STATISTICAL ANALYSIS PLAN

(For the 24-Week Treatment Period)

Protocol Title:	ENLIGHTEN 1: A Phase III, Randomized, Blinded, Controlled, Parallel-Group Trial to Evaluate the Efficacy and Safety of LYR-210 for the Treatment of Chronic Rhinosinusitis (CRS) in Adults
Protocol Number:	LYR-210-2021-004
Protocol Version/Date:	4.0/ 31 October 2023
Investigational Product:	LYR-210 System (7500 µg)
Sponsor:	Lyra Therapeutics, Inc. 480 Arsenal Way Watertown, MA USA 02472
SAP Version/Date:	2.0/ 26 March 2024

SIGNATURE PAGE

Protocol Title:	ENLIGHTEN 1: A Phase III, Randomized, Blinded, Controlled, Parallel-Group Trial to Evaluate the Efficacy and Safety of LYR-210 for the Treatment of Chronic Rhinosinusitis (CRS) in Adults
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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature **Date**

Signatures have been redacted

VERSION HISTORY

Version	Version Date	Description
1.0	01 NOV 2023	Original signed Version
2.0	26 March 2024	Second version upon FDA's feedback. [redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AECRS	Acute exacerbation of CRS
ANCOVA	Analysis of covariance
AR	Allergic rhinitis
CFBL	Change from baseline
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CRS	Chronic Rhinosinusitis
CS	Cardinal symptoms
CSR	Clinical Study Report
CT	Computed tomography
eCRF	Electronic case report form
ePRO	Electronic patient-reported outcomes questionnaire
EQ-5D-5L	EuroQoL 5-dimension, 5-level
ET	Early termination
[redacted]	
ICE	Intercurrent event
IOP	Intraocular pressure
IRC	Independent review committee
K-M	Kaplan-Meier
LS-means	Least squares means
MAR	Missing at random
MCID	Minimum clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MF	Mometasone furoate
MI	Multiple imputation
MMRM	Mixed model with repeated measures
MNAR	Missing not at random
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SCS	Systemic corticosteroids
SD	Standard deviation
SF-36v2	36-Item short form health survey, version 2
SNOT-22	Sino-Nasal Outcome Test
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
WHO	World Health Organization

LIST OF KEY TERMS

Terms	Definitions
Initial Treatment Period	The 24 weeks of treatment after the first administration of study treatment and prior to second administration of study treatment in the extension period. Only this period will be evaluated for statistical comparisons between LYR-210 and sham for the efficacy.
Extension Treatment Period	Period after the first administration of study treatment in the extension period after completing initial 24-week of sham controlled treatment until the last day of study completion at Week 52 or early discontinuation.
Follow-up Period	Period after the last study treatment (EOT) or last assessment of the protocol. Additional safety data and follow-up observations for adverse events are conducted during this period.

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 the Week-24 analysis database lock and unblinding the subject treatment assignments. The analyses described in the SAP will be conducted after all subjects have completed the randomized, blind treatment period at Week 24 (or prematurely discontinued from the study prior to Week 24). Only data pertaining to the first 24 weeks of treatment period (i.e., all data for subjects early discontinued during the initial 24-Week period, or data from 24-week blind period prior to re-randomization in the extension period) will be included. [redacted]

The finalized Version 1.0 of this SAP was submitted to FDA. Version 2.0 is created after receiving feedback from FDA and will be approved prior to the 24-week analysis database lock. The changes that impact on the statistical analyses between Version 1.0 and Version 2.0 are listed in Appendix C.

Changes from the planned analyses in the finalized SAP that impact on 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 the efficacy of LYR-210, compared with a sham procedure control, in improving the 3 cardinal symptoms (3CS) of Chronic Rhinosinusitis (CRS) in CRS participants without nasal polyps, who had previously failed medical management. The 3CS are nasal blockage/obstruction/congestion, anterior/posterior nasal discharge, and facial pain/pressure.

2.1.2 Secondary Objectives

The secondary objectives are to:

1. Evaluate the efficacy of LYR-210, compared with sham control, in improving the 3 cardinal symptoms of CRS in CRS participants without nasal polyps or with nasal polyps of grade 1, who had previously failed medical management.
2. Evaluate the efficacy of LYR-210, compared with sham control, in improving the individual CRS symptoms, CRS-related quality of life, the extent of inflammation in the ethmoid sinuses, and the need for rescue treatment in surgery naïve CRS participants without nasal polyps or with nasal polyps of Grade 1, who had previously failed medical management.

2.2 Study Design

2.2.1 Overview

This global, multicenter study will be conducted in a randomized, controlled, parallel-group, participant-blinded fashion in approximately 180 symptomatic adult CRS participants who have failed previous medical management. Participants enrolled in the study will include participants

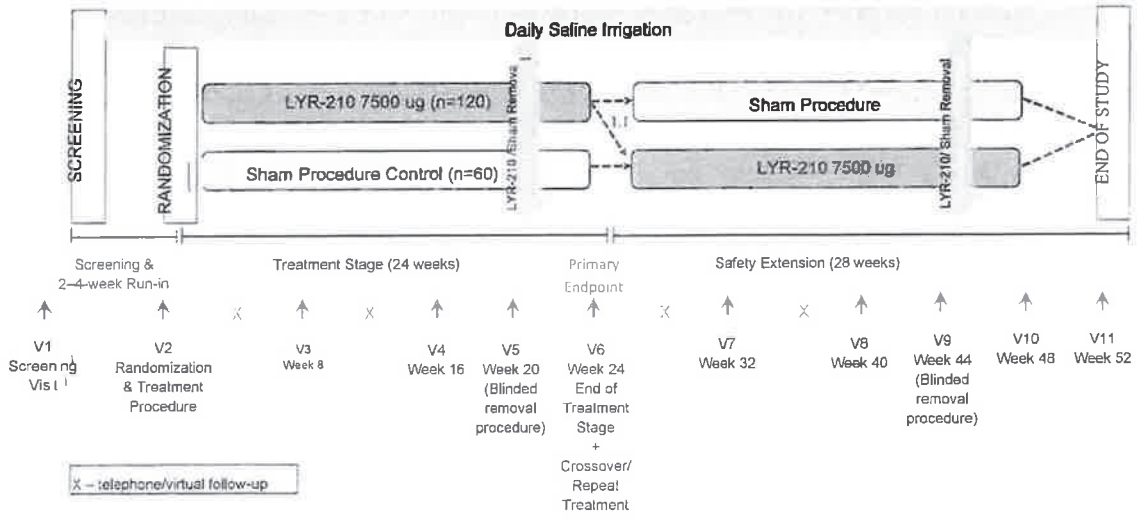
who have accessible and intact middle meatuses. The efficacy and safety of LYR-210 matrix (7500 µg) versus a control group receiving a sham procedure will be assessed on a background therapy of daily saline irrigation. Participants will be randomized 2:1 to either treatment with LYR-210 or to control.

The study will consist of 3 stages:

- Screening and run-in stage: 2-4 weeks before randomization and treatment procedure
- Treatment stage (LYR-210 or control): randomization and treatment procedure through 24 weeks
- Safety extension: Weeks 25 through 52

A safety extension phase after the Week 24 visit will involve crossover to active treatment for control participants while treatment participants will be re-randomized 1:1 to either sham or a second round of active treatment with follow-up through Week 52.

Figure 1. Study Design.



2.2.2 Randomization and Blinding

On Day 1, after confirmation of eligibility and baseline assessments, and before any treatment, participants will be randomized in a 2:1 ratio to receive LYR-210 treatment or control (sham procedure) with stratification based on region (North America vs Europe) and nasal polyp status (yes vs no). Randomization will be conducted using Interactive Response Technology (IRT) and treatment will be assigned according to a randomization scheme generated by an unblinded biostatistician. The person generating the randomization scheme will not be involved in the collection, review, and/or analysis of study data before database lock and unblinding of the database.

To maintain the participant blind to treatment assignment, each participant will wear an eye mask (i.e., blindfold) and headphones at the time of the LYR-210 administration/sham procedure. Except for the cases of spontaneous matrix dislodgement, participants should remain blinded to their treatment assignment (LYR-210 or control) until the study is completed.

[redacted]

After Week 24, using IRT, control participants will be assigned to active treatment and treatment participants will be re-randomized 1:1 to either sham procedure or a second active treatment procedure stratified by geographic region and nasal polyp status at baseline. Follow-up visits will continue through Week 52.

The sponsor will be blinded to participants' initial study treatment assignments until database lock for the Week 24 primary analysis (initial randomized phase).

Due to the nature of the procedure, the treating investigator/surgeon will not be blinded to the treatment assignment. Efforts will be made to keep the study coordinator and other study staff blinded.

Breaking the blind to the participant is expressly forbidden except in the event of spontaneous dislodgment of LYR-210, or a medical emergency where the identity of the treatment assignment must be known to properly treat the participant. If breaking the blind is required because of a medical emergency, decision to unblind lies solely with the investigator. In all cases where the blind is broken to the participant, the investigator must record the date and reason for breaking the blind. The unblinding should be noted in the participant's electronic case report form (eCRF).

Every effort will be made to maintain the integrity of the study while conducting the 24-week analysis.

2.2.3 Study Drug

The LYR-210 System is a combination product comprised of a single-use applicator, preloaded with an anti-inflammatory drug matrix. LYR-210 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, and asthma. LYR-210 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.

Each LYR-210 contains a total MF dose of 7500 µg. LYR-210 is intended to be administered bilaterally into the middle meatus by an otolaryngologist under endoscopic visualization using the provided single-use applicator. Once administered, each LYR-210 is designed to gradually deliver sustained doses of MF to the inflamed mucosal tissue over a 24-week resident time. Bilateral placement of LYR-210 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 human participant (or approximately 45 µg MF per nostril).

On Day 1, participants who are assigned to the active treatment arm will have the LYR-210 administered bilaterally into the middle meatus according to the sponsor's instructions for use. Participants who are assigned to the control arm, will undergo mock administration (i.e., sham procedure) [redacted]

After the procedure, all participants will be instructed to continue daily saline irrigation and completion of daily 4CS electronic patient-reported outcomes questionnaire (ePRO).

2.2.4 Sample Size Determination

Per the null and alternative hypotheses described in Section 3.1.6, 2:1 randomization (LYR-210:control), in the participants without polyps, [redacted]

With a sample size of 150 participants (n=50 control and n=100 LYR-210), alpha = 0.05, and power of 0.95, we will be able to detect an effect size of 0.63, which represents a mean difference of 1.31. This effect size is 18% smaller than the observed difference in the Phase 2 study (1.61 versus 1.31 3CS mean change scores). For the first key secondary endpoint (an analysis of the primary endpoint in all participants; n=60 control and n=120 LYR-210), the study will have 95% power to detect an effect size of 0.57, which represents a mean difference of 1.19.

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoint

The primary endpoint is the change from baseline (CFBL) in the 7-day average composite score of the 3CS of nasal blockage/obstruction/congestion, facial pain/pressure, and anterior/posterior nasal discharge at Week 24 **in participants without nasal polyps** at baseline.

2.3.2 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints.

1. CFBL in the 7-day average composite score of 3CS at Week 24 in all participants.
2. CFBL in the 22-item Sino-Nasal Outcome Test (SNOT-22) total score at Week 24 in all participants.
3. CFBL in the percent opacification of the bilateral anterior and posterior ethmoids at Week 20 as determined by 3-D volumetric CT analysis in all participants.
4. Rescue treatment (SCS for any reason/ESS) requirement through Week 24. (This endpoint will be descriptively summarized in this study and the statistical testing will be conducted on pooled data from this [ENLIGHTEN 1] study and the ENLIGHTEN 2 study)

The above key secondary and the below secondary endpoints will be analyzed for all participants.

If the primary efficacy endpoint is met, the key secondary endpoints will be tested, each at a 2-sided significance level of 0.05, using the hierarchical method in the above order.

2.3.3 Additional Secondary Efficacy Endpoints

Additional secondary endpoints include:

1. CFBL in 3CS score at Weeks 4, 8, 12, 16, and 20
2. CFBL in the symptom score for individual cardinal symptoms of nasal blockage/obstruction/congestion, anterior/posterior nasal discharge, and facial pain/pressure at Weeks 4, 8, 12, 16, 20, and 24
3. CFBL in loss of smell score at Weeks 4, 8, 12, 16, 20, and 24, for all participants and for participants with baseline score ≥2

4. Improvement of ≥1 point, ≥2 points, and ≥3 points from baseline in 3CS score at Week 24
5. CFBL in SNOT-22 total score at Weeks 4, 8, 12, 16, and 20
6. CFBL in SNOT-22 subdomain scores at Weeks 4, 8, 12, 16, 20, and 24
7. Improvement of ≥8.9 and ≥12 from baseline in SNOT-22 total score at Week 24
8. CFBL in the Zinreich score of the bilateral anterior and posterior ethmoids at Week 20
9. Time to first rescue treatment requirement through Week 24
10. Sinonasal surgery requirement through Week 24
11. Rescue medicine use through Week 24
12. Total systemic corticosteroids (SCS) dose prescribed through Week 24
13. Number of days on SCS through Week 24

[redacted]

16. CFBL in 36-Item short form health survey, version 2 (SF-36v2) physical health, mental health, and domain scores at Week 24
17. CFBL in EuroQoL 5-dimension, 5-level (EQ-5D-5L) score at Week 24
18. Improvement of ≥1 category and ≥2 categories in the severity of CRS-related symptoms as indicated by the Patient Global Impression of Severity (PGIS) at Week 24
19. Overall change of "very much better" or "much better" in the CRS-related symptom severity as indicated by the Patient Global Impression of Change (PGIC) at Week 24
20. CFBL in Medical Outcomes Study Sleep Scale (MOS Sleep-R) score at Week 24
21. CFBL in Work Productivity and Activity Impairment-Specific Health Problem (WPAI-SHP), version 2.0 at Weeks 4, 12, and 24

[redacted]

2.3.5 Safety Endpoints

Safety endpoints include:

1. Treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) through Week 24.
2. Abnormal (clinically significant) laboratory values (hematology and chemistry) through Week 24.
3. Newly identified adverse endoscopic findings in middle meatus including epistaxis, mucosal erosion or ulceration, and perforation through Week 24.
4. Clinically significant increase of intraocular pressure (IOP) through Week 24.
5. Newly identified or worsened cataract in one or both eyes by slit-lamp examination through Week 24.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

The analysis for 24-week will include all data collected prior to the date of re-randomization. The analysis of AE will include all data collected prior to the date of successful insertion in the safety

extension. The analysis of clinical laboratory tests, nasal endoscopy, vital signs, and ophthalmologic assessments will include all data collected prior to and on the date of successful insertion in the safety extension.

3.1.1 Analysis Day

Analysis day for analysis visit windows (i.e., "Aday") will be calculated from the date of study treatment (LYR-210 or sham) administration. The day of study treatment administration will be Aday 1, and the day immediately before Aday 1 will be Aday -1.

3.1.2 Analysis Visits

Analysis visits will be used for efficacy and safety endpoint analysis.

For CS endpoints (3CS and 4 individual cardinal symptoms), analysis visits will be assigned according to the analysis windows specified in Table 1a. Analysis Visit Window for Weekly 3CS, 4 Individual Cardinal Symptom Scores, SNOT-22 [redacted] using daily CS weekly scores defined in section 3.1.4.3 and 3.1.4.4. The daily CS weekly score that is closest to the target day will be selected for analysis. If two daily CS weekly scores are equally distanced, select the value before the target day.

For other endpoints, 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 defined 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 multiple ePRO are completed at the same day and the entry for individual questions is different, the entry having the worst score will be selected for analysis. Total score will then be calculated using selected worst individual scores. If multiple ePRO are completed at the same day and the entry for individual questions are identical, the earliest entry will be used for analysis.

3.1.2.1 Analysis Visit Windows for Efficacy Endpoints

For the subjects into safety extension, all days must be prior to re-randomization date in safety extension. For the subjects early discontinued from the treatment or completed the treatment stage but not into safety extension, all the follow-up data will be included for the Week 24 analysis using the windows below.

Table 1a. Analysis Visit Window for Weekly 3CS, 4 Individual Cardinal Symptom Scores, SNOT-22 [redacted]

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 2	15	8	21
Week 4	29	22	35
Week 8	57	36	63
Week 12	85	64	91
Week 16	113	92	119

Week 20	141	120	147
Week 24	169	148	210*

*The last day of the Week 24 is 6 weeks longer to minimize missing data at the Week 24 timepoint.
For Weekly 3CS and 4 Individual Cardinal Symptom Scores, one calculated 7-day average score will be selected for analysis according to the study day that is closest to the target day for the time point, with the one before the target day selected in the case of a tie.

Table 1b. Analysis Visit Window for Ethmoid Cavity Opacification

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 20	141	85	210*

*The last day of the Week 24 is 6 weeks longer to minimize missing data at the Week 24 timepoint.

Table 1c. Analysis Visit Window for SF-36v2, EQ-5D-5L, PGIC, and MOS Sleep-R

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 24	169	85	210*

*The last day of the Week 24 is 6 weeks longer to minimize missing data at the Week 24 timepoint.

Table 1d. Analysis Visit Window for PGIS

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 8	57	36	63
Week 16	113	92	119
Week 24	169	148	210*

*The last day of the Week 24 is 6 weeks longer to minimize missing data at the Week 24 timepoint.

Table 1e. Analysis Visit Window for WPAI-SHP

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 4	29	8	35
Week 12	85	64	91
Week 24	169	148	210*

*The last day of the Week 24 is 6 weeks longer to minimize missing data at the Week 24 timepoint.

3.1.2.2 Analysis Visit Windows for Safety Endpoints

For the subjects into safety extension, all days must be prior to re-randomization date in safety extension. For the subjects early discontinued from the treatment or completed the treatment stage but not into safety extension, all the follow-up data will be included for the Week-24 analysis using the windows below.

Table 1f. Analysis Visit Window for Laboratory and Slit-Lamp Examination Assessments

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day

Week 24	169	85	210*

*The last day of the Week 24 is 6 weeks longer to minimize missing data at the Week 24 timepoint.

Table 1g. Analysis Visit Window for IOP Assessments

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 8	57	36	63
Week 16	113	92	119
Week 24	169	148	210*

*The last day of the Week 24 is 6 weeks longer to minimize missing data at the Week 24 timepoint.

Table 1h. Analysis Visit Window for Nasal Endoscopy Assessments

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 8	57	36	63
Week 16	113	64	119
Week 20	141	120	147
Week 24	169	148	210*

*The last day of the Week 24 is 6 weeks longer to minimize missing data at the Week 24 timepoint.

3.1.3 Definition of Baseline

For cardinal symptoms (3CS and individual symptoms), the baseline score 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 value is the last non-missing value prior to or on the day of treatment administration.

3.1.4 Endpoint Related Definition and Calculation

3.1.4.1 Chronic Rhinosinusitis Cardinal Symptoms ePRO through Week 24

Enrolled participants will be asked to complete a daily ePRO questionnaire to assess the severity of the 4 individual cardinal symptoms of CRS (nasal blockage/obstruction/congestion, facial pain/pressure, anterior/posterior nasal discharge, and reduction/loss of smell). Each symptom is scored on a 0-3 scale as follows: 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

3.1.4.2 Daily 3 Cardinal Symptoms Score

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 for that day will be considered missing.

3.1.4.3 Individual Cardinal Symptoms Weekly Score

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

3.1.4.4 3 Cardinal Symptoms Weekly Score

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

For example, the 7-day average 3CS score at Day 57 can be interpretated as "the average 3CS scores in the daily score from Day 51 to Day 57 if at least 4 of them are non-missing".

3.1.4.5 SNOT-22

The SNOT-22 questionnaire is a 22-item disease-specific quality of life instrument validated for use in CRS. Each symptom is scored 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 SNOT-22 total score is the sum of the 22 items and can range from 0 to 110 with higher scores indicating worse symptoms. The minimum clinically important difference (MCID) for the SNOT-22 total score has been determined to be 8.9 units. Additionally, the SNOT-22 scores can be divided into subcategories of rhinologic symptoms, extra-nasal rhinologic symptoms, ear/facial symptoms, psychological dysfunction, and sleep dysfunction. For each subcategory, the subdomain score is the sum of the items within that subcategory.

Table 2. Categorized survey items for separate domains of the SNOT-22 instrument

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

3.1.4.6 Sinus CT Scoring (Zinreich and 3-D Volumetric Scoring)

Opacification of the ethmoid sinuses will be assessed using CT images. Two scoring methodologies will be employed to assess sinus opacification - Zinreich modified Lund-Mackay and 3-D volumetric analysis.

The Zinreich modified Lund-Mackay scoring system uses a 0-5 scale for scoring each sinus. The scoring is based on the percentage of sinus opacification as follows: 0 = 0%, 1 = 1% to 25%, 2 = 26% to 50%, 3 = 51% to 75%, 4 = 76% to 99%, and 5 = 100% or completely occluded. The left and right sides are graded, and the sum is the total score out of maximum of 20.

3-D volumetric scoring will involve evaluations of each slice of 3-D coronal CT sequences and summing of all the slices to create a volumetric score ranging from 0% to 100%.

3.1.4.7 Time to first rescue treatment requirement through Week 24

Rescue treatment is defined as, after enrollment, participants receiving SCS for any reason, and/or recommended for sinonasal surgery to relieve CRS symptoms. See protocol section 3.4.3 for details.

Time to first rescue treatment requirement will be calculated from date of randomization, i.e., date of first rescue treatment requirement – date of successful insertion + 1. If a participant is lost to follow up/discontinues the study before Week 24 and does not have rescue treatment requirement by that time, then it will be censored at the date of last assessment. If a participant does not have rescue treatment required through Week 24, it will be censored at Week 24.

3.1.4.8 Rescue medication use through Week 24

The rescue medicine use through Week 24 is derived by checking whether the rescue medications are taken before Week 24, inclusive.

3.1.4.9 Sinonasal surgery requirement through Week 24

For participants 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, functional endoscopic sinus surgery, balloon sinuplasty, turbinate reduction, septoplasty or polypectomy, or any endoscopic procedure that results in sinonasal tissue removal.

The study treatment will be discontinued and all procedures/assessments for the ET and end of treatment phase (EOTP) visits will be completed prior to the surgery. The participant will be discontinued from the study.

The sinonasal surgery requirement through Week 24 is derived by checking whether the sinonasal surgery is indicated before Week 24, inclusive. If a participant is lost to follow up/discontinues the study before Week 24 and does not have sinonasal surgery requirement at that time, this will be considered as a missing data for the analysis.

3.1.4.10 Total systemic corticosteroid (SCS) dose prescribed through Week 24

SCS for rescue treatment of CRS or for another reason that are prescribed to the participant are to be recorded in the eCRF.

If possible, an endoscopy should be performed before starting treatment with SCS. The participant should continue with the study treatment and follow-up visits per protocol. 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 SCS use will also be captured by selecting 1 or more of the following categories:

1. CRS
2. Asthma
3. Other respiratory or ENT disease (specify)
4. Other reason (specify).

A course of SCS is considered continuous if treatment is separated by less than 7 days.

The daily average will be calculated then multiplied by 168 days (24 weeks). If a participant is lost to follow up/discontinues the study before Week 24, the average calculation will be using the data from Day 1 to the last assessment date.

3.1.4.11 Number of days on SCS through Week 24

If a participant is lost to follow up/discontinues the study before Week 24 and does not have sinonasal surgery requirement at that time, the number of days on SCS will be calculated as

percent of days on SCS from Day 1 to the last assessment date multiplied by 168 days (24 weeks).

[redacted]

3.1.4.14 36-Item short form health survey, version 2 (SF-36v2) physical health, mental health, and domain scores

The SF-36v2 health survey captures participants' perceptions of their health and well-being in 8 dimensions: physical functioning, physical limitations, emotional limitations, social functioning, bodily pain, general health, and mental health. The items of the SF-36v2 are transformed and summed to a norm-based scale (mean=50, SD=10) for each physical and mental component domain in which higher scores indicate a better health-related quality of life status.

3.1.4.15 EuroQoL 5-dimension, 5-level (EQ-5D-5L) score

The EQ-5D-5L descriptive system comprises the following 5 dimensions, each describing a different aspect of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/ depression. Each dimension has 5 response levels of severity: no problems, slight problems, moderate problems, severe problems, 'unable to' /extreme problems. In addition, the EQ-VAS records the overall current health on a vertical visual analogue scale, where the anchors are labelled 'the best health you can imagine' and 'the worst health you can imagine'.

3.1.4.16 PGIS

Participants will be asked a single question to rate their severity of CRS-related symptoms over the past 7 days[redacted]

3.1.4.17 PGIC

The PGIC is a self-assessment of the participant's overall change in CRS-related symptom severity compared to pretreatment. [redacted]

3.1.4.18 Medical Outcomes Study Sleep Scale (MOS Sleep-R) score

MOS Sleep-R is a 12-item instrument with a 4-week recall designed to measure key aspects of sleep, such as disturbance, adequacy, somnolence, and quantity. The score ranges from 0 to 100, lower scores indicating better sleep and higher scores indicating worse sleep. The scale yields a sleep problem index and scores on the following 6 subscales: sleep disturbance, snoring, shortness of breath or headache, sleep adequacy, sleep somnolence, and sleep quantity.

3.1.4.19 Work Productivity and Activity Impairment-Specific Health Problem (WPAI-SHP)

The WPAI-SHP is a questionnaire to measure the effect of a specific health problem on the participant's work productivity and normal daily activities. Employed participants report absenteeism (time absent from work), and presenteeism (time at work but not fully productive), which are calculated to a work productivity index. All participants report time away from normal activities.

[redacted]

3.1.5 Summary Statistics

Categorical data will generally be summarized with counts and percentages of subjects. Percentages by categories will be based on the number of subjects with no missing data, i.e. the percentages for the non-missing categories will add up to 100%. Quantitative data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, interquartile range (Q1, Q3) and range (minimum, and maximum).

3.1.6 Hypothesis Testing

For the primary efficacy endpoint, the null and alternative hypotheses to be tested are:

$H0: \mu L = \mu C$

vs

$H1: \mu L \neq \mu C$

where μL and μC are true mean CFBL in 3CS at Week 24 for participants receiving the LYR-210 (7500 μg) treatment and the control (sham) treatment, respectively.

Unless otherwise specified, all hypothesis tests will be conducted at a 2-sided significance level of 0.05. Two-sided equal tailed 95% (asymptotic) confidence intervals (CIs) will also be calculated.

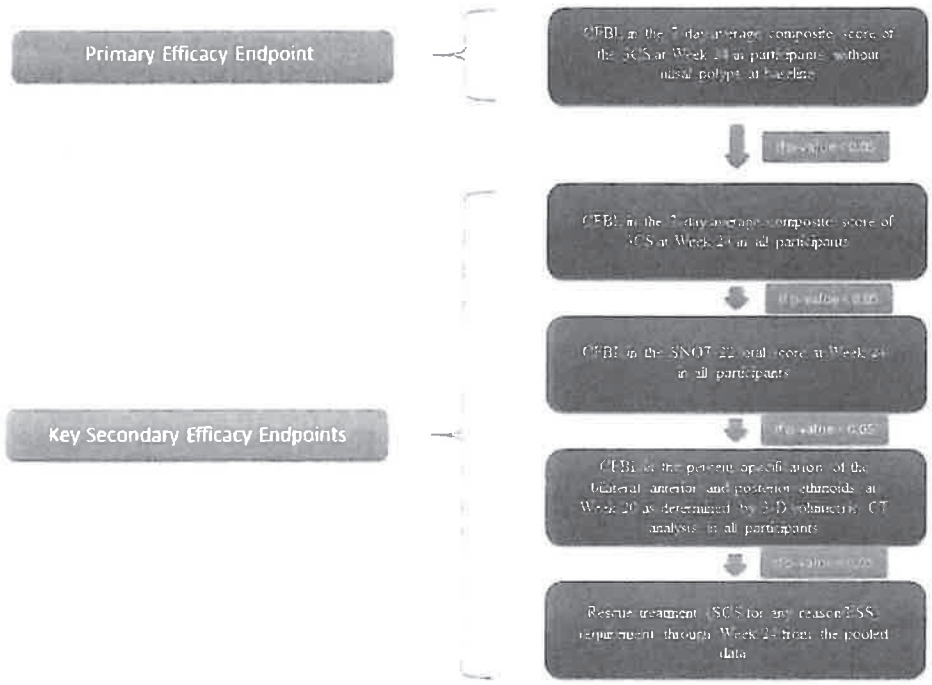
3.1.7 Multiplicity

As described in Section 2.3.2, a fixed sequential testing procedure will be implemented. In a hierarchical step-down manner, the primary efficacy endpoint will be tested at the 2-sided 0.05 level first, followed by testing the prespecified key secondary endpoints, each at a 2-sided significance level of 0.05, in the order specified in Section 2.3.2. Inferential conclusions

about these efficacy endpoints will require statistical significance of the previous key secondary endpoints and the primary efficacy endpoint.

With this method, statistical significance cannot be achieved for a key secondary endpoint unless statistical significance is achieved for all key secondary endpoints already tested. This approach ensures that the overall study-wise type-1 error rate is controlled at 0.05 for the comparisons between treatment and control on the primary and all 4 key secondary endpoints.

Figure 2. Multiplicity



3.1.8 Handling of Dropouts and Missing Data

3.1.8.1 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. The imputation rules in Table 3 will be used unless otherwise specified.

Table 3. 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 all listings, missing or partial dates will be left as they have been recorded.

3.1.8.2 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 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 First IMP administration = 2022-08-11 and several AEs have incomplete start dates.

Table 4. 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 [First IMP admin.]	YYYY-MM-01	2022-07-XX	2022-07-01
YYYY-MM = YYYY-MM of [First IMP admin.]	Min ([First IMP admin.], AE end date)	2022-08-XX	Min (2022-08-11, AE end date)
YYYY-MM > YYYY-MM of [First IMP admin.]	YYYY-MM-01	2022-09-XX	2022-09-01
Day and month are missing			
YYYY < YYYY OF [First IMP admin.]	YYYY-01-01	2021-XX-XX	2021-01-01
YYYY = YYYY OF [First IMP admin.]	Min ([First IMP admin.], AE end date)	2022-XX-XX	Min (2022-08-11, AE end date)
YYYY > YYYY OF [First IMP admin.]	YYYY-01-01	2023-XX-XX	2023-01-01
Day, month, and year are missing			

XXXX-XX-XX	Min ([First 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.

3.1.8.3 Missing data

All efforts will be made to minimize missing data. Participants who discontinued treatment early are encouraged to continue completing ePRO assessments through Week 24. Data collected after treatment discontinuation will be included in the analysis. For participants who undergo rescue treatment (SCS and/or sinonasal surgery for any reason), data collected post rescue treatment will be censored and imputed using the participant's worst possible.

3.2 Analysis Sets

3.2.1 Safety Analysis Set

Safety analysis set: all randomized participants who successfully received the study treatment (LYR-210 or control) on Day 1. Participants will be analyzed according to the treatment received. This is the primary analysis set for assessment of safety.

3.2.2 Intent-to-Treat (ITT) Analysis Set

ITT analysis set: all randomized participants who successfully received the study treatment (LYR-210 or control) on Day 1. This is the primary analysis set for assessment of efficacy. The primary analysis will be conducted for ITT Analysis Set without nasal polyp while the remaining efficacy analyses will be conducted for ITT Analysis Set. Participants will be analyzed according to the treatment they were assigned to at randomization.

3.2.3 Per-Protocol (PP) Analysis Set

PP analysis set: all randomized participants who successfully received the study treatment on Day 1, have specific post-Day 1 assessments, and are without any matrix dislodgement before Week 13 or important protocol deviations that might affect the accuracy and/or reliability of efficacy assessments.

3.2.4 Pharmacokinetic (PK) Analysis Set

PK analysis set: the approximately 30 randomized participants who successfully received the study treatment on Day 1 and have specific post-Day 1 PK assessments.

3.3 Subject Data and Study Conduct

Data will be listed by site and subject.

3.3.1 Subject Disposition

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

- Screened (only in the total column),
- Randomized (used as denominator when calculating the percentages for the following items),
- Successfully received the study treatment (LYR-210 or control) on Day 1,

- Completed the treatment phase,
- Early terminated the study treatment,
- Primary reasons for discontinuation of study treatment.

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

3.3.2 Protocol Deviations

Counts and percentages of subjects with CSR reportable protocol deviations by deviation category will be summarized by treatment and in total based on ITT Analysis Set.

3.3.3 Analysis Populations

Counts and percentages of subjects in each analysis set will be summarized by treatment and in total based on ITT Analysis Set. Reasons for exclusion from PP analysis Set will also be summarized.

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
- Region (North America vs Europe)
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2) and BMI categories (<30 kg/m^2, ≥30 kg/m^2)
- Randomized nasal polys status (with or without nasal polys)
- Actual nasal polys status (with or without nasal polys)

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by treatment and in total for ITT Analysis Set, ITT Analysis Set without nasal polyp, and Safety Analysis Set.

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 ITT Analysis Set and ITT Analysis Set without nasal polyp:

- 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 ITT Analysis Set and ITT Analysis Set without nasal polyp:

- 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 ITT Analysis Set and ITT Analysis Set without nasal polyp.

3.3.8 Concomitant Medications and Procedures

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHODrug Dictionary version B3 Global, Sep2021 (or later version). For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of study drug and concomitant medications if they were taken at any time after the first dose of study drug but no later than 31 days (>31 days) after discontinuation of study treatment. Medications that started prior to the first insertion of study treatment and continued while study treatment was given will be counted in both prior and concomitant medications. 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 3.1.8.1.

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

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 ITT Analysis Set and ITT Analysis Set without nasal polyp.

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-210 or sham) administration. Days of exposure to study drug will be summarized by treatment and in total for the ITT Analysis Set with descriptive statistics and with counts and percentages of subjects with exposure in the following categories:

- <4 weeks (1 - 28 days)
- 4 - <8 weeks (29 - 56 days)
- 8 - <12 weeks (57 - 84 days)
- 12 - <16 weeks (85 - 112 days)
- 16 - <18 weeks (113 - 126 days)
- 18 - <20 weeks (127 - 140 days)
- 20 - <22 weeks (141 - 154 days)
- 22 - <24 weeks (155 - 168 days)
- 24 - <26 weeks (169 – 182 days)
- ≥26 weeks (≥183 days)

Compliance to the study drug regimen will not be calculated.

The LYR-210 administration/Sham procedure will be summarized by treatment and in total for all randomized subjects for the following items:

- Pre-procedure endoscopy performed
- Topical anesthesia applied before endoscopy
- Topical decongestant sprays applied before endoscopy
- Pre-procedure endoscopy assessments
  - Septal Deviation
  - Nasal Polyps
  - Concha Bullosa
- Was bilateral insertion procedure successful

[redacted]

3.4 Efficacy Analysis

The data derivation is described in Section 3.1.4. This Section will focus on the analysis and output.

Hypothesis testing for all efficacy endpoints will be conducted on the ITT Analysis Set with 2-sided testing and present a 2-sided 95% CI. For subjects with nasal 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 summarized by treatment based on the ITT Analysis Set. The primary efficacy endpoint will also be summarized based on the PP Analysis Set.

Efficacy data will be listed by site and subject.

3.4.1 Primary Efficacy Endpoints

The primary objective is to evaluate the efficacy of LYR-210, compared with a sham procedure control, in improving the 3 cardinal symptoms of CRS in CRS participants without nasal polyps, who had previously failed medical management.

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

Treatment LYR-210 7500 µg drug matrix over a 20-week period or sham procedure, with daily saline nasal irrigation

Population adults with CRS who do not have nasal polyps at baseline, have failed medical management (including treatment with intranasal corticosteroid sprays [INCS]), and have not had endoscopic sinus surgery (ESS)

Variable CFBL in the 7-day average composite score of the 3 cardinal symptoms (3CS) of nasal blockage/obstruction/congestion, anterior/posterior nasal discharge, and facial pain/pressure at Week 24

Population-level summary the difference in the mean change from baseline at Week 24 in the 3CS score between LYR-210 and sham

Analysis model mixed model with repeated measures (MMRM) model will include the fixed, categorical effects of treatment, visit, treatment-by-visit interaction, and nasal polyp stratum as well as covariates of baseline score and baseline score-by-visit interaction.

Intercurrent events (ICE) and strategy the intercurrent events (ICEs) by category and the corresponding strategies for addressing these ICEs are listed in

If both Category 1 ICE and Category 2 ICE occur for the same subject, the Category 1 ICE takes precedence over Category 2 ICE. For example, if a subject took rescue medication at Week 10, and subsequently dropped out at Week 12 with no 3CS score at Week 24, then the method addressing Category 1 ICE will be used.

Table 5. ICEs by Category and Strategies for Addressing ICEs in the Primary Estimand

Category 1 ICE: SCS use or ESS between baseline and Week 24	**Category 2 ICE:** Decongestants use or INCS use or early termination of study treatment due to any reasons (e.g., spontaneous bilateral matrix dislodgement of LYR-210)	**Category 3 ICE:** Infection with COVID-19
Composite Variable Strategy: The 3CS score post SCS use or ESS will be censored and imputed with the participant's post-baseline worst observed score.	**Treatment Policy Strategy:** The 3CS scores reported by the participants will be used regardless of whether the ICE occurs.	**Hypothetical Strategy:** The 3CS score reported by the participants post the ICE will be censored as if the COVID-19 infection did not occur.

Sensitivity analyses for the primary endpoints with various supplementary estimands such as treatment policy strategy will be conducted as specified in Section 3.4.1.3 to assess the robustness of the primary analysis.

3.4.1.1 Primary Analysis Method

The primary analysis to test difference between LYR-210 and sham in the mean change from baseline in 3CS score at week 24 will be performed on the ITT Analysis Set without nasal polyp using a mixed model with repeated measures (MMRM).

The MMRM will use change from baseline as the dependent variable, and include the fixed, categorical effects of treatment, visit, treatment-by-visit interaction, and 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. The impact of this assumption will be evaluated by sensitivity analyses specified in Section 3.4.1.2.

Least-squares means (LS-means) for change from baseline at each analysis visit will be provided for each treatment group and the difference in LS means between LYR-210 and sham treatment at each analysis visit, corresponding standard error, two-sided 95% confidence intervals and two-tailed p-value will be estimated from the MMRM model.

Descriptive summary statistics on the values and changes from baseline will be presented for the 3CS 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 by the analysis visit. In addition, the by-visit least squares mean changes and the standard errors for each treatment will also be plotted by the analysis visit.

3.4.1.2 Sensitivity Analyses

- Sensitivity analysis 1: Multiple Imputation (MI) under Missing at Random

If there is missing data in the 3CS score, a multiple imputation model for missing observations will be constructed from the observed data under the MAR assumption. The imputation model will include nasal polyp stratum, baseline score, treatment group and post-baseline scores to impute the missing 3CS score with monotone regression method and MCMC method will be used to produce monotone missing pattern (by treatment). There will be 100 imputed datasets derived using SAS PROC MI based on the pre-specified model above with a given random seed (protocol date). The same MMRM model will be performed on each dataset after imputing the missing scores and PROC MIANALYZE will be used to combine the results.

- Sensitivity analysis 2: Tipping Point Analysis for Missing Not at Random (MNAR)

If there is missing data in the 3CS score, tipping point analysis will be used to impute missing value at 24 weeks as follows.

- Step 1. Monotone missing pattern was induced by Markov Chain Monte Carlo (MCMC) method using PROC MI: for patients who have intermediate missing values, the intermediate missing values will be imputed assuming a multivariate normal distribution over observations from all visits. 100 datasets with a monotone missing pattern will be obtained using this method with a given random seed (protocol date).
- Step 2. For each of the imputed dataset with monotone missing pattern obtained in Step 1, the remaining missing data will be imputed using the regression method for the monotone pattern with adjustment for covariates including response variable, treatment groups, nasal polyp status, and baseline value. All available data in the monotone missing pattern data will be used. One imputed dataset will be obtained for each of the imputed dataset at Step 1. So, 100 fully imputed datasets will be obtained altogether.
- Step 3. The imputed values in LYR-210 group are added by a positive amount d (by 0.5 from 0 to 9) for each imputed data sets.
- Step 4. The imputed values in sham group are subtracted by a positive amount p (by 0.5 from -9 to 0) for each imputed data sets.
- Step 5. Change from baseline in endpoint will be analyzed using ANCOVA model same as the one in primary analysis. Then the SAS MIANALYZE procedure will be used to generate statistical inferences by combining results from the 100 analyses using Rubin's formula.

Step 3 to Step 5 will be repeated iteratively until the p-value for treatment effect of LYR-210 compared to sham estimated in Step 5 is >0.05.

LS mean difference between LYR-210 and sham in change from baseline of 3CS score at Week 24 and the corresponding p-values will be provided for each combination of shift parameters.

3.4.1.3 Supplementary Analysis

- The same MMRM model defined in the primary analysis will be performed based on the Per-Protocol Population

Additional sensitivity analyses (supplementary estimands) will be conducted by the following alterations of the primary estimand regarding the handling of intercurrent event of SCS use or ESS while keeping the same strategy as the primary estimand for the other intercurrent events.

1) Supplementary 1: Treatment policy strategy for the use of SCS for any indication or ESS
2) Supplementary 2: Composite strategy of participant's worst post-baseline value for SCS for CRS indication and ESS; Treatment policy for SCS use for other indication.

3.4.2 Key Secondary Efficacy Endpoints

The estimand attributes for the following key secondary efficacy endpoints are defined in the same manner as for primary efficacy endpoint in Section 3.4.1:

1. CFBL in the 7-day average composite score of 3CS at Week 24 in all participants.

2. CFBL in the 22-item Sino-Nasal Outcome Test (SNOT-22) total score at Week 24 in all participants.

The same analysis methods used for the primary efficacy endpoint will be used for the above key secondary efficacy endpoints by including an additional term for polyp status as a stratum. The LS-means for change from baseline at each analysis visit will be provided for each treatment group and the difference between LYR-210 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. CFBL in the percent opacification of the bilateral anterior and posterior ethmoids at Week 20 as determined by 3-D volumetric CT analysis in all participants.

The above endpoints will be analyzed by ANCOVA with fixed-effect terms for treatment group and nasal polyp status. LS-means in each treatment group and their difference with 95% confidence interval (CI) and p-value will be provided.

4. Rescue treatment requirement through Week 24

Rescue treatment requirement through Week 24 will be summarized descriptively. Statistical comparisons between Lyra and Sham groups will be conducted on the pooled data with ENLIGHTEN 2 according to the integrated summary of efficacy SAP following the prespecified hierarchical testing method to adjust the multiplicity adjustment.

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

In addition, the point estimate and the two-sided 95% exact binomial confidence intervals (using the Clopper-Pearson method) will be presented for the proportion of subjects requiring rescue treatment through Week 24 will be tabulated by treatment group in the ISE.

3.4.3 Additional Secondary Efficacy Endpoints

The endpoints derivation and data handling are described in Section 3.1.4. The numbering of the following endpoints is consistent with Section 2.3.3.

- CFBL in the 22-item Sino-Nasal Outcome Test (SNOT-22) total score at Week 24 in participants without nasal polyps
- CFBL in 3CS score at Weeks 4, 8, 12, 16, and 20
- CFBL in the symptom score for individual cardinal symptoms of nasal blockage/obstruction/congestion, anterior/posterior nasal discharge, and facial pain/pressure at Weeks 4, 8, 12, 16, 20, and 24
- CFBL in loss of smell score at Weeks 4, 8, 12, 16, 20, and 24, for all participants and for participants with baseline score ≥2
- CFBL in SNOT-22 total score at Weeks 4, 8, 12, 16, and 20
- CFBL in SNOT-22 subdomain scores at Weeks 4, 8, 12, 16, 20, and 24

[redacted]

The endpoints above will be analyzed similarly to the primary efficacy endpoint but without the sensitivity analysis and supplemental analysis, and the data derivation and handling are described in Section 3.1.4. LS-means of the CFBL in each treatment group and their difference with 95% confidence interval (CI) and p-value will be provided.

- Improvement of ≥1 point, ≥2 points, and ≥3 points from baseline in 3CS score at Week 24
- Improvement of ≥8.9 and ≥12 from baseline in SNOT-22 total score at Week 24
- Sinonasal surgery requirement through Week 24
- Rescue medicine use through Week 24

- Improvement of ≥1 category and ≥2 categories in the severity of CRS-related symptoms as indicated by the Patient Global Impression of Severity (PGIS) at Week 24
- Overall change of "very much better" or "much better" in the CRS-related symptom severity as indicated by the Patient Global Impression of Change (PGIC) at Week 24

Participants who receive SCS for any reason and/or are indicated for sinonasal surgery will be considered non-responders for time points after SCS use or surgery. Unless otherwise specified in Section 3.1.4. participants with missing data will be included as non-responders. Comparison between LYR-210 group and the sham procedure group will be performed using logistic regression including nasal polyp status and baseline value. The general association p-value will be provided. The odds ratio and the corresponding CI will also be provided.

- CFBL in the percent opacification of the bilateral anterior and posterior ethmoids at Week 20 as determined by 3-D volumetric CT analysis in participants without nasal polyps
- CFBL in the Zinreich score of the bilateral anterior and posterior ethmoids at Week 20
- CFBL in 36-Item short form health survey, version 2 (SF-36v2) physical health, mental health, and domain scores at Week 24
- CFBL in Medical Outcomes Study Sleep Scale (MOS Sleep-R) score at Week 24

The above endpoints will be analyzed by ANCOVA with fixed-effect terms for treatment group and nasal polyp status, and with baseline score as a covariate. LS-means in each treatment group and their difference with 95% confidence interval (CI) and p-value will be provided.

- Time to first rescue treatment requirement through Week 24

Time to first rescue treatment requirement through Week 24 will be analyzed using the Kaplan-Meier (K-M) method. The K-M estimate of median time to first recommendation of rescue treatment requirement 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-210 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.

- Total SCS dose prescribed through Week 24
- Number of days on SCS through Week 24

The above endpoints will be analyzed by ANCOVA with fixed-effect terms for treatment group and nasal polyp status. LS-means in each treatment group and their difference with 95% confidence interval (CI) and p-value will be provided.

Counts and percentages of subjects taking SCS medications by ATC class and preferred term will be summarized.

- CFBL in EuroQoL 5-dimension, 5-level (EQ-5D-5L) score at Week 24

The EQ-5D-5L descriptive system will be summarized as categorical variables by presenting the frequency and proportion of each level for each dimension by visit and by treatment arm, and analyzed by the Cochran–Mantel–Haenszel (CMH) test controlling for nasal polyp status and baseline score.

The overall health score on a 100-point vertical (visual analogue scale: 0 = worst imaginable health state; 100 = best imaginable health state) will be summarized as continuous variable and analyzed by ANCOVA including fixed-effect terms for treatment group and nasal polyp, and with baseline score as a covariate. LS-means in each treatment group and their difference with 95% confidence interval (CI) and p-value will be provided.

- CFBL in Work Productivity and Activity Impairment-Specific Health Problem (WPAI-SHP), version 2.0 at Weeks 4, 12, and 24

The following will be summarized by visit and analyzed by ANCOVA including fixed-effect terms for treatment group and nasal polyp status, and baseline value as covariate. LS-means in each treatment group and their difference with 95% confidence interval (CI) and p-value will be provided.

- Percent work time missed due to CRS: Q2/(Q2+Q3) x 100%
- CRS affected productivity: Q5 x 10%
- CRS affected ability to do regular daily activities, other than work at a job: Q6 x 10%

[redacted]

3.4.5 Subgroups

The primary and key secondary efficacy endpoints will be summarized descriptively for the ITT Analysis Set based on the following subgroup factors:

- Nasal polyp status (with nasal polyp vs without nasal polyp)
- Age (<65, ≥65)
- Gender (male, female)
- Baseline BMI categories (<25, >=25-<30 kg/m^2, ≥30 kg/m^2)
- Race (Caucasian/White, Black/of African Descent, Others)
- Region (US vs EU)
- Ethnicity (Hispanic, non-Hispanic)

Formal subgroup analysis including the interaction by treatment group testing will be conducted in the ISE according to the prespecified ISE SAP.

Other subgroups may also be explored.

3.5 Pharmacokinetic Assessment

At Day 1 visit, the blood sample for plasma PK analysis will be collected before the LYR-210 administration/sham procedure. Subsequent blood samples (at Weeks 8. 16. 20, and 24) may be collected at any time of the day during the scheduled study visits. The concentration of MF in plasma will be measured at a central core lab.

A summary table will be used to present descriptive statistics (number, mean, SD, coefficient of variation, median, minimum, and maximum) of these PK parameters for the LYR-210 treatment group. Detail of the PK analysis (e.g., methods used in measuring the PK parameters, and how to handle below the limit of quantitation concentrations) will be documented separately.

3.6 Safety Analysis

Safety data will be summarized on the Safety Analysis Set.

3.6.1 Adverse Events (AEs)

An AE is any untoward medical occurrence (signs, symptoms, abnormal laboratory findings) in a participant regardless of relationship to the investigational product or procedure. Adverse events that occur prior to the insertion of the study treatment in the extension period will be included in this period summary.

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

Treatment emergent adverse events (TEAEs) are defined as AEs that start during or after the implantation procedure of study drug or sham procedure 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 study product related TEAEs (overall and by maximum severity)
- Any study procedure related TEAEs (overall and by maximum severity)
- Any serious AEs (SAEs)
- Any treatment-emergent serious AEs (TESAEs)
- Any TEAEs leading to discontinuation of study product
- Any TEAEs leading to discontinuation of study procedure
- 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 SAEs and TEAEs leading to discontinuation of study product.

Adverse events of Special Interests (AESI) and TEAEs leading to Discontinuation

Certain treatment emergent adverse events will be designated as AESI. These categories are:

- Ocular safety adverse events
    - Cataract: Preferred Terms of Cataract, cataract cortical, cataract subcapsular, cataract nuclear

- Increase in IOP: Preferred Terms of Intra ocular pressure increased, Ocular hypertension
- Glaucoma: Preferred Terms of Glaucoma, Open angle glaucoma, Angle closure glaucoma

- Nasal mucosal safety adverse events
  - Mucosal injury: Preferred Terms of Nasal mucosal disorder, Nasal mucosal erosion, Nasal septum ulceration, Nasal septum perforation, Nasal mucosal erythema, Nasal mucosal ulceration
  - Epistaxis: Preferred Term of Epistaxis.

The number and percentage of participants reporting each category of AESI will be summarized by each treatment group. Difference and odds ratio in proportion of participants between the treatment groups will be calculated with its 95% confidence intervals.

Additionally, the difference and odds ratio in proportion of participants between the treatment groups and its 95% CI for the percentage of subjects with TEAEs leading to discontinuation of study treatment will be calculated.

3.6.2 Clinical Laboratory Tests

Samples for hematology and blood chemistry assessments will be obtained during Screening and Week 24 visits, and processed by [redacted] the central laboratory. A list of laboratory tests to be performed is included in Appendix B.

Descriptive summary statistics for hematology and chemistry parameters at baseline and Week 24 will be presented. Descriptive statistics for change from baseline at Week 24 will also be presented.

3.6.3 Nasal Endoscopy

Nasal endoscopies will be performed to evaluate presence/absence of and grade of nasal polyps and to document presence of epistaxis, mucosal erosion or ulceration, perforation, and any other local adverse effects.

Counts and percentages of subjects will be provided at baseline, Week 8, Week 16, Week 20, and Week 24 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]

Counts and percentages of subjects with newly identified or worsened endoscopic findings will be presented at Week 8, Week 16, Week 20, Week 24 and in overall.

3.6.4 Vital Signs

Vital sign measurements will include seated blood pressure (systolic and diastolic, mm Hg), and pulse rate (beats per minute), body temperature (°C)) measured per local practice, and respiration rate (breaths per minute). All measurements will be obtained after the participant has been resting for at least 5 minutes.

Descriptive statistics for vital signs at baseline will be presented.

3.6.5 Ophthalmologic Assessments

Ophthalmologic assessments will include measurement of corrected VA, IOP and a slit-lamp examination of the anterior segment of the eyes to identify new or worsening cataract development. The cataract assessment will be conducted according to the Simplified Cataract Grading System authored by the World Health Organization Cataract Grading Group.[4] IOP may be measured using Goldmann applanation tonometer, non-contact tonometer, or tonopen; however, it is recommended that the same method be used for consistency across serial assessments on a given participant. A clinically significant increase of IOP is defined as IOP in 1 or both eyes >28 mm Hg or an increase of IOP from baseline in 1 or both eyes 10 mm Hg. Assessments will be conducted by an ophthalmologist/optometrist who is blinded to the participant treatment assignment.

The number and percentage of subjects with IOP in 1 or both eyes >23 mm Hg at post-baseline or an increase of IOP from baseline in 1 or both eyes ≥10 mm Hg will be presented at baseline, Week 8, Week 16, Week 24 and in overall. Descriptive summary statistics for IOP at baseline, Week 8, Week 16, and Week 24 will be presented. Descriptive statistics for change from baseline of IOP at Week 8, Week 16, and Week 24 will also be presented.

The number and percentage of subjects with newly identified or worsened cataract will be presented at baseline, Week 8, Week 16, Week 24 and in overall. Details of change from baseline at each post-baseline visits will also be presented (e.g. the number and percentage of subjects changed from grade 0 to 9 at Week 24).

4 ANALYSIS TIMING

4.1 Interim Analysis

There will be no planned interim analysis.

The efficacy analysis comparing Lyr-201 to sham results will be primarily from the first phase of the 24-weeks treatment period. This analysis will be conducted once as a final analysis therefore adjustment of type 1 error would not be necessary. There will be no additional statistical comparisons between Lyr-210 vs sham beyond week 24 timepoint. The efficacy data that are collected beyond week 24 will be descriptively summarized without a formal statistical comparison.

4.2 Final Analysis

Details on final analysis for the 52-week data will be prespecified in a separate SAP.

5 CHANGES FROM PROTOCOL

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

6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All data presented in subject data listings 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.

[4] WHO Cataract Grading Group. (2002). A Simplified Cataract Grading System. World Health Organization.

APPENDIX B: LABORATORY TESTS

Hematology:

- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count with percent and absolute differential counts (neutrophils, lymphocytes, eosinophils, monocytes, and basophils)

Chemistry:

- Albumin
- Alkaline phosphatase (AP)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Blood urea nitrogen (BUN)
- Bicarbonate
- Calcium
- Chloride
- Creatinine
- Glucose
- Lactate dehydrogenase (LDH)
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Total bilirubin
- Total protein
- Uric acid
- Human chorionic Gonadotropin (β-HCG, Pregnancy)

Appendix C

List of Changes in SAP Version 2.0 from Version 1.0

SAP Sections	Description	Rationale
3.4.1.1	Stratum Nasal Polyp is removed from the primary analysis model MMRM	Remove as the primary analysis population is the participants without nasal polyp.
3.4.3.1	Added sensitivity analysis with a treatment policy for ICE of SCS use and ESS	To incorporate treatment policy in consideration of FDA's feedback.
3.4.3.1	Added sensitivity analysis of composite strategy for ICE of SCS use and ESS for CRS indication and a treatment policy for SCS use for non-CRS indication.	To assess robustness of the primary estimand.
3.6.1	Added definition of treatment emergent AESI. Added summary measures for AESI and AEs leading to discontinuation, ie risk difference between the treatment groups and its 95% CI.	To incorporate FDA's feedback.