.1**):

- Cross-sectional area of FSO (Day 180) and change from baseline
- FSOT volume (Day 180) and change from baseline
- FSO minimum diameter (Day 180) and change from baseline
- Zinreich's modified Lund-Mackay score for the frontal sinus (change from baseline to Day 45)
- Zinreich's modified Lund-Mackay score for the frontal sinus (Day 180) and change from baseline
- Lund-Mackay score for the frontal sinus (Day 45, 180) and change from baseline

CT grading by clinical investigators (see Section **9.2.1**):

- Lund-Mackay score for the frontal sinus (Day 45, 180) and change from baseline

Endoscopic grading by clinical investigators (see Section **9.2.2**):

- Need for post-operative intervention in the frontal recess/FSO as determined by clinical investigators (Day 21, 90, 180)
- Adhesion/scarring grade in the frontal recess/FSO (Day 21, 45, 90, 180):
- Adhesion/scarring grade in the ethmoid sinus (Day 21, 45, 90, 180):
- Inflammation score in the frontal recess/FSO (Day 21, 45, 90, 180):
- Polypoid edema in the frontal recess/FSO (Day 21, 45, 90, 180):

Patient-reported outcomes (see Section **9.2.4**):

- CRS side-specific questionnaire (Day 21, 45, 90, 180)
- SNOT-22 score (Day 180)
- RSI score (Day 180)

Implant delivery success rate (see Section **9.2.5**)

9.6 Exploratory Endpoint Analysis

- Patient satisfaction (Day 90, 180)
- Health-economic measures to determine health-care resource utilization (see Section **9.8**)

9.7 Safety Measures

All descriptive summaries for the safety measures will be presented for the safety population analysis.

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 implant, accessory devices, study implant procedure, and/or dilation procedure will be presented in subject/AE level summaries.

The incidence and percentages of subjects with an AE and serious adverse events (SAE) through Day 180, including adverse device effects, UADEs, and USADEs, will be presented by MedDRA system organ class (SOC) and preferred term (PT). In addition to the number of subjects experiencing each SOC/PT AE, the number of events will also be reported by SOC and PT. Complete subject listings of all AEs 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

9.8 Economic Measures

Economic measures include additional medical and surgical interventions needed during the course of study (through Day 180).

- Treatment with antibiotics for CRS treatment
- Use of intranasal corticosteroid (INCS) sprays after Day 7 for CRS treatment
- 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, or other drug eluting stents) for CRS treatment

- Regimens of leukotriene inhibitors and/or immunotherapy for allergies
- Post-Operative Surgical Interventions:
  - Post-operative debridement will be tracked separately but is within the expected post dilation outcome.
  - Use of post-operative intervention is a composite endpoint that includes:
    - Device procedure reintervention including repeat balloon dilation or repeat implant placement will be tracked, and /or
    - Oral steroid intervention warranted to resolve recurrent inflammation or edema in the frontal recess/FSO. The sinus type (frontal) and side warranting surgical intervention is noted on the endoscopic assessment CRF.
- All-cause hospitalizations
- ENT-related office visits

9.9 Prior and 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 by therapeutic class and PT.

10 STATISTICAL CONSIDERATIONS RELATED TO COVID-19

The statistical considerations detailed in this section are consistent with the FDA's guidance on the conduct of clinical trials during the COVID-19 pandemic and recommendations for the statistical analysis of the primary and key secondary endpoints to help ensure that the COVID-19-related changes to the EXPAND study conduct will provide interpretable findings with correct statistical quantification of uncertainty.

10.1 Impact of COVID-19 on Study Integrity

Unavoidable protocol modifications may be required due to COVID-19 illness and/or COVID-19 control measures to protect subject safety and to address its impact on the ability to collect data. The context and/or reasons for post-baseline events as they relate to COVID-19, such as discontinuation of treatment, withdrawal from the trial, use of intervention treatments, missed endpoint assessments, and the use of alternative endpoint assessment methods will be captured at the subject level. Information not specific to individual subjects, such as information on site closure and its impact on disrupting administration of the investigational study device (i.e., implant placement procedure, CT, endoscopic evaluation) will also be captured. This information at both the subject and site levels may be useful for incorporating into additional sensitivity analyses related to the impact of COVID-19.

10.2 COVID-19 Analysis Considerations

The impact of COVID-19 on the study integrity will be assessed and included into summaries of data with information on missing data, protocol deviations, subject discontinuation or interruption of the investigational treatment, subject withdrawal, and changes in endpoint assessments (e.g., virtual visit) in accordance with the Guidance for Industry: Statistical Considerations for Clinical Trials during the COVID-19 Public Health Emergency" (June 2020 or later): To address adequately the impact of COVID-19 on evaluating the primary and key secondary endpoints, the following analysis strategies may be considered:

- If the study is stopped earlier than planned because of COVID-19, a smaller sample size or less follow-up time may result in less statistical power than was anticipated for the final analysis. A blinded power assessment will be conducted to estimate the power of the modified study. The assessment will use the actual event rates pooled over treatment group or the observed variability pooled over treatment group in the completed portion of the trial.
- Stopping the study earlier because of COVID-19 may impact the statistical inference (e.g., p-values, confidence intervals). Any modification to the study, including the original planned analyses, should not be based on data that reveal information on the treatment effect.
- If the study is stopped earlier because of COVID-19, an interim analysis may be considered for the statistical interference. Modifications can be considered to maintain control over Type 1 error. The actual results may be less statistically significant or have a wider confidence interval than the trial was designed for because of reduced information.
- Extending the protocol-defined windows and using alternative remote methods for assessment of the primary and secondary efficacy endpoints may be warranted to address the impact of COVID-19. The data from these late or modified assessments can be leveraged based on scientifically based rationale and clinical judgement.
- Any differences in the assessment methods between treatment groups or among subjects with different baseline characteristics will be explored through sensitivity analyses stratified by the method and timing of the endpoint assessment. Additional sensitivity analyses will examine differences in baseline characteristics and post-baseline events (including endpoints and AEs) between the originally enrolled subjects and those with missing endpoint assessments or interrupted investigational treatment because of COVID-19.
- The available data at baseline and post-baseline, including COVID-19-related information will be leveraged using the prespecified methods for handling missing data in Section **6.7**. The analysis will take into consideration the actual event rates pooled over treatment groups or the observed variability pooled over treatment groups in the completed portion of the study.

11 REFERENCES

CP-00030 Clinical Study Protocol P500-1220 (The EXPAND Study); Rev 5.0, May 20, 2022

CP-00038 Radiographic Evaluation Protocol for P500-1220 (The EXPAND Study); Rev 2.0, May 18, 2022

R 28020 P500-0514 PROGRESS Nova Clinical Study Report, Rev 4.0; December 28, 2016

APPENDIX A: SCHEDULE OF ASSESSMENTS

Assessments	**Screening**	**Baseline/ Procedure** (≤ 30 d from consent date)	**Day 21** (± 7 d)	**Day 45** (primary endpoint) (± 7 d)	**Day 90** (± 14 d)	**Day 180** (end of study) (± 14 d)
Informed consent	X					
Medical/surgical history	X					
CT scan[1]	X			X		X
Endoscopic evaluation & video recording	X[2]	X[2]	X	X	X	X
SNOT-22 questionnaire		X[3]				X
RSI questionnaire		X[3]				X
CRS side-specific questionnaire		X[3]	X	X	X	X
In-office bilateral frontal BSD		X				
Randomization		X				
PROPEL Contour placement in FSO[4]		X				
Patient satisfaction questionnaire					X	X
Adverse event reporting	X	X	X	X	X	X
Device deficiency reporting		X	X	X	X	X
Concomitant medications	X	X	X	X	X	X

Abbreviations: BSD, balloon sinus dilation; CT, computed tomography; d, day; FSO, frontal sinus ostia/ostium; RSI, Rhinosinusitis Symptom Inventory; SNOT, Sino-Nasal Outcome Test.

[1] Screening CT must be performed ≤ 90 days prior to the baseline procedure to confirm the diagnosis of CRS. The follow-up CT at Day 45 and 180 shall be performed after endoscopic evaluation and debridement to ensure no implant remnants are present on the scan. All CTs should be uploaded for centralized blinded review.

[2] Screening endoscopic evaluation can be done at the baseline. Baseline values are entered into EDC.

[3] Complete endoscopic evaluation, SNOT-22, RSI and CRS side-specific questionnaires prior to the baseline procedure. Assess implant apposition after the baseline procedure.

[4] Treatment side only.

APPENDIX B: TABLE MOCKUPS

APPENDIX C: LISTING MOCKUPS