# STATISTICAL ANALYSIS PLAN

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| **Protocol Title:** | BEACON: A Phase II, Patient-blinded, Two-part, Randomized, Parallel-group Trial to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of LYR-220 in Chronic Rhinosinusitis (CRS) Patients Who Have Had a Prior Ethmoidectomy |
| **Protocol Number:** | LYR-220-2021-001 |
| **NCT#** | NCT05035654 |
| **Sponsor:** | Lyra Therapeutics, Inc.<br>480 Arsenal Way<br>Watertown, MA USA 02472 |
| **SAP Version/Date:** | 1.0/24 August 2023 |

# SIGNATURE PAGE

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| **Protocol Number:** | LYR-220-2021-001 |
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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

## VERSION HISTORY

| Version | Version Date | Description |
|---|---|---|
| 1.0 | 24 August 2023 | Original signed version |
| | | |

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## LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| ANCOVA | Analysis of covariance |
| AR | Allergic rhinitis |
| ATC | Anatomical therapeutic chemical |
| EOT | End of Treatment |
| EOS | End of Study |
| ET | Early termination |
| CFBL | Change from baseline |
| CI | Confidence interval |
| CMH | Cochran-Mantel-Haenszel |
| CRF | Case report form |
| CRS | Chronic Rhinosinusitis |
| CRS-PRO | Patient-Reported Outcome Measure for Chronic Rhinosinusitis |
| CS | Cardinal symptoms |
| CSR | Clinical Study Report |
| CT | Computed tomography |
| eCRF | Electronic case report form |
| ePRO | Electronic patient-reported outcomes questionnaire |
| ET | Early termination |
| HEENT | Head, eyes, ears, nose, and throat |
| IB | Investigator's brochure |
| IMP | Investigational medicinal product |
| IOP | Intraocular pressure |
| IRT | Interactive Response Technology |
| K-M | Kaplan-Meier |
| LOCF | Last observation carried forward |
| LS-means | Least-squares means |
| MAR | Missing at random |
| MCID | Minimal Clinically Important Difference |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MF | Mometasone furoate |
| MMRM | Mixed Model with Repeated Measures |
| MVN | Multivariate Normality |
| NSAIDs | Nonsteroidal Anti-Inflammatory Drugs |
| PGIC | Patient Global Impression of Change |
| PGIS | Patient Global Impression of Severity |
| PK | Pharmacokinetics |
| RBC | Red blood cell |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SCS | Systemic corticosteroids |

| Abbreviation | Definition |
|---|---|
| SD | Standard deviation |
| SNOT-22 | Sino-Nasal Outcome Test (22-item) |
| TEAE | Treatment-emergent adverse event |
| TESAE | Treatment-emergent serious adverse event |
| WBC | Blood cell count |
| WHO | World Health Organization |

# 1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains technical and detailed elaboration of the principal features of the analysis described in the protocol and includes procedures for executing the statistical analysis to fulfil the objectives of the study. The final version of this SAP will be approved prior to database lock and unblinding the subject treatment assignments. Changes from the planned analyses in the final SAP that impact the statistical analyses will be documented in the Clinical Study Report (CSR).

# 2 STUDY OVERVIEW

## 2.1 Study Objectives

### 2.1.1 Primary Objective

The primary objective is to evaluate serious adverse events related to LYR-220.

### 2.1.2 Secondary Objectives

The secondary objectives are to:

1. Evaluate the safety and tolerability of LYR-220.
2. Evaluate the efficacy of LYR-220 in improving total 22-item Sino-Nasal Outcome Test (SNOT-22) and subdomain scores through Week 28/Follow Up.
3. Evaluate the efficacy of LYR-220 in improving 3 cardinal symptoms (3CS) and individual cardinal symptom score through Week 28/Follow Up.
4. Evaluate the efficacy of LYR-220 in improving loss of smell symptom score through Week 28/Follow Up for subjects with moderate-to-severe score at baseline.
5. Evaluate the efficacy of LYR-220 in improving total Patient-Reported Outcome Measure for Chronic Rhinosinusitis (CRS-PRO) and subdomain scores through Week 28/Follow Up.
6. Evaluate the time to first rescue treatment recommendation through Week 28/Follow Up.
7. Evaluate the percentage of subjects who have uncontrolled CRS symptoms requiring systemic/oral corticosteroids or sinonasal surgery through Week 28/Follow Up.
8. Evaluate the effect of LYR-220 in reducing ethmoid cavity opacification as per computed tomography (CT).
9. Evaluate the efficacy of LYR-220 in improving subject perception of symptom severity and improvement.
10. Evaluate the effect of LYR-220 in converting a subject to not requiring revision surgery.
11. Evaluate the effect of LYR-220 in reducing nasal inflammatory marker levels at Week 25/Follow Up.

### 2.1.3 Pharmacokinetics Objectives

The pharmacokinetics objective is to evaluate the pharmacokinetics of LYR-220.

## 2.2 Study Design

### 2.2.1 Overview

This multicenter study will be conducted in a patient-blinded, two-part, randomized, parallel-group manner in approximately 50 symptomatic adult subjects with CRS who have had a prior bilateral ethmoidectomy. The safety, tolerability, pharmacokinetics, and efficacy of 2 designs, LYR-220-32 drug matrix and LYR-220-16 drug matrix, will be assessed in Part 1. Both designs of LYR-220 matrices contain 7500 µg of mometasone furoate (MF).

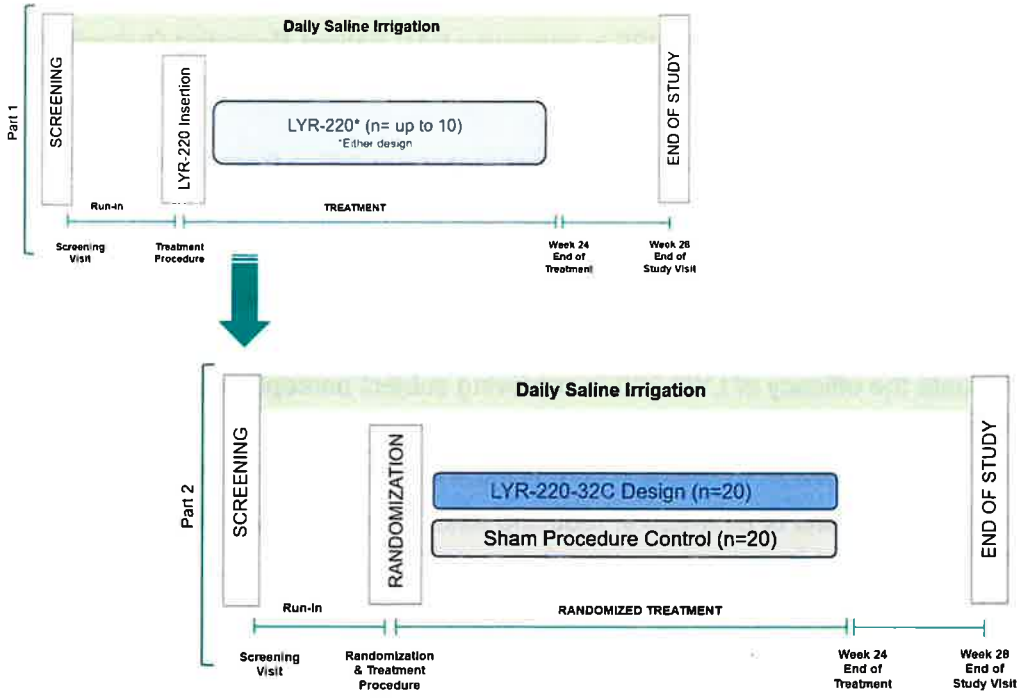
The study will consist of 2 parts. In Part 1 of the study, up to 10 subjects will be treated with either design of LYR-220 bilaterally. The primary objective of the Part 1 study, in addition to the safety and pharmacokinetics assessments of LYR-220, is to evaluate the feasibility of placement and optimize the LYR-220 insertion procedure before beginning Part 2 of the study, in which approximately 40 subjects (20 per treatment arm) will be randomized 1:1 to either LYR-220-32 (7500 µg) or a sham procedure.

Each subject will undergo 3 stages during the study:

- Screening and Run-in Stage: 2-4 weeks
- Treatment Stage: 24 weeks
- Post-treatment Follow-Up Stage: 4 weeks

The overall study design flow diagram of subject enrollment and follow-up schedule is shown below.

**Figure 1: Study Design Schematic**



The schedule of study assessments for subjects is summarized in protocol Section 8.1. All subjects in Part 1 and Part 2 will undergo these study assessments per the schedule.

Vital signs and a limited physical exam, focusing on physical appearance of head, eyes, ears, nose, and throat (HEENT) will be performed at Screening visit. Samples for hematology and chemistry will be collected at Screening and Week 25/Follow Up visits.

Nasal cavities will be assessed by endoscopy at Screening, Day 1 (before the LYR-220 insertion procedure), and at Weeks 4, 12, 24 (before LYR-220 removal), and Week 25/Follow Up visits. Local safety evaluation of the ethmoid cavity will be performed at these visits to document presence of epistaxis, mucosal injury, and any other local adverse effects. On Day 1 (before LYR-220 insertion) and at Week 25/Follow Up visits, nasal swabs will be collected in ethmoid cavities to evaluate the impact of LYR-220 on nasal inflammatory marker level by protein and mRNA assays.

Ophthalmologic assessments will include intraocular pressure (IOP) and slit-lamp examination during Screening and at Week 25/Follow Up visit. IOP assessment will also be performed at Week 4 and 12 visits.

For female subjects of childbearing potential, a serum pregnancy test will be performed at the Screening visit and a urine pregnancy test will be performed on Day 1 prior to treatment to confirm eligibility for participating in the study. Additionally, a urine pregnancy test will be performed at Weeks 4, 12, and 24 or early termination (ET) visits in these female subjects.

Plasma samples for pharmacokinetics (PK) will be collected from all subjects at Day 1 pre-procedure, 1 hour (±10 minutes) post procedure on Day 1, Day 2 or 3, Day 5 or 8, and Weeks 4, 12, 16 or 20, 24, and Week 25/Follow Up visits.

Enrolled subjects will be asked to complete a daily electronic patient-reported outcomes (ePRO) questionnaire to assess the severity of the 4 CS of CRS (nasal blockage/obstruction/congestion, facial pain/pressure, anterior/posterior nasal discharge, and loss of smell). In addition, the ePRO will capture use of daily saline irrigation by the subjects. Subjects will also complete 2 validated CRS-specific quality of life questionnaires, the SNOT-22 and CRS-PRO, at Screening, on Day 1 before treatment, and at Weeks 2, 4, 6, 8, 12, 16, and 20, at Week 24 before matrix removal, and at Week 28/Follow Up. CRS-PRO will also be assessed at Day 8 and Week 3. The Patient Global Impression of Severity (PGIS) will be administered on Day 1 (pretreatment) and at Weeks 8, 16, and 24. The Patient Global Impression of Change (PGIC) will be assessed at Week 24. At Week 28/Follow Up visit, an end-of-study questionnaire will be administered.

Ethmoid cavity opacification will be assessed by CT scans obtained during Screening (or using a historical scan taken within 3 months of Screening) and at Week 25/Follow Up visit, unless medically contraindicated. Subjects will be instructed to stop use of saline rinse approximately 24 hours prior to the scheduled sinus CT. Daily saline irrigation should then continue following the sinus CT. If a subject is experiencing or recovering from a cold, acute exacerbation of nasal allergy, or upper respiratory tract infection at Week 25/Follow Up visit, the CT assessment should be performed 4 weeks after resolution of the adverse event. If a subject early terminates from the study or requires oral/systemic corticosteroids (SCS) or sinonasal surgery as rescue treatment during the study, every attempt should be made to perform the follow-up CT before subject receives the rescue treatment.

### 2.2.2 Randomization and Blinding

The study will consist of 2 parts. Part 1 is open-label and non-randomized. Based on feedback from study Investigators in Part 1 regarding maneuverability and ease of use of the LYR-220-16 matrix, the Sponsor decided to drop this treatment arm in Part 2 of the study.

Approximately 40 subjects who complete the study Screening assessments and the run-in period, and meet all eligibility criteria on Day 1 in the Part 2 of the study will, before any treatment, be randomized in a 1:1 ratio to 1 of the 2 study arms:

- Treatment Arm A: bilateral insertion of LYR-220-32 (7500 µg)
- Treatment Arm B: bilateral sham treatment control

Subjects will be stratified for treatment assignment according to the following criteria:

- Nasal polyps (Yes vs No)

No more than 10 subjects with nasal polyps will be randomized in each treatment arm. Treatment will be assigned according to a randomization scheme generated by the Sponsor or designee. Randomization will be conducted using Interactive Response Technology (IRT).

Subjects should remain blinded to their treatment assignment until the final study database is locked. To maintain subject blinding (LYR-220 or sham) in Part 2 of the study, each subject will wear an eye mask (i.e., blindfold) and ear/headphones at the time of the LYR-220 administration/sham procedure and at all post Day 1 visits (scheduled or unscheduled) during any endoscopy assessments and during the LYR-220 administration/sham removal procedure.

Breaking the blind is expressly forbidden except in the event of spontaneous dislodgment of LYR-220, or a medical emergency where the identity of the treatment assignment must be known in order to properly treat the subject. If breaking the blind is required because of a medical emergency, decision to unblind lies solely with the investigator.

In all cases where the code is broken, the investigator must record the date and reason for code breaking.

A Sponsor blind was implemented in Part 2 of the study, as outlined in the Study Blinding Plan.

### 2.2.3 Investigational Product

The LYR-220 System is a combination product comprised of a single-use applicator, preloaded with an anti-inflammatory drug matrix. The LYR-220 drug matrix contains mometasone furoate (MF), an active ingredient in multiple FDA-approved products indicated for therapeutic and prophylactic management of seasonal and perennial allergic rhinitis (AR), nasal polyps, a phenotype of CRS disease, as well as asthma. The LYR-220 drug matrix is designed to gradually soften over time and is made of bioabsorbable polymers that have been used as components of approved pharmaceutical drugs and/or medical devices.

LYR-220 has a tubular braid configuration with a uniform diamond pattern throughout. It is designed to be self-retaining against the mucosal tissues to allow effective drug transfer for up to 24 weeks. The matrix is comprised of a base structure and a drug formulation layer. The base structure is composed of poly(L-lactide-co-glycolide) and poly(L-lactide-co-ε-caprolactone) elastomer to provide a 3-dimensional structure and elasticity. The drug formulation layer

consists of the active ingredient, MF, embedded in the inactive ingredients containing poly(L-lactide-co-ε-caprolactone) and poly(L-lactide) to control the release rate of MF. Two designs of LYR-220, LYR-220-32 drug matrix and LYR-220-16 drug matrix, manufactured with 32 and 16 woven fibers, respectively, will be assessed in this study. Both designs have the same nominal dimensions of 20 mm in diameter and 16 mm in length in the unconstrained state.

Each LYR-220 drug matrix contains 7500 µg MF. LYR-220 is intended to be administered bilaterally into the ethmoid cavity, in which ethmoid sinuses have been removed previously by a bilateral ethmoidectomy, by an otolaryngologist under endoscopic visualization using the provided single-use applicator. Once administered, each LYR-220 is designed to gradually deliver sustained doses of MF to the inflamed mucosal tissue over a 24-week resident time. Bilateral placement of LYR-220 (7500 µg) is designed to deliver a total dose of 15,000 µg MF over the 24 weeks, or an average daily dose of 89 µg MF per person (or 45 µg MF per nostril).

### 2.2.4 Discontinuation of Study Subjects

Subjects will be encouraged to complete the study through the post-treatment follow-up period. Each subject is free to discontinue from the study at any time, for any reason, and without penalty or loss of benefit. Participation in the study treatment may be discontinued for any of the following reasons:

- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol, including early removal of LYR-220.
- Any serious adverse event, clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the subject.
- Subject's decision to withdraw.
- Requiring sinonasal surgery as rescue treatment.
- If deviations to the use of prohibited medications occur during run-in or study treatment periods, the Investigator, in consultation with the Sponsor and Sponsor's medical monitor will decide on a case-by-case basis whether the subject may continue in the study based on the time the prohibited medication was administered and its pharmacology.
- Subject's failure to comply with protocol requirements or study related procedures.
- Termination of the study by the Sponsor or a regulatory authority that has provided approval to proceed.

Subjects who withdraw or are withdrawn from the study treatment will be requested to return to the clinic for the assessments and procedures scheduled for the EOT and EOS visits.

### 2.2.5 Sample Size Determination

Because the primary objective of this study is to assess the safety, tolerability, and pharmacokinetics of LYR-220, the sample size determination is not based on statistical power considerations. Up to 10 subjects will be treated in the Part 1 and approximately 40 subjects will be treated in Part 2 of the study, respectively.

## 2.3 Study Endpoints

### 2.3.1 Primary Endpoint

The primary endpoint is product-related treatment-emergent serious adverse events (TESAEs).

### 2.3.2 Secondary Safety Endpoints

The secondary safety endpoints include:

1. Treatment-emergent adverse events (TEAEs) and serious adverse events through Week 28/Follow Up.
2. Clinically significant abnormal laboratory values (hematology and chemistry) through Week 25/Follow Up.
3. Newly identified or worsened endoscopic findings (epistaxis and mucosal injury) in ethmoid cavity through Week 25/Follow Up.
4. Clinically significant increase of IOP through Week 25/Follow Up.
5. Newly identified or worsened cataract in 1 or both eyes by slit-lamp examination through Week 25/Follow Up.

### 2.3.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

1. Change from baseline (CFBL) in SNOT-22 total and subdomain scores at Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28/Follow Up.
2. CFBL in the 7-day average composite score of 3CS and individual cardinal symptom scores at Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28/Follow Up.
3. CFBL in the 7-day average score of loss of smell for subjects with baseline score ≥2 at Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28/Follow Up.
4. CFBL in CRS-PRO total and subdomain scores at Weeks 2, 3, 4, 6, 8, 12, 16, 20, 24, and 28/Follow Up.
5. Time to first rescue treatment recommendation through Week 28/Follow Up.
6. Systemic/oral corticosteroid use or sinonasal surgery recommendation through Week 28/Follow Up.
7. CFBL in bilateral percent ethmoid cavity opacification by CT at Week 25/Follow Up.
8. CFBL in PGIS score at Weeks 8, 16, and 24.
9. PGIC score at Week 24.
10. No longer a candidate for revision surgery.
11. CFBL in nasal inflammatory marker levels at Week 25/Follow Up.

### 2.3.4 Pharmacokinetic Endpoints

The pharmacokinetic endpoint is plasma MF concentrations at 1 hour (±10 minutes) post study treatment administration and at Days 2 or 3, Days 5 or 8, and Weeks 4, 12, 16 or 20, 24, and 25/Follow Up.

# 3 STATISTICAL METHODOLOGY

## 3.1 General Considerations

Unless otherwise specified, the efficacy data will be presented separately for Part 1 and Part 2 as Part 1 is not randomized and does not include a placebo arm. The efficacy data from Part 1 will be descriptively summarized by arms (LYR-220-16 and LYR-220-32) without statistical testing. The safety data will be presented combining data from both Part 1 and Part 2. Specifically, the safety data from the subjects who received LYR-220-32 in Part 1 will be combined with the subjects who received LYR-220-32 in Part 2 in order to assess the totality of safety of LYR-220-32 from the study. The safety data from the subjects who received LYR-220-16 in Part 1 and from the subjects who received sham in Part 2 will be summarized without combining with the other arms (i.e., LYR-220-16 from Part 1, LYR-220-32 combining Part 1 and Part 2, and sham from Part 2).

### 3.1.1 Analysis Day

Analysis day for analysis visit windows (i.e., "Aday") will be calculated from the date of study treatment (LYR-220 or sham) administration. The day of study treatment administration will be Aday 1, and the day immediately before Aday 1 will be Aday -1.

Additionally, analysis day relative to the last dose day (i.e., "Aenday") will be calculated from the date of last dose of study treatment. The day of last dose of study treatment will be Aenday 0, and the day immediately after Aenday 0 will be Aenday 1. Data collected up to 31 days after end of treatment will be included in the analysis.

### 3.1.2 Analysis Visits

Analysis visits will be used for efficacy and safety endpoint analysis. Follow up visits are defined as any visits during 1 day and up to 31 days after end of treatment. Scheduled visits will be assigned to analysis visits as recorded on the Case Report Form (CRF) if they are within the corresponding analysis visit windows described in the tables below. Scheduled visits that do not fall in the corresponding analysis visit windows are considered unscheduled visits when assigning analysis visits. In order to maximize the data available for assessments with regular scheduled visits, where possible, results from unscheduled visits will be assigned to analysis visits according to the following visit windows. When multiple visits are within the same analysis visit window, the one closest to the target day will be used. For efficacy endpoints, if two values are equally distanced, select the value before the target day. For safety endpoints, if two values are equally distanced, select the value after the target day.

If both paper-based patient-reported outcomes and ePRO are completed at the same day, ePRO will be used for analysis.

If multiple ePRO are completed at the same day and the input are different, the entry having the worst total score will be used for analysis. If multiple ePRO are completed at the same day and the input are identical, the earliest entry will be used for analysis.

An unscheduled visit that does not fall under any window will remain in the database and will be included in the listings.

3.1.2.1 Analysis Visit Windows for Efficacy Endpoints

**Table 1a. Visit Windows for SNOT-22**

| Analysis Visit | Target Analysis Day | Low Analysis Day | High Analysis Day |
|---|---|---|---|
| Week 2 | Aday 15 | Aday 2 | Aday 21 |
| Week 4 | Aday 29 | Aday 22 | Aday 35 |
| Week 6 | Aday 43 | Aday 36 | Aday 49 |
| Week 8 | Aday 57 | Aday 50 | Aday 70 |
| Week 12 | Aday 85 | Aday 71 | Aday 98 |
| Week 16 | Aday 113 | Aday 99 | Aday 126 |
| Week 20 | Aday 141 | Aday 127 | Aday 154 |
| Week 24 | Aday 169 | Aday 155 | Aday 182 |
| Week 28/follow-up* | Aenday 28 | Aenday 1 | Aenday 31 |

* post-treatment follow-up.

**Table 1b. Visits for Weekly 3CS and 4 Individual Cardinal Symptom Scores**

| Analysis Visit | Analysis Week (Days) |
|---|---|
| Week 1 | Aday 2 - Aday 8 |
| Week 2 | Aday 9 - Aday 15 |
| Week 3 | Aday 16 - Aday 22 |
| Week 4 | Aday 23 - Aday 29 |
| Week 5 | Aday 30 - Aday 36 |
| Week 6 | Aday 37 - Aday 43 |
| Week 7 | Aday 44 - Aday 50 |
| Week 8 | Aday 51 - Aday 57 |
| Week 9 | Aday 58 - Aday 64 |
| Week 10 | Aday 65 - Aday 71 |
| Week 11 | Aday 72 - Aday 78 |
| Week 12 | Aday 79 - Aday 85 |
| Week 13 | Aday 86 - Aday 92 |
| Week 14 | Aday 93 - Aday 99 |
| Week 15 | Aday 100 - Aday 106 |
| Week 16 | Aday 107 - Aday 113 |
| Week 17 | Aday 114 - Aday 120 |
| Week 18 | Aday 121 - Aday 127 |
| Week 19 | Aday 128 - Aday 134 |
| Week 20 | Aday 135 - Aday 141 |
| Week 21 | Aday 142 - Aday 148 |
| Week 22 | Aday 149 - Aday 155 |

| | |
|---|---|
| Week 23 | Aday 156 - Aday 162 |
| Week 24 | Aday 163 - Aday 169 |
| Week 25/follow-up* | Aenday 1 - Aenday 7 |
| Week 26/follow-up* | Aenday 8 - Aenday 14 |
| Week 27/follow-up* | Aenday 15 - Aenday 21 |
| Week 28/follow-up* | Aenday 22 - Aenday 28 |

Note: score for a week is the average of the non-missing daily scores over the 7-day period of the week. If less than 4 daily scores are available for a week, the individual CS score will be considered missing for that week.

* post-treatment follow-up.

**Table 1c. Visit Windows for CRS-PRO**

| Analysis Visit | Target Analysis Day | Low Analysis Day | High Analysis Day |
|---|---|---|---|
| Week 2 | Aday 15 | Aday 12 | Aday 18 |
| Week 3 | Aday 22 | Aday 19 | Aday 25 |
| Week 4 | Aday 29 | Aday 26 | Aday 35 |
| Week 6 | Aday 43 | Aday 36 | Aday 49 |
| Week 8 | Aday 57 | Aday 50 | Aday 70 |
| Week 12 | Aday 85 | Aday 71 | Aday 98 |
| Week 16 | Aday 113 | Aday 99 | Aday 126 |
| Week 20 | Aday 141 | Aday 127 | Aday 154 |
| Week 24 | Aday 169 | Aday 155 | Aday 182 |
| Week 28/follow-up* | Aenday 28 | Aenday 1 | Aenday 31 |

* post-treatment follow-up.

**Table 1d. Visit Windows for PGIS**

| Analysis Visit | Target Analysis Day | Low Analysis Day | High Analysis Day |
|---|---|---|---|
| Week 8 | Aday 57 | Aday 29 | Aday 84 |
| Week 16 | Aday 113 | Aday 85 | Aday 140 |
| Week 24 | Aday 169 | Aday 141 | Aday 196 |

**Table 1e. Visit Windows for PGIC**

| Analysis Visit | Target Analysis Day | Low Analysis Day | High Analysis Day |
|---|---|---|---|
| Week 24 | Aday 169 | Aday 141 | Aday 196 |

**Table 1f. Visit Windows for Ethmoid Cavity Opacification**

| Analysis Visit | Target Analysis Day | Low Analysis Day | High Analysis Day |
|---|---|---|---|
| Week 25/follow-up* | Aenday 7 | Aenday 0 | Aenday 31 |

* post-treatment follow-up.

3.1.2.2 Analysis Visit Windows for Safety Endpoints

**Table 2a. Visit Windows for Laboratory and Slit-Lamp Examination Assessments**

| Analysis Visit | Target Analysis Day | Low Analysis Day | High Analysis Day |
|---|---|---|---|
| Week 25/follow up* | Aenday 7 | Aenday 0 | Aenday 31 |

* post-treatment follow-up.

**Table 2b. Visit Windows for Nasal Endoscopy Assessments**

| Analysis Visit | Target Analysis Day | Low Analysis Day | High Analysis Day |
|---|---|---|---|
| Week 4 | Aday 29 | Aday 2 | Aday 56 |
| Week 12 | Aday 85 | Aday 57 | Aday 126 |
| Week 24 | Aday 169 | Aday 127 | Aday 196 |
| Week 25/follow-up* | Aenday 7 | Aenday 1 | Aenday 31 |

* post-treatment follow-up.

**Table 2c. Visit Windows for IOP Assessments**

| Analysis Visit | Target Analysis Day | Low Analysis Day | High Analysis Day |
|---|---|---|---|
| Week 4 | Aday 29 | Aday 2 | Aday 56 |
| Week 12 | Aday 85 | Aday 57 | Aday 196 |
| Week 25/follow-up* | Aenday 7 | Aenday 0 | Aenday 31 |

* post-treatment follow-up.

3.1.3 Definition of Baseline

For cardinal symptoms (3CS and individual symptoms) and loss of smell score, the baseline is the average of non-missing daily scores over the 7-day period prior to and including Day 1. For other efficacy and safety assessments, the baseline is the last non-missing measurements prior to or on the day of treatment administration.

3.1.4 Endpoint Related Definition and Calculation

3.1.4.1 Product-Related Treatment-Emergent Serious Adverse Event (SAE)

Treatment-emergent adverse event is defined in Section 3.6.1.

A product-related treatment-emergent SAE must meet all the following criteria:

1. The treatment-emergent adverse event is serious.
2. The causality of an SAE is definitely related or possibly related to LYR-220 study drug product according to the investigator's assessment.

3.1.4.2 Newly Identified or Worsened Endoscopic Findings (Epistaxis and Mucosal Injury) in Ethmoid Cavity through Week 25/Follow Up

A newly identified endoscopic finding in ethmoid cavity is a development of epistaxis or mucosal injury at post-baseline visits.

A worsened endoscopic finding in ethmoid cavity is an increased severity change of either epistaxis or mucosal injury from baseline.

3.1.4.3 Clinically Significant Increase of IOP through Week 25/Follow Up

A clinically significant increase of IOP is defined as IOP in 1 or both eyes >23 mm Hg or an increase of IOP from Baseline in 1 or both eyes ≥10 mm Hg.

3.1.4.4 Newly Identified or Worsened Cataract in 1 or Both Eyes by Slit-Lamp Examination through Week 25/Follow Up

A newly identified cataract is a development of posterior subcapsular cataract of grade 1 or higher, nuclear cataract of grade 1 or higher, or cortical cataract of grade 1 or higher or involving a minimum of center optic zone of 3-mm diameter at post-baseline visits.

A worsened cataract is an increased grade change of posterior subcapsular cataract, nuclear cataract, or cortical cataract from baseline.

3.1.4.5 SNOT-22 through Week 28/Follow Up

The SNOT-22 questionnaire is a 22-item disease-specific quality of life instrument validated for use in CRS. Subjects will score the severity of their symptoms and social/emotional consequences of CRS on a 6-point scale over the past 2 weeks: 0 = no problem, 1 = very mild problem, 2 = mild or slight problem, 3 = moderate problem, 4 = severe problem, and 5 = problem as bad as it can be.

The scores are summed; higher scores on the SNOT-22 instrument total score or subdomain scores (as defined in Table 3) indicate higher severity of symptoms or social/emotional consequences of CRS.

If any of the individual item scores is missing, the total score and the corresponding domain score will be considered missing.

**Table 3. Categorized Survey Items for Separate Domains of the SNOT-22 Instrument**

| SNOT-22 Domains | Survey Items | Score Range |
|---|---|---|
| Rhinologic Symptoms | #1, #2, #3, #4, #7, #12 | 0–30 |
| Extra-Nasal Rhinologic Symptoms | #5, #6, #7 | 0–15 |
| Ear/Facial Symptoms | #3, #8, #9, #10, #11 | 0–25 |
| Psychological Dysfunction | #16, #17, #18, #19, #20, #21, #22 | 0–35 |
| Sleep Dysfunction | #13, #14, #15, #16, #17 | 0–25 |

3.1.4.6 CRS Cardinal Symptoms through Week 28/Follow Up

Enrolled subjects will be asked to complete a daily ePRO to assess the severity of the 4 CS of CRS (nasal blockage/obstruction/congestion, facial pain/pressure, anterior/posterior nasal discharge, and reduction/loss of smell). Enrolled subjects will start recording their symptoms on the ePRO at least 14 days preceding the Day 1 visit. A minimum of 4 daily entries are required for composite score calculation over the preceding 7 days prior to Day 1 (not including Day 1) for assessing subject's eligibility for participating in the study.

Enrolled subjects will complete the daily assessment of their CS severity each morning (between 06:00:00AM to 11:59:59AM local time) and rate the severity of each symptom at its worst over the past 24 hours on a 4-point scale: 0 = absent symptoms (no sign/symptom evident), 1 = mild symptoms (sign/symptom present but minimal awareness; easily tolerated), 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable), and 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping).

#### 3.1.4.7 Daily 3CS Score through Week 28/Follow Up

The daily 3CS score is the sum of the daily scores of the 3 cardinal symptoms (nasal blockage/obstruction/congestion, facial pain/pressure, and anterior/posterior nasal discharge). If any of the 3 daily scores is missing, the daily 3CS score will be considered missing.

#### 3.1.4.8 Weekly Individual CS Score through Week 28/Follow Up

The nasal blockage/obstruction/congestion (or anterior/posterior nasal discharge or facial pain/pressure or reduction/loss of smell) score for a week is the average of the non-missing daily scores over the 7-day period of the week. If less than 4 daily scores are available for a week, the individual CS score will be considered missing for that week.

#### 3.1.4.9 Weekly 3CS Score through Week 28/Follow Up

The 3CS score for a week is the average of the non-missing daily 3CS scores over the 7-day period of the week. If less than 4 daily 3CS scores are available for a week, the 3CS score will be considered missing for that week.

#### 3.1.4.10 CRS-PRO through Week 28/Follow Up

The CRS-PRO questionnaire is a 12-item disease-specific health-related impairment for use in CRS. The questionnaire assesses CRS in 3 domains including physical symptoms, sensory impairment, and psychosocial effects. Subjects will score the severity of their CRS symptoms on a 5-point scale over the past 7 days, with higher score representing worse quality of life: 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much.

The scores are summed; higher scores on the CRS-PRO instrument total score or subdomain scores (as defined in Table 4) indicate higher severity of CRS symptoms.

If any of the individual item scores is missing, the total score and the corresponding domain score will be considered missing.

**Table 4. Categorized Survey Items for Separate Domains of the CRS-PRO Instrument**

| CRS-PRO Domains | Survey Items | Score Range |
|---|---|---|
| Physical Symptoms | #1, #2, #3, #4, #5, #6, #7 | 0–28 |
| Sensory Impairment | #8 | 0–4 |
| Psychosocial Effects | #9, #10, #11, #12 | 0–16 |

#### 3.1.4.11 Rescue Treatment Recommendation through Week 28/Follow Up

Rescue treatment is defined as, after subject enrollment, worsening of or uncontrolled severe symptoms of CRS in a subject resulting in the treating physician reporting an escalation of

treatment, including SCS, and/or sinonasal surgery. Rescue treatment is not recommended if worsening of symptoms is for less than 3 days duration. The following rescue medication is recommended:

- A course of oral or systemic corticosteroids. Typical indications include persistent sinus infection after an initial course of antibiotics while starting another course of antibiotics, uncontrolled sinus inflammation, or a flare-up of asthma. The dose, duration of use, and rationale for the use of oral or systemic corticosteroid must be recorded.
- Sinonasal surgery as rescue treatment according to the Investigator's recommendation. The type and rationale for sinonasal surgery must be recorded.

The rescue treatment recommendation through Week 28/Follow Up is derived by checking whether the rescue treatment is taken before Week 28/Follow Up, inclusive. If a subject is lost to follow up/discontinues the study before Week 28/Follow Up and does not have rescue treatment requirement at that time, then it will be considered as missing data.

3.1.4.12 Time to First Rescue Treatment Recommendation through Week 28/Follow Up

Time to first rescue treatment recommendation will be counted from date of insertion procedure, i.e., date of first rescue treatment recommendation – date of LYR-220 administration/sham insertion procedure + 1. If a subject is lost to follow up/discontinues the study before Week 28/Follow Up and does not have rescue treatment requirement by that time, then it will be censored at the date of last assessment. If a subject does not have rescue treatment required through Week 28/Follow Up, it will be censored at Week 28/Follow Up.

3.1.4.13 Ethmoid Cavity Opacification by CT at Week 25/Follow Up

Ethmoid cavity opacification will be assessed by CT. The Screening CT should be performed anytime between the Screening and Day 1 visits. Alternatively, a historical CT scan can be used, if done within 3 months preceding the Screening visit. The follow-up CT will be conducted within 5-9 days after the LYR-220 removal procedure at Week 25/Follow Up visit. If a subject is experiencing or recovering from a cold, acute exacerbation of nasal allergy, or upper respiratory tract infection at the Week 25/Follow Up visit, the CT assessment should be performed 4 weeks after resolution of the adverse event. If a subject early terminates from the study or requires oral/systemic corticosteroids or sinonasal surgery as rescue treatment during the study, every attempt should be made to perform the follow-up CT before subject receives the rescue treatment. The percent opacification of ethmoid cavity will be evaluated by an imaging core lab.

Bilateral percent opacification of ethmoid cavity is the average of percent opacification of ethmoid cavity on each side of the nose.

3.1.4.14 PGIS at Week 8, 16, and 24

Responses to the PGIS questionnaire will be collected via the ePRO. Subjects will be asked a single question to rate their severity of CRS-related symptoms over the past 7 days on a 5-point ordinal scale: 1 = none, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe.

3.1.4.15 PGIC at Week 24

Responses to the PGIC questionnaire will be collected at Week 24 via the ePRO. The PGIC is a self-assessment of the subject's overall change in CRS-related symptom severity compared to

pretreatment. The PGIC 7-point balanced scale is as follows: 1 = very much better, 2 = much better, 3 = a little better, 4 = no change, 5 = a little worse, 6 = much worse, and 7 = very much worse.

3.1.4.16 No longer a candidate for revision surgery

Subjects will be deemed as having converted if they do not undergo revision sinonasal surgery (planned or actual) during the study and if they meet the following criteria:

- 3CS score ≤4 at Week 24, or
- No disease in ethmoid cavities on Week 25/Follow Up CT.

3.1.4.17 Nasal Inflammatory Marker Levels

Nasal inflammatory marker levels will be assessed by collecting nasal swabs. The baseline nasal swabs will be collected before LYR-220 administration at Day 1 visit. The follow-up nasal swabs will be collected at Week 25/Follow Up visit. Nasal swabs will be collected from each side nasal passage to assess levels of T2 inflammatory markers. Two nasal swabs per side (1 for protein sample collection and 1 for RNA sample collection) will be collected. Nasal swabs will be collected according to the guidelines provided by the Sponsor.

3.1.5 Summary Statistics

Categorical data will generally be summarized with counts and percentages of subjects. The denominator used for the percentage calculation will be clearly defined. Quantitative data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation (SD), minimum, and maximum.

3.1.6 Hypothesis Testing

No hypothesis testing will be performed for Part 1.

For Part 2, unless stated otherwise, tests will be carried out on one-sided. Two-sided equitailed 90% (asymptotic) confidence intervals (CIs) will also be calculated.

3.1.7 Multiplicity

There will be no adjustment of the significance level for multiple comparisons across the endpoints.

3.1.8 Adjustment for Covariates

Unless otherwise noted, all analyses of efficacy outcome measures will include subject's baseline score as a covariate and nasal polyp status (yes or no) as a factor in the analysis model.

3.1.9 Evaluation of Site Effect

The number of subjects at each site is expected to be too small to evaluate site effect. No site effect will be evaluated in this study.

3.1.10 Handling of Dropouts and Missing Data

3.1.10.1 Handling of Partial or Missing Dates for Prior and Concomitant Medications

The goal for imputing a partially missing date is to select the most conservative date within the possible range specified by the non-missing data.

**Table 5. Imputation Rules for Missing Date**

| Date | Type of Missing Date | Handling of Missing Date |
|---|---|---|
| Event Start Date (e.g., YYYY-MM-DD) | Completely missing | No imputation will be applied. |
| | Only YYYY is available | Use the first day of YYYY to impute the missing month and date parts of the start date. |
| | YYYY and MM are available, but DD is missing | Use the first day of MM to impute the missing date part of the start date. |
| Event End Date (e.g., YYYY-MM-DD) | Completely missing | No imputation will be applied. The event will be considered ongoing at the end of study. |
| | Only YYYY is available | Use the last day of YYYY to impute the missing month and date parts of the end date |
| | YYYY and MM are available, but DD is missing | Use the last day of MM to impute the missing date part of the end date |

In the case where the imputed start date is later than the reported stop date, the imputed date will be set equal to the stop date.

In listings, missing or partial dates will be left as they have been recorded in the eCRF.

3.1.10.2 Algorithm for Treatment Emergent Adverse Events (TEAE)

TEAE is defined in Section 3.6.1.

For deriving the TEAE flag, the following process of temporary date imputation is done for adverse event (AE) start date. The date imputation algorithm for incomplete adverse event start dates is described in the following table. Classification of adverse event (TEAE or not) is then done using the imputed date.

In the following table, all dates are presented using an YYYY-MM-DD format. As an example, suppose the investigational medicinal product (IMP) administration = 2022-08-11 and several AEs have incomplete start dates.

**Table 6. Imputation Rules for Missing AE start Date**

| Description of incomplete date | Imputed numeric date | Example | |
|---|---|---|---|
| | | Character date | Imputed date |
| Day is missing | | | |
| YYYY-MM < YYYY-MM of [IMP admin.] | YYYY-MM-01 | 2022-07-XX | 2022-07-01 |

| | | | |
|---|---|---|---|
| YYYY-MM = YYYY-MM of [IMP admin.] | Min ([IMP admin.], AE end date) | 2022-08-XX | Min (2022-08-11, AE end date) |
| YYYY-MM > YYYY-MM of [IMP admin.] | YYYY-MM-01 | 2022-09-XX | 2022-09-01 |
| Day and month are missing | | | |
| YYYY < YYYY OF [IMP admin.] | YYYY-01-01 | 2021-XX-XX | 2021-01-01 |
| YYYY = YYYY OF [IMP admin.] | Min ([IMP admin.], AE end date) | 2022-XX-XX | Min (2022-08-11, AE end date) |
| YYYY > YYYY OF [IMP admin.] | YYYY-01-01 | 2023-XX-XX | 2023-01-01 |
| Day, month, and year are missing | | | |
| XXXX-XX-XX | Min ([IMP admin.], AE end date) | | Min (2022-08-11, AE end date) |

YYYY = non-missing year, MM = non-missing month, DD = non-missing day, XX = missing field.

Actual data values as they appear in the original eCRFs will be presented in the data listings.

3.1.10.3 Handling of Missing Data and Data Post-Rescue Treatment for Efficacy Endpoints

3.1.10.3.1 Part 1

No imputation will be performed. All efficacy data will be summarized descriptively.

3.1.10.3.2 Part 2

The details for handling missing data and intercurrent events for the secondary efficacy endpoints are specified in the estimand framework in Section 3.4.2. There will be no imputation for missing bilateral percent ethmoid cavity opacification by CT or nasal inflammatory biomarker assessments.

3.1.10.4 Handling of Missing Data for PK

Missing data handling for PK are specified in Section 3.5.2.

## 3.2 Analysis Sets

See Section 3.1 General Considerations for handling the subjects from Part 1 and Part 2.

### 3.2.1 Safety Analysis Set

The safety analysis set is defined as subjects who successfully received the study treatment on Day 1. Subjects will be analyzed according to the treatment received. This is the primary analysis set for assessment of safety. The subjects from Part 1 will be combined with the subjects from Part 2 (see Section 3.1).

### 3.2.2 Efficacy Analysis Set

The efficacy analysis set is defined as subjects who successfully received the study treatment on Day 1. This is the primary analysis set for assessment of efficacy. Subjects will be analyzed according to the planned/randomized treatment. The subjects from Part 1 and the subjects from Part 2 will be separated (see Section 3.1).

### 3.2.3 PK Analysis Set

The PK analysis set is defined as subjects who receive at least one dose of study drug and have at least one measured concentration.

## 3.3 Subject Data and Study Conduct

Data will be listed by site and subject.

### 3.3.1 Screening

The number and percentage of subjects in each of the following categories will be presented in total for all consented subjects:

- Screened,
- Screen failure,
- Primary reason for screen failure,
- Enrolled and successfully received the study treatment on Day 1 in Part 1,
- Randomized and successfully received the study treatment on Day 1 in Part 2.

In addition, the number and percentage of subjects who screen failed due to COVID-19 will also be presented.

### 3.3.2 Subject Disposition

The number and percentage of subjects in each of the following categories will be presented by treatment and in total for the Safety Analysis Set as well as for the Efficacy Analysis Set in Part 2:

- Successfully completed bilateral insertion procedure on Day 1,
- Completed the treatment,
- Completed the study,
- Early terminated the study treatment,
- Early terminated the study,
- Primary reasons for discontinuation of study treatment,
- Primary reasons for discontinuation of study.

In addition, the number and percentage of subjects who discontinued study treatment due to COVID-19 and discontinued the study due to COVID-19 will also be presented.

### 3.3.3 Protocol Deviations

Counts and percentages of subjects with CSR-reportable protocol deviations by deviation category will be summarized by treatment and in total for the Safety Analysis Set as well as for the Efficacy Analysis Set in Part 2.

### 3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (<65 years, ≥65 years)
- Sex
- Childbearing potential

- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m$^2$) and BMI categories (<30 kg/m$^2$, ≥30 kg/m$^2$)
- Geologic category (United States, Australia)
- Randomized stratum (with or without nasal polys, only for randomized subjects in Part 2)
- Actual stratum (with or without nasal polys, only for randomized subjects in Part 2)

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by treatment and in total for the Safety Analysis Set as well as for the Efficacy Analysis Set in Part 2.

### 3.3.5 Chronic Rhinosinusitis History

The following baseline disease characteristics for chronic rhinosinusitis will be summarized by treatment group and in total for the Safety Analysis Set as well as for the Efficacy Analysis Set in Part 2:

- Time from diagnosis of CRS (years)
  - Time from diagnosis of CRS (years) is calculated as (date of informed consent – date of diagnosis + 1)/365.25 if the dates are full; (month difference of date of informed consent and date of diagnosis)/12 if only day is missing; year difference of date of informed consent and date of diagnosis if both month and day are missing.
- Asthma status (yes or no)
- Perennial Allergic Rhinitis (yes or no or unknown)
- Seasonal Allergic Rhinitis (yes or no or unknown)
- Chronic Obstructive Pulmonary Disease (COPD) (yes or no)
- Smoking History (never, current, and former)
- Sensitive to nonsteroidal anti-inflammatory drugs (yes or no)
- Current or history of medication related to CRS:
  - Intranasal corticosteroid spray
  - Oral corticosteroids
  - Antibiotics
  - Saline irrigation
  - Other medication

### 3.3.6 Chronic Rhinosinusitis Surgical History

The following baseline disease characteristics for chronic rhinosinusitis surgery will be summarized by treatment group and in total for the Safety Analysis Set as well as for the Efficacy Analysis Set in Part 2:

- Complete bilateral ethmoidectomy (yes or no)
- Nasal Polyps (yes or no)
- Septoplasty (yes or no)
- Nasal surgery involving turbinates (yes or no)

- Sinuplasty (yes or no)
- Polypectomy (yes or no)
- Facial Trauma (yes or no)

3.3.7 Medical History

Medical history (non-chronic rhinosinusitis medical/surgical history) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 (or later version). Counts and percentages of subjects with medical history by primary system organ class and preferred term will be summarized by treatment and in total for the Safety Analysis Set as well as for the Efficacy Analysis Set in Part 2.

3.3.8 Prior and Concomitant Medications

Prior and concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred name using the WHODrug Dictionary version B3 Global, Sep2021 (or later version). For summary purposes, medications will be considered prior medications if they were stopped prior to study treatment administration and concomitant medications if they were taken after treatment administration but no later than 31 days (>31 days) after discontinuation of study treatment. Medications stopping on the same day as study treatment administration will be considered as concomitant medications.

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior medication or concomitant medication based on the rules in Section 3.1.10.1

Counts and percentages of subjects taking prior and concomitant medications by ATC class and preferred name will be summarized by treatment and in total for the Safety Analysis Set as well as for the Efficacy Analysis Set in Part 2.

Incomplete start and stop dates will be listed as collected without imputation.

3.3.9 Study Drug Exposure (Up to Matrices Removal or Dislodgement) and Compliance

Days of exposure to study drug will be calculated from the date of study treatment (LYR-220 or sham) administration. Days of exposure to study drug will be summarized by treatment and in total for the Safety Analysis Set as well as for the Efficacy Analysis Set in Part 2 with descriptive statistics and with counts and percentages of subjects with exposure in the following categories:

- <2 weeks (1 - 14 days)
- 2 - <4 weeks (15 - 28 days)
- 4 - <8 weeks (29 - 56 days)
- 8 - <12 weeks (57 – 84 days)
- 12 - <16 weeks (85 – 112 days)
- 16 - <20 weeks (113 – 140 days)
- 20 - <24 weeks (141 – 168 days)
- 24 - <25 weeks (169 – 175 days)

- 25 - <26 weeks (176 – 182 days)
- ≥26 weeks (≥183 days)

Compliance to the study drug regimen will not be calculated.

The LYR-220 administration/Sham procedure will be summarized by treatment and in total for the Safety Analysis Set as well as for the Efficacy Analysis Set in Part 2 for the following items:

- Pre-procedure endoscopy performed
- Topical anesthesia applied before imaging
- Topical decongestant sprays applied before imaging
- Pre-procedure endoscopy assessments
    - Septal deviation
    - Nasal polyps
    - Concha bullosa
    - Other

## 3.4 Efficacy Assessment

Efficacy data will be summarized by treatment for each part based on the Efficacy Analysis Set.

For Part 1, efficacy data will be summarized descriptively by arms (LYR-220-16 and LYR-220-32) without formal statistical test.

For Part 2, hypothesis testing for efficacy endpoints will be conducted comparing LYR-220-32 to sham on the Efficacy Analysis Set with 1-sided testing and present a 2-sided 90% CI. For subjects with polyp status is different from the IRT and eCRF, the polyp status that is recorded on Day 1 before the insertion procedure in the eCRF will be used.

Efficacy data will be listed by site and subject.

### 3.4.1 Primary Efficacy Endpoint

Not applicable. Efficacy analyses are considered secondary for this study.

### 3.4.2 Secondary Efficacy Endpoints

#### 3.4.2.1 CFBL in SNOT-22 Total and Subdomain Scores at Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28/Follow Up

##### 3.4.2.1.1 Definition of Estimand for Part 2

The key attributes of the estimand are as following (ICH E9(R1) (FDA 2021))[1]:

**Treatment** LYR-220 7500 µg drug matrix over a 24-week period or sham procedure

**Population** subjects with CRS who have had prior bilateral ethmoidectomy meeting the defined inclusion/exclusion criteria

**Variable** CFBL in SNOT-22 total and subdomain scores at Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28/Follow Up

**Population-level summary** mean change from baseline of the difference between LYR-220-32 and sham

**Analysis model** MMRM model will include the fixed, categorical effects of treatment, visit, treatment-by-visit interaction, and nasal polyp stratum as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction. The ANCOVA model will include treatment, nasal polyp stratum as fixed-effect terms and baseline score as a covariate.

**Intercurrent events (ICE) and strategy**

(1) ICE1: Rescue treatment: efficacy data collected after rescue treatment will not be used (Hypothetical Strategy)
(2) ICE2: Premature treatment discontinuation: efficacy data collected after treatment discontinuation will be included in the analysis regardless of attribution to treatment (Treatment Policy Strategy)

If both ICE1 and ICE2 occur for the same subject, addressing ICE1 takes precedence over ICE2. For example, if a subject took rescue medication at Week 10, and subsequently dropped out at Week 12 with no score at Week 24, then the method addressing ICE1 will be used.

3.4.2.1.2 Statistical Analysis for CFBL in SNOT-22 Total and Subdomain Scores

3.4.2.1.2.1 Part 1

Descriptive summary statistics on the values and changes from baseline will be presented for the SNOT-22 total and subdomain score at each analysis visit by treatment group.

3.4.2.1.2.2 Part 2

Statistical analysis of the CFBL in SNOT-22 total and subdomain scores at Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28/Follow-up will be carried out based on the Efficacy Analysis Set.

MMRM model without imputation: analysis will be carried out using MMRM model with the CFBL in SNOT-22 score as the dependent variable, and include the fixed, categorical effects of treatment, visit, treatment-by-visit interaction, and nasal polyp stratum as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction. An unstructured covariance structure shared across treatment groups will be used to model the within-subject errors. The covariance parameters in the above model will be fitted through a working model that assumes joint multivariate normality (MVN) of responses by maximizing the restricted likelihood (REML) under the working model, and the mean parameters will be estimated by generalized least squares after plugging in REML estimate of covariance parameters. In case the model does not converge with the unstructured covariance structure, the heterogenous Toeplitz structure (TOEPH) will be used instead. In case the model will not converge with the TOEPH structure, heterogenous compound symmetry (CSH) will be used instead. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust nominal standard errors based on the inverse observed information from the working MVN model. Missing data will be handled by the MMRM under the missing at random (MAR) assumption.

Least-squares means (LS-means) for change from baseline at each analysis visit will be provided for each treatment group and the difference between LYR-220 and sham treatment at each analysis visit will be estimated from the MMRM model.

Descriptive summary statistics on the values and changes from baseline will be presented for the SNOT-22 total and subdomain score at each analysis visit by treatment group.

Graphic displays of the results will be presented. The by-visit means and the standard errors for each treatment will be plotted against the analysis visit. In addition, the by-visit least squares mean changes and the standard errors for each treatment will also be plotted against the analysis visit.

- MMRM model with subject's worst score imputation: analysis will be carried out in the same manner as MMRM model without imputation except that post-rescue assessments will be imputed with subject's worst score from baseline (including baseline) through Week 28/Follow Up. Other missing data will be handled by MMRM model.
- Analysis of covariance (ANCOVA) with multiple imputation: an ANCOVA model will be performed to compare mean change from baseline in the SNOT-22 total and subdomain scores at Week 24 and Week 28/Follow-up between the LYR-220 and the sham treatment. Post-rescue Week 24 and Week 28/Follow-up assessments will be imputed with subject's worst score from baseline (including baseline) through Week 28/Follow Up. The ANCOVA model will include treatment, nasal polyp stratum as fixed-effect terms and baseline score as a covariate. The least-squares (LS) mean change for each treatment group, the LS mean difference between treatment groups will be reported. Missing data will be imputed with a multiple imputation procedure under the assumption of MAR. The imputation model will include nasal polyp stratum, baseline score and post baseline scores to impute the missing SNOT-22 score with monotone regression method and MCMC method will be used to produce monotone missing pattern. In case the imputation model does not converge, the model will be reduced to include nasal polyp stratum, baseline score, partial or no post baseline scores. There will be 50 imputed datasets derived using SAS PROC MI based on the pre-specified model above with a given random seed (protocol date). The ANCOVA model will be performed on each dataset after imputing the missing scores and PROC MIANALYZE will be used to combine the results.
- Analysis of covariance (ANCOVA) with last observation carried forward (LOCF) imputation: an ANCOVA model will be carried out in the same manner as ANCOVA model with multiple imputation. Post-rescue Week 24 and Week 28/Follow-up assessments will be imputed with subject's worst score from baseline (including baseline) through Week 28/Follow Up. Other missing data at Week 24 and Week 28/Follow-up will be imputed with the last value observed before missingness.

Descriptive summary statistics on the values and changes from baseline will be presented for the above secondary efficacy endpoints at each analysis visit by treatment group. In addition, reduction in SNOT-22 total score will be descriptively summarized for the following aspects:

- Percentage of subjects with total score < 20 at Week 24,

- Percentage of subjects with a minimal clinically important difference (MCID) = 9 reduction from baseline at each timepoint,
- Percentage of subjects with a ≥ 50% reduction from baseline at each timepoint,
- Percentage of subjects with a ≥ 75% reduction from baseline at each timepoint.

3.4.2.2 CFBL in Cardinal Symptom Scores, Loss of Smell Score at Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28/Follow-up

3.4.2.2.1 Part 1

Descriptive summary statistics on the values and changes from baseline will be presented at each analysis visit by treatment group.

3.4.2.2.2 Part 2

The estimands attributes for the following secondary efficacy endpoints are defined in the same manner as for "CFBL in SNOT-22 Total and Subdomain Scores" in Section 3.4.2.1.1:

- CFBL in the composite and individual cardinal symptom score at Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28/Follow Up;
- CFBL in loss of smell score at Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28/Follow-up for subjects with baseline score ≥ 2.

The same analysis methods used for the SNOT-22 total and subdomain scores will be used for the above secondary efficacy endpoints. The LS-means for change from baseline at each analysis visit will be provided for each treatment group and the difference between LYR-220 and sham treatment at each analysis visit will be estimated along with the CIs. The p-value for the comparison at each analysis visit will also be presented.

Descriptive summary statistics on the values and changes from baseline will be presented for the above secondary efficacy endpoints at each analysis visit by treatment group.

3.4.2.3 CFBL in CRS-PRO at Weeks 2, 3, 4, 6, 8, 12, 16, 20, 24, and 28/Follow-up

3.4.2.3.1 Part 1

Descriptive summary statistics on the values and changes from baseline will be presented at each analysis visit by treatment group.

3.4.2.3.2 Part 2

CRS-PRO subdomain scores will be summarized descriptively without formal statistical test.

Descriptive summary statistics on the values and changes from baseline will be presented for CRS-PRO total and subdomain scores at each analysis visit by treatment group.

The estimands attributes for CRS-PRO are defined in the same manner as for "CFBL in SNOT-22 Total and Subdomain Scores" in Section 3.4.2.1.1. Missing data will not be imputed. The same MMRM analysis method used for the SNOT-22 total and subdomain scores will be used for CRS-PRO total score. The LS-means for change from baseline at each analysis visit will be provided for each treatment group and the difference between LYR-220 and sham treatment at each analysis visit will be estimated along with the CIs. The p-value for the comparison at each analysis visit will also be presented.

#### 3.4.2.4 CFBL in PGIS at Weeks 8, 16, and 24

##### 3.4.2.4.1 Part 1

Descriptive summary statistics on the values and changes from baseline will be presented at each analysis visit by treatment group.

##### 3.4.2.4.2 Part 2

The estimands attributes are defined in the same manner as for "CFBL in SNOT-22 Total and Subdomain Scores" in Section 3.4.2.1.1. Missing data will not be imputed. The same MMRM analysis method used for the SNOT-22 total and subdomain scores will be used. The LS-means for change from baseline at each analysis visit will be provided for each treatment group and the difference between LYR-220 and sham treatment at each analysis visit will be estimated along with the CIs. The p-value for the comparison at each analysis visit will also be presented.

Descriptive summary statistics on the values and changes from baseline will be presented for the above secondary efficacy endpoints at each analysis visit by treatment group.

#### 3.4.2.5 Time-to-First Recommendation of Rescue Treatment through Week 28/Follow-up

##### 3.4.2.5.1 Part 1

Time to first recommendation of rescue treatment will be analyzed using Kaplan-Meier (K-M) method. The K-M estimate of median time to first recommendation of rescue treatment with CI (if estimable) will be presented for each treatment group. K-M estimates of quartiles (25th and 75th percentiles) will also be presented for each treatment group.

##### 3.4.2.5.2 Part 2

Time to first recommendation of rescue treatment will be analyzed using Kaplan-Meier (K-M) method. The K-M estimate of median time to first recommendation of rescue treatment with CI (if estimable) will be presented for each treatment group. Estimates of quartiles (25th and 75th percentiles) will also be presented for each treatment group. Time to first recommendation of rescue treatment will be compared between LYR-220 group and the sham procedure group using the log-rank test stratified by the stratification factor. P-value from the log-rank test will be presented.

K-M estimates of the survival function for time to first recommendation of rescue treatment will be graphically displayed for each treatment group.

#### 3.4.2.6 Systemic/Oral Corticosteroid Use or Sinonasal Surgery Recommendation through Week 28/Follow-up

##### 3.4.2.6.1 Part 1

The endpoint will be summarized using the number and percentage of subjects being recommend by treating physician for systemic/oral steroid use or sinonasal surgery in each treatment group.

##### 3.4.2.6.2 Part 2

The endpoint will be summarized using the number and percentage of subjects being recommended by treating physician for systemic/oral corticosteroid use or sinonasal surgery in each treatment group. Comparison between LYR-220 group and the sham procedure group will

be performed using a Cochran-Mantel-Haenszel (CMH) test controlling for nasal polyp status. The general association p-value will be provided. The odds ratio and the corresponding CI will also be provided. The point estimates and CI for the treatment group differences in proportions will be calculated using Agresti's (2013, page 231)[2] approximation to the Miettinen and Nurminen (1985)[3] method by using pseudo-standard errors.

3.4.2.7 CFBL in Bilateral Percent Ethmoid Cavity Opacification by CT at Week 25/Follow-up

3.4.2.7.1 Part 1

Descriptive summary statistics on the values and changes from baseline to Week 25/Follow-up will be presented.

3.4.2.7.2 Part 2

Mean CFBL in bilateral percent ethmoid cavity opacification by CT at Week 25/Follow-up will be compared between the LYR-220 group and the sham procedure group using an analysis of covariance (ANCOVA) model with fixed-effect terms for treatment group and nasal polyp status with baseline score as a covariate.

LS-means in LYR-220 group and the sham procedure group, and their difference with CIs and p-values will be provided.

Descriptive summary statistics on the values and changes from baseline to Week 25/Follow-up will be presented.

3.4.2.8 CFBL in Nasal Inflammatory Biomarker Level at Week 25/Follow-up

Data will not be available by the time of final analysis. Hence, data will not be summarized and analyzed.

3.4.2.9 PGIC at Week 24

3.4.2.9.1 Part 1

Descriptive summary statistics on the values will be presented.

3.4.2.9.2 Part 2

The endpoint will be summarized using the number and percentage of subjects in each category by treatment group. Comparison between LYR-220 group and the sham procedure group in having "very much better" or "much better" impression will be performed using a Cochran-Mantel-Haenszel (CMH) test controlling for nasal polyp status. The general association p-value will be provided. The odds ratio and the corresponding CI will also be provided. The point estimates and CI for the treatment group differences in proportions will be calculated using Agresti's (2013, page 231)[2] approximation to the Miettinen and Nurminen (1985)[3] method by using pseudo-standard errors.

3.4.2.10 Conversion to a Candidate No Longer Requiring Revisions Surgery

3.4.2.10.1 Part 1

This responder endpoint will be summarized using the number and percentage of subjects that meet the criteria for no longer requiring revision surgery in each treatment group.

3.4.2.10.2 Part 2

This responder endpoint will be summarized using the number and percentage of subjects that meet the criterion for no longer requiring revision surgery in each treatment group. Comparison between each LYR-220 group and the sham procedure group will be performed using the CMH test controlling for nasal polyp status. The general association p-value will be provided. The odds ratio and the corresponding CI will also be provided. The point estimates and CI for the treatment group differences in proportions will be calculated using Agresti's (2013, page 231)[2] approximation to the Miettinen and Nurminen (1985)[3] method by using pseudo-standard errors.

3.4.2.11 End-of-Study Questionnaire at Week 28/Follow Up

Descriptive summary statistics on the values will be presented.

3.4.3 Subgroups

SNOT-22 total score and 3CS will be descriptively summarized for the Efficacy Analysis Set by nasal polyp status (with nasal polyp vs without) for Part 2 subjects.

## 3.5 Pharmacokinetic Assessment

3.5.1 Sample Collections for Pharmacokinetic Analysis

PK blood samples for assessment of plasma mometasone furoate concentrations will be collected from all subjects on 9 occasions as specified:

- Day 1 pre-procedure
- 1 hour (±10 minutes) post procedure on Day 1
- Day 2 or 3
- Day 5 or 8
- Week 4
- Week 12
- Week 16 or 20
- Week 24, and
- Week 25/Follow Up

At Day 1 visit, the blood samples for plasma PK analysis will be collected before the LYR-220 administration procedure and 1 hour (±10 minutes) after the procedure. At the Week 24 visit, the blood sample will be collected before the LYR-220 removal procedure. Blood samples may be collected at any time of the day during all the other scheduled study visits.

3.5.2 Handling Missing or Below the Lower Limit of Quantification Data

For PK concentration data, if the actual sampling time is missing, but a valid concentration value has been measured, the concentration value will be flagged, and the scheduled time point may be used for the calculation of PK parameters.

In cases of missing pre-dose concentrations for each treatment, the missing components may be assumed as zero. For the other cases, the missing data will not be imputed.

For the individual concentration and PK parameter calculation of each treatment, the following rules will be applied:

- If one or more BLQ values occur before the first measurable concentration, they will be assigned a value of zero.
- If BLQ values occur between measurable concentrations in a profile, the BLQ should be omitted (set to missing).
- If BLQ values occur after the last measurable concentration in a profile, the BLQ should be omitted (set to missing).

For the concentration summary and mean concentration plot preparation of each treatment, the following rules will be applied:

- Mean concentration at any individual time point will only be calculated if at least half of the subjects have valid values (i.e., quantifiable and not missing) at this time point for each treatment.
- In cases where a mean value is not calculated due to the above criterion not being met, the value will be set to missing.
- BLQ values will be set to zero.

### 3.5.3 Pharmacokinetic Concentration

Individual plasma concentrations of mometasone furoate will be summarized by treatment at each nominal time point for the PK Population descriptively. Individual plasma concentrations will also be listed for the PK Population. Listing of nominal times post dose and actual times will be provided. Deviations from the nominal times per protocol will be given in a separate listing. In listings, concentrations below the lower limit of quantification (LLOQ) will be reported as "<LLOQ", where LLOQ will be the actual value of LLOQ (to be determined).

Individual plasma concentration will be plotted by treatment on a linear and semi-log scale against actual sampling time points relative to dosing time. Mean (±SD) concentration will be plotted on a linear and semi-logarithmic scale against nominal time points by treatment, when available. LLOQ will be plotted as a reference line in both instances.

Actual sampling times that are outside the sampling time windows may be excluded from concentration summary and mean concentration plotting but will still be used in the calculations of PK parameters and individual concentration plotting.

A descriptive statistics summary of concentrations by LYR-220 design and actual PK sampling time, including number (n), mean, geometric mean, SD, coefficient of variation (CV), median, minimum, maximum, and the number of concentrations ≥LLOQ. The "<LLOQ" values will be set to zero based on Beal's method M7.

### 3.5.4 Pharmacokinetic Parameters

The following plasma PK parameters of mometasone furoate will be determined using non-compartmental methods as appropriate:

| **Parameters** | **Description** |
|---|---|
| $C_{max}$ | Maximum plasma concentration; determined directly from the concentration time profile; if the maximum plasma concentration occurs at more than one time point, $C_{max}$ is defined as the first maximum value |

| | |
|---|---|
| $T_{max}$ | Time to $C_{max}$; If the maximum value occurs at more than one time point, $T_{max}$ is defined as the first time point with this value. |
| $C_{last}$ | Observed plasma concentration corresponding to $T_{last}$where $T_{last}$ is the time of last measurable observed concentration |
| $AUC_{0\text{-}last}$ | Area under the plasma concentration vs time curve (AUC) from predose (time 0) to the time of the last quantifiable plasma concentration ($C_{last}$) |
| $AUC_{0\text{-}12h}$ | Area under the plasma concentration vs time curve (AUC) from predose (time 0) to 12 hours post dose |
| $AUC_{12havg}$ | Calculated as $AUC_{0\text{-}last}/T_{last}$*12 h |

Actual collection times will be used in PK parameter calculations. The Linear-Log Trapezoidal method (equivalent to the Linear Up/Log Down option in WinNonlin) will be used in the computation of all AUC values.

No PK parameters will be calculated for subjects with 2 or fewer detectable concentrations in their PK profile.

PK parameters will be summarized descriptively as follows: n, arithmetic mean, standard deviation, geometric mean, geometric standard deviation, coefficient of variation (CV%), geometric CV% (calculated as: gCV% =SQRT($e^{s^2}$-1)*100; where s is the standard deviation of the log-transformed values), minimum, maximum and median. Tmax will include median, minimum and maximum. No descriptive statistics will be determined when fewer than three individual PK parameters are available.

## 3.6 Safety Assessment

Safety data will be summarized by actual treatment received based on the Safety Analysis Set.

Safety data will be listed by site and subject.

### 3.6.1 Adverse Events (AEs)

An AE is any untoward medical occurrence (signs, symptoms, clinically significant abnormal laboratory findings) in a subject regardless of relationship to the investigational product or procedure.

All AEs will be coded to system organ class and preferred term using the MedDRA version 24.1 (or later version).

TEAEs are defined as AEs that start after the initiation of study treatment administration but no later than 31 days (>31 days) after discontinuation of study treatment.

Treatment-emergent serious adverse events (TESAEs) are defined as SAEs that start after the initiation of study treatment administration but no later than 31 days (>31 days) after discontinuation of study treatment.

An overview of AEs will be provided including counts and percentages of subjects (and event counts) with the following:

- Any TEAEs (overall and by maximum severity)
- Any product related TEAEs (overall and by maximum severity)
- Any study procedure related TEAEs (overall and by maximum severity)
- Any treatment-emergent serious AEs (TESAEs)
- Any TEAEs leading to discontinuation of study product
- Any AEs leading to death
- Any TEAEs related to COVID-19

Counts and percentages of subjects (and event counts) will also be presented by primary system organ class and preferred term for each of the categories in the overview. Listings will be presented specifically for product related TESAEs/TEAEs, and TEAEs leading to discontinuation of study drug.

### 3.6.2 Clinical Laboratory Tests

Samples for hematology and blood chemistry assessments will be obtained during Screening and Week 25/Follow Up visits, and processed by [redacted] Reference Labs, the central laboratory. A list of laboratory tests to be performed is included in Appendix C.

Descriptive statistics for values will be presented.

### 3.6.3 Nasal Endoscopy Assessments

Ethmoid cavities will be assessed by endoscopy during Screening, on Day 1 prior to LYR-220 administration/sham procedure, and at Week 4, 12, 24 (before LYR-220/sham removal), and 25/Follow Up visits.

Local safety evaluation of ethmoid cavity will be performed on Day 1 prior to LYR-220 administration/Sham procedure and at Week 4, 12, 24, and 25/Follow Up visits to document presence of epistaxis, mucosal injury, and any other adverse local observations in ethmoid cavity.

The severity of epistaxis will be determined by the Investigator on the basis of his or her clinical judgment and the following definitions:

- Mild: blood-tinged mucus, nonactive nose bleeding
- Moderate: active nose bleeding that does not require medical intervention
- Severe: frank nose bleeding that requires medical intervention

The severity of mucosal injury will be determined by the Investigator because of his or her clinical judgment and the following definitions:

- Mild: evidence of epithelial erosion
- Moderate: evidence of ulceration through the epithelial layer with exposed underneath tissue

- Severe: perforation

Counts and percentages of subjects will be presented at baseline for the following:

- Severity of Epistaxis (Left): [MILD | MODERATE | SEVERE | NA]
- Severity of Epistaxis (Right): [MILD | MODERATE | SEVERE | NA]
- Severity of Mucosal injury (Left): [MILD | MODERATE | SEVERE | NA]
- Severity of Mucosal injury (Right): [MILD | MODERATE | SEVERE | NA]

Newly identified or worsened endoscopic findings will be presented at each scheduled visit and in overall.

### 3.6.4 Vital Signs

Vital sign measurements will include blood pressure (systolic and diastolic, mm Hg), and pulse rate (beats per minute), aural/oral temperature (°C or °F), and respiration rate (breaths per minute). All measurements will be obtained after the subject has been seated for at least 5 minutes.

Vital signs will be measured at the Screening visit. Descriptive statistics for values will be presented.

### 3.6.5 Ophthalmologic Assessments

The ophthalmologic assessment of IOP and slit-lamp examination to identify development or worsening of cataract will be conducted at Screening and Week 25/Follow Up visits. The cataract assessment will be conducted according to the Simplified Cataract Grading System authored by the World Health Organization (WHO) Cataract Grading Group. Subject's eyes will be dilated with mydriatics following the WHO guidance for cataract assessment. IOP may be measured using Goldmann applanation tonometer, noncontact tonometer, or tono-pen; however, it is recommended that the same method be used for consistency across serial assessments on a given subject. IOP assessment will also be performed at Week 4 and 12 visits. Assessments will be conducted by an ophthalmologist/optometrist who is blinded to the subject's treatment assignment.

The number and percentage of subjects with clinically significant increase of IOP will be presented by visit and in overall. Descriptive summary statistics on the values and change from base line of IOP will be presented by visit.

The number and percentage of subjects with newly identified or worsened cataract will be presented by visit and in overall.

### 3.6.6 Oral/Systemic Corticosteroids Rescue

Other oral steroids for rescue treatment of CRS or intravenous or oral steroids for another reason that are prescribed to the subject are to be recorded in the eCRF. All efforts should be made to complete the Week 25/Follow Up assessments including nasal endoscopy and CT before starting treatment with oral/systemic corticosteroids. However, the subject should continue with the study treatment and follow-up visits. The investigator (or designee) will record the dates and dosing information (dosage form, daily dose, duration, name of drug) on the appropriate page(s) of the eCRF. Indication for oral/systemic corticosteroid use will also be

captured. A course of oral/systemic corticosteroids is considered continuous if treatment is separated by less than 7 days.

The number and percentage of subjects with oral/systemic corticosteroids rescue will be presented by treatment group.

3.6.7 Sinonasal surgery (actual or planned) for CRS

For subjects who have a surgery or have a scheduled date for sinonasal surgery as rescue for CRS, the reason (worsening signs and/or symptoms during the study), the date the surgery was indicated, expected or actual surgery date, and the type and outcome of surgery will be recorded in the eCRF. Types of sinonasal surgery include, but are not limited to, repeat functional endoscopic sinus surgery, balloon sinuplasty, turbinate reduction, septoplasty or polypectomy, or any endoscopic procedure that results in sinonasal tissue removal.

If the surgery is to be performed during the study treatment period, the study treatment will be discontinued and all procedures/assessments for the Week 24 visits will be completed prior to the surgery. Additionally, all efforts should be made to complete the Week 25/Follow Up assessments including nasal endoscopy and CT prior to the surgery. The subject will be discontinued from the study.

If the surgery is scheduled after the planned end of study, the investigator (or designee) should follow-up with the subject on the occurrence and outcome of the surgery until the time of database closure for the study.

The number and percentage of subjects with sinonasal surgery will be presented by treatment group for the following:

- Full Endoscopic Sinus Surgery (FESS),
- Balloon Sinuplasty,
- Turbinate Reduction,
- Septoplasty or Polypectomy,
- Other.

# 4 ANALYSIS TIMING

## 4.1 Interim Analysis

No interim analysis is planned.

## 4.2 Primary Lock Analysis

A Primary Lock Analysis (PA) will be conducted to support a late-breaking presentation of high-level results from this BEACON study at the annual meeting of the American Rhinologic Society (ARS) in September 2023. The SAP will be finalized and signed prior to this analysis. Any changes to the pre-planned analyses in this SAP that affects statistical analysis after the primary lock analysis will be considered posthoc. The study team members who are involved in data cleaning for the final data base lock will not receive the detailed patient-level results from the PA.

The PA will be performed after all subjects in Part 1 and Part 2 complete Week 24 visit. After the database is locked (i.e., freeze of eCRFs), the subject's treatment allocation will be unblinded.

The analysis data sets (i.e., SDTM and ADaM) for this analysis will be locked. Selected data will be generated as listed below.

- Disposition,
- Demographics,
- Baseline disease characteristics,
- Change from baseline (CFBL) in SNOT-22 total score at Weeks 2, 4, 6, 8, 12, 16, 20, 24 and 28,
- CFBL in the average composite score over the preceding 7 days of 3 cardinal symptoms (3CS) and individual cardinal symptom scores at Weeks 2, 4, 6, 8, 12, 16, 20, 24 and 28,
- Overview of Adverse Events,
- Treatment-Emergent Adverse Events by Preferred Term,
- Treatment-Emergent Adverse Events by System Organ Class and Preferred Term,
- Product-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term,
- Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term,
- Product-Related Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term,
- Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment by System Organ Class and Preferred Term.

### 4.3 Final Analysis

The final database lock and analysis will occur after all subjects in Part 1 and in Part 2 have completed the study (Week 28/Follow Up visit). After the database is locked, the final analysis will be generated. TFLs, SDTM data and AdaM data along with associated files will be provided. Associated files may include annotated CRFs, SDTM specifications, SDTM programs, AdaM specifications, AdaM programs, TFL programs, and CDISC Define packages for both SDTM and ADaM data. The CSR will be written based on the final TLFs.

## 5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

There is no change from the protocol-specified statistical analyses.

## 6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. PK parameters will be calculated via SAS® and confirmed with the results of Phoenix WinNonlin™ (version 8.1 or higher). All data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

## APPENDIX A: REFERENCE

[1] Center for Drug Evaluation and Research. (2021). E9 (R1) statistical principles for clinical trials: addendum: estimands and sensitivity analysis in clinical trials.

[2] Agresti. (2013). Categorical data analysis, Wiley, 3rd edition.

[3] Miettinen O, Nurminen M. Comparative analysis of two rates. Statistics in Medicine 1985; 4: 213–226.