STATISTICAL ANALYSIS PLAN

LYR-210-2018-002

A Phase II, Randomized, Blinded, Sham Procedure-Controlled, Parallel-Group Trial to Evaluate the Efficacy, Safety and Tolerability of LYR-210 in Adult Subjects with Chronic Sinusitis (LANTERN Study)

AUTHOR: [redacted]

VERSION NUMBER AND DATE: V1.0, 06OCT2020

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan (SAP) v1.0 (dated 06OCT2020) for protocol LYR-210-2018-002.

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety and pharmacokinetics (PK) data for protocol LYR-210-2018-002. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. This statistical analysis plan (SAP) is based on protocol version 8.0 dated 30th of June 2020.

A separate SAP has been prepared for the Data Monitoring Committee (DMC) meetings.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is to evaluate the efficacy of LYR-210 in improving the composite score of 7-day average scores of 4 chronic sinusitis (CS) cardinal symptoms (CS7DA4S) at Week 4.

2.2. KEY SECONDARY OBJECTIVES

The key secondary objectives are:

- To evaluate the efficacy of LYR-210 in improving CS7DA4S score at end of treatment.
- To evaluate the effect of LYR-210 in reducing sinus inflammation as per magnetic resonance imaging (MRI).
- To evaluate the time-to-treatment failure.

2.3. OTHER SECONDARY OBJECTIVES

The other secondary objectives are:

- To evaluate the safety and tolerability of LYR-210.
- To evaluate the time-to-onset of action of LYR-210.
- To evaluate the efficacy of LYR-210 in improving CS7DA4S score and the 7-day average score of each of the 4 CS cardinal symptoms.
- To evaluate the effect of LYR-210 in improving CS disease-specific quality of life as per 22-item sino-nasal outcome test (SNOT-22) questionnaire.

- To evaluate the effect of LYR-210 in reducing sinus inflammation as per MRI.
- To evaluate the effect of LYR-210 in reducing subjects' needs for medical or surgical treatment for CS.
- To evaluate the PK of LYR-210.
- To evaluate the effect of LYR-210 in improving subjects' general quality of life as per 36-item short form health survey version 2 (SF-36v2) questionnaire.
- To evaluate LYR-210 in improving smell function assessed by the University of Pennsylvania Smell Identification Test (UPSIT™).

2.4. EXPLORATORY OBJECTIVES

The exploratory objectives are:

- To evaluate the percentage of subjects experiencing acute exacerbations of CS (AECS).
- To assess effect of LYR-210 in reducing polyp severity within middle meatus in subgroup of CS subjects with nasal polyps (CSwNP).
- To assess efficacy of LYR-210 in improving of the below scores in the subgroups of CS subjects without nasal polyps (CSsNP) and CSwNP subjects:
    - CS7DA4S score
    - The 7-day average score of each of 4 CS cardinal symptoms
    - The SNOT-22 total and subdomain scores
    - The SF-36v2 physical health, mental health, and domain scores
- To assess efficacy of LYR-210 in reducing sinus inflammation in CSsNP and CSwNP subjects.
- To assess effect of LYR-210 in improving smell function in CSsNP and CSwNP subjects.
- To assess the safety of subjects, post LYR-210 treatment.
- To assess the durability of efficacy post LYR-210 treatment.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

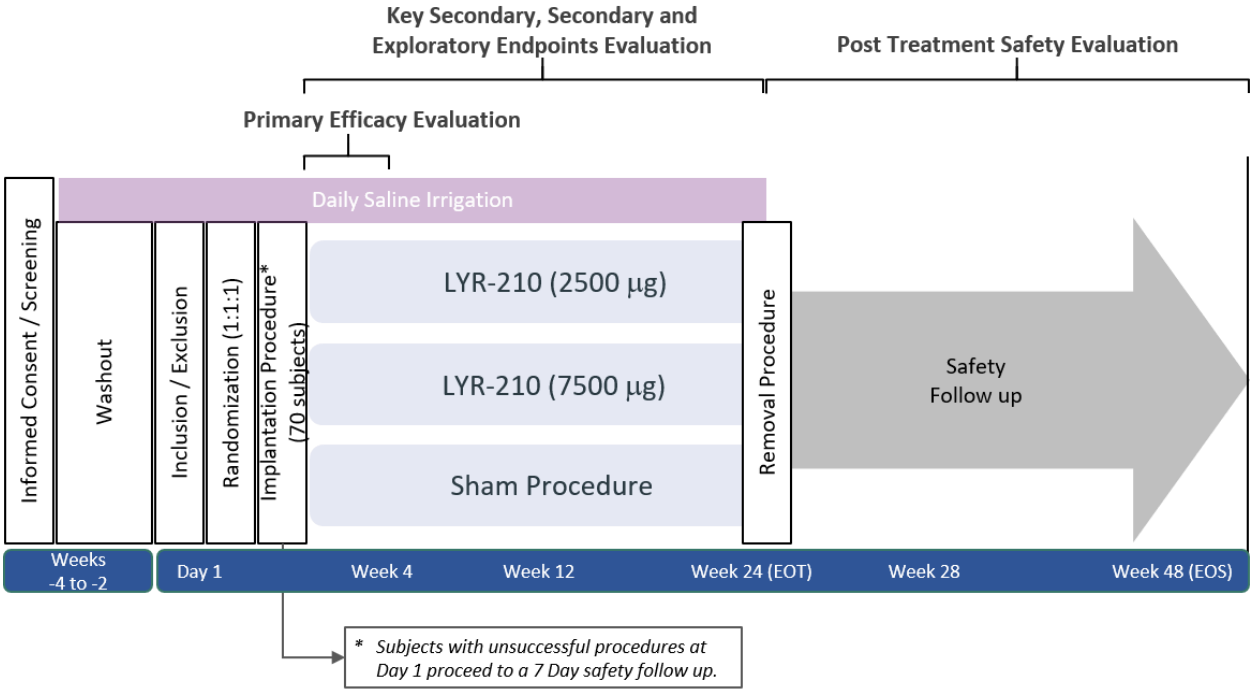
This global, multicenter study will be conducted in a randomized, Sham procedure-controlled, parallel-group, subject-blinded fashion in approximately 70 adult CS subjects who have failed previous medical management and have not undergone endoscopic sinus surgery (ESS). The efficacy and safety of LYR-210 (2500 μg) and LYR-210 (7500 μg) versus a Sham procedure only control will be assessed. Additionally, LYR-210 (2500 μg) and LYR-210 (7500 μg) will be compared to evaluate dose related responses.

The study will consist of three stages:

- Screening and washout stage: 2 to 4 weeks.
    - During washout, subjects will receive no active treatment for CS but will be recommended to start daily saline irrigation twice a day.
- Randomized and blinded treatment stage: 24 weeks.
    - Subjects who complete washout and meet all Day 1 eligibility criteria on Day 1 will be stratified according to presence or absence of: 1) nasal allergy (yes vs. no), 2) nasal polyps (yes vs. no).
    - Subjects will be randomized in a 1:1:1 ratio to receive LYR-210 (2500 μg) bilaterally, LYR-210 (7500 μg) bilaterally or Sham procedure bilaterally. Subjects who are assigned to the experimental arms will have the LYR-210 administered bilaterally on Day 1 into the middle meatus and then, removed at Week 24. Subjects who are assigned to the Sham procedure will undergo bilateral mock administration on Day 1 and then, undergo a Sham removal procedure to remain blinded.
    - If spontaneous dislodgement of LYR-210 occurs before Week 24 in subjects who receive either dose of LYR-210, subjects are required to call the study clinic immediately to report the event. If a subject experiences a dislodgement of one of the two LYR-210 depots, the subject will continue the study treatment unless an early treatment discontinuation is recommended by the treating physician or subject requests depot removal from the remaining side of the nose. If depots spontaneously dislodge from both sides of the nose, subject will complete Week 24/End of Treatment (EOT) assessments and subsequently, the post-treatment follow-up stage.
- Blinded post-treatment follow-up stage: 24 weeks.
    - After the Week 24/EOT visit, subjects will undergo post-treatment follow-up for approximately 24 weeks.
    - Except for depot dislodgement, subjects should remain blinded until the final study database is locked.

The overall flow diagram of subject enrolment and follow-up schedule is shown in Figure 1: Study Design Schematic below:

Figure 1: Study Design Schematic



3.2. SCHEDULE OF ASSESSMENTS

Schedule of assessments can be found in Section 8.1 of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

- The Study Design Schematic was presented in the protocol in Section 4.1. The protocol version 8 did not include the LYR-210 7500 µg treatment arm. An updated version that differs from the protocol is included in the SAP in Section 3.1.
- The endpoint regarding the reduction in subjects' need for specified concomitant medications and medical or surgical treatment for CS will not be analyzed as the data was not collected.
- Section 10.1 of the protocol defines the safety analysis set (SAF) as consisting of all randomized subjects who received the study treatment or treatment attempt on Day 1. For the purposes of the SAP, this has been re-

defined to remove the randomization criteria. It is possible a subject may receive treatment without being formally randomized. Hence the SAF should not contain the randomization restriction.

- Section 10.2 of the protocol states that subject disposition will be summarized for the Intention-to-Treat analysis set (ITT). For the SAP this has been updated to use the All Subjects Consented analysis set (CONS). The ITT for this study includes the condition that subjects will have a post-Day 1 assessment. It is recommended that disposition summaries include all subjects enrolled into the study. Restricting to the ITT will lead to an incomplete summary of subject disposition.

- Section 10.6.1.1 of the protocol describes the one missing value analysis approach as multiple imputation with treatment group as an independent variable in the multiple imputation model. This approach will be conservatively adjusted to apply control-based multiple imputation.

- Section 10.6.1.2 of the protocol describes the model to assess treatment effect across study regions but excludes the stratification variables. The model for the SAP includes the stratification variables. Per ICH E9 all statistical tests/models should be adjusted for any stratification variables.

- Section 10.6.1.2 of the protocol states that subgroup analysis will be performed to assess the treatment effect for the subgroups outlined in Section 7.6 of this SAP and the same model as the region analysis will be used. Due to the small sample size, for the purpose of the SAP one ANCOVA model will be fitted per subgroup to keep the model parsimonious.

- Section 10.6.3 of the protocol states that missing responses to questionnaires at a visit will be imputed using the median of non-missing responses at that visit. For SNOT-22 the literature on this scale indicates that missing responses should be imputed using the mean value of the responses if more than 50% of responses are complete at a visit. The SAP follows this approach and not the protocol defined approach (Hopkins, Gillett, Slack , Lund, & Browne, 2009).

- Section 10.6.4 of the protocol states that, for the generalized estimating equation (GEE) exploratory analysis, if the treatment-by-visit interaction is not significant at the 0.10 level of significance it will be removed from the GEE model. This SAP does not include this criterion, as this is not standard practice. The interaction term will remain in the model even if not significant.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Analyses for the DMC meetings.

- Primary data analysis.
- Final data analysis.

4.1. DMC MEETINGS

There were two planned timepoints for DMC meetings to review the safety and tolerability data:

- DMC 1: After the first 30 enrolled subjects completed the Week 4 visit or terminated early from the study, whichever occurs first.
- DMC 2: After all subjects completed the Week 4 visit or terminated early from the study, whichever occurs first.

These two DMC analyses have been described in a separate SAP which was authorized prior to each of the DMC analyses. Refer to the DMC SAP for further details.

4.2. PRIMARY DATA ANALYSIS

The trigger for the planned primary data analysis is when all subjects have completed the Week 28 visit (that is when all subjects have completed the last visit during the treatment stage at Week 24 or early terminated from the study or treatment, whichever occurs first, plus 4 weeks post-treatment follow-up). All planned analyses described in this SAP, except for analysis for visits after Week 28 (which will be analyzed as part of the Final Analysis, see Section 4.3), will be performed by [redacted] Biostatistics following:

- Sponsor authorization of this SAP.
- Sponsor authorization of the analysis sets as relevant (refer to Section 5 for details).
- The relevant data cut-off being reached and the database lock for primary data analysis (refer to the latest version of the Interim Database Lock Plan for specific details).
  - No data collected or protocol deviations recorded after the cut-off date will be included in the analysis.
- Study unblinding (refer to the latest version of the unblinding plan for specific details around blinding).
  - Project teams will be unblinded, subjects to remain blinded until end of study.

4.3. FINAL DATA ANALYSIS

The trigger for the planned final data analysis is when all subjects have completed the Week 48 visit or early

terminated from the study, whichever occurs first.

All planned analyses relevant to the final data analysis identified in this SAP will be performed by [redacted] Biostatistics following final database lock. The final analyses will include:

- Disposition
- Concomitant medications during the Post-Treatment period
- CS7DA4S score by Post-Treatment visit
- 7-day average score of each of 4 CS cardinal symptoms by Post-Treatment visit
- SNOT-22 by Post-Treatment visit
- SF-36 by Post-Treatment visit
- Adverse events (AEs) during the Post-Treatment period
- Vital Signs by Post-Treatment visit
- Physical examination by Post-Treatment visit
- Ophthalmology assessments by Post-Treatment visit

Analysis Sets will be defined as per the primary data analysis.

5. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to the unblinding of the study (Section 4.2).

5.1. PROCESS FOR ANALYSIS SET ASSIGNMENT

- Preliminary analysis set assignments to each of the analysis sets will be prepared and shared with the sponsor based on an "as clean as possible" data transfer from data management prior to the interim database lock for the primary data analysis.
    - An "as clean as possible" transfer refers to a data transfer where at most there can be limited list of known open queries on the data.
- This preliminary analysis set assignments will be used in the discussions and decisions during the blind data review.

- During the blind data review the impact of those open queries on the data should be assessed with regards to the influence it might have on the analysis set assignments.

- Based on the discussion and decisions made during the blind data review, the final "blinded" analysis set assignments for each analysis set (excluding the PK analysis set, refer to Section 5.7) will be prepared and authorized prior to the interim database lock.
  - "Blinded" analysis set assignment refers to the fact that there are a few reasons that might lead to exclusion from various analysis sets which cannot be assessed in a blinded manner. For example, randomized arm assignment differing to actual arm assignment is a major protocol deviation and will lead to exclusion from the per-protocol analysis set which can only be determined after lock.
  - The outcome of the blind data review will be documented in a Blind Data Review Report and an Excel file indicating the analysis set assignment for all subjects.
- Following primary analysis interim database lock and study unblinding, the various reasons leading to exclusion from analysis sets based on unblinded data will be assessed. The final analysis set assignments will be prepared and shared with the sponsor for final authorization and use in the primary and final data analyses.

5.2. ALL SUBJECTS CONSENTED ANALYSIS SET [CONS]

The all subjects consented (CONS) analysis set will include all subjects who provide informed consent for this study.

Subjects will be included in CONS based on the availability of a date of informed consent, as recorded on the Demography electronic case report form (eCRF).

5.3. ALL SUBJECTS RANDOMIZED ANALYSIS SET [RND]

The all subjects randomized (RND) analysis set will include all subjects in the CONS set who are randomized to study treatment regardless of whether the subject receives study treatment. For analyses and displays based on RND, subjects will be classified according to randomized treatment.

Subjects will be included in RND based on the availability of a randomization date, as recorded on the Randomization eCRF.

5.4. SAFETY ANALYSIS SET [SAF]

The safety (SAF) analysis set will contain all subjects who receive the study treatment (Sham procedure or a dose of

LYR-210) or have a treatment attempt on Day 1. Subjects will be analyzed according to the treatment actually received or attempted. This is the primary analysis set for safety analyses.

Subjects will be included in SAF based on the availability of a procedure date regardless of whether the bilateral insertion procedure was successful, as recorded on the Procedure eCRF page.

5.5. INTENTION-TO-TREAT ANALYSIS SET [ITT]

The Intention-To-Treat (ITT) analysis set will include all randomized subjects who receive the study treatment (Sham procedure or a dose of LYR-210) or have a treatment attempt on Day 1 and have post-Day 1 assessments available. This is the primary analysis set for assessment of efficacy. Subjects will be analyzed according to the treatment they were assigned to at randomization.

For post-Day 1 assessments availability, the following assessments will be considered: MRI (vendor data), UPSIT (UPSIT eCRF), endoscopy (Endoscopy eCRF), a single cardinal CS symptom (electronic patient reported outcomes [ePRO]), or the ePRO questionnaires of SNOT-22 or SF-36v2.

5.6. PER PROTOCOL ANALYSIS SET [PPAS]

The per-protocol analysis set (PPAS) will contain all randomized subjects who received the study treatment, have post-Day 1 assessments as specified in Section 5.5, and are without major protocol deviations at the time of the primary analysis. A major protocol deviation is defined as any protocol deviation potentially affecting the evaluation of the primary and key secondary efficacy endpoints. It is to be noted that a protocol deviation classified as major by the Biostatistical team (resulting in the exclusion of a subject from the PPAS) might be classified as critical, major or even minor by the Clinical team as the Clinical and Biostatistical teams are using different criteria. Please refer to the Protocol Deviations Management Plan for the criteria used by the Clinical team to classify each protocol deviation as critical, major or minor.

This analysis set will be used to perform supportive analysis for the primary, key secondary, and other secondary efficacy including CS7DA4S, 7-day average score of individual symptoms, SNOT-22, and MRI analyses. Major protocol deviations and other reasons for exclusion from the PP analysis set will be identified and finalized by [redacted] Biostatistics based on blinded review of the data, prior to the data extraction for the primary analysis and unblinding of the treatment code.

Major protocol deviations and other reasons for excluding subjects from the PPAS include:

- Insufficient essential efficacy data
    - The primary efficacy variable is the change from baseline (CFBL) in the CS7DA4S score at Week 4. The

CFBL for this score will be derived in the ePRO data at the Week 4 timepoint. The subject must have a non-missing CFBL value for CS7DA4S at Week 4.

- Non-eligibility with the protocol specified inclusion/exclusion criteria
  - The subject must have a composite score of CS7DA4S ≥ 7 at Day 1, as derived by [redacted] Biostatistics. A minimum of five daily entries are required for composite score calculation over the seven days leading up to and including Day 1 for assessing the subject's eligibility for participating in the study.
- Use of prohibited rescue medications prior to Week 4 visit, as identified in a regular Medical Data Review and recorded in the Clinical Trial Management System (CTMS) log for protocol deviations. Such medications include:
  - Oral antihistamine, excluding perennial allergic rhinitis patients who have been on a stable dose of antihistamine since screening
  - Nasal decongestants
  - Intranasal corticosteroid sprays
- Insufficient exposure to the study treatment
  - The subject must have been exposed to the treatment for at least 16 weeks. Exposure will be derived as described in Section 13.1.
- Actual and planned treatments are not the same
  - This will be identified at study unblinding, at the time of the primary analysis, by comparing the subject's allocated treatment arm to the kit type of the kit administered to the subject. The randomization data provided by the randomization vendor will be used.
- Pregnancy: Pregnant subjects are not allowed to participate in the study. Pregnancy results are recorded on the Urine Pregnancy Test, and Serum Pregnancy Test eCRFs.

5.7. PHARMACOKINETIC ANALYSIS SET [PK]

The PK analysis set (PKAS) will contain all subjects in the SAF set who received LYR-210 and have at least one evaluable plasma drug concentration data point post-Day 1 available. As concentration data are required to assign the PK analysis set, this can only be done at study unblinding, at the time of the primary analysis. Subjects will be analyzed according to the actual treatment successfully received.

Subjects who have used any Mometasone Furoate drugs within one day prior to a PK blood draw would be

identified by "MOMETASONE" in the Base Name of concomitant medications. These PK blood draw timepoints will be excluded from analysis. Similarly, results from PK blood draw timepoints after subjects reported any depot dislodgement will also not be analyzed.

5.8. ASSIGNMENT OF ACTUAL TREATMENT

If a subject receives a study treatment or treatment attempt that is different from their randomized treatment, then the assignment of the actual treatment will be as per the bilateral treatment received or attempted.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of LYR-210 administration/Sham procedure or treatment attempt. Study Day will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference start date, then:

$$Study\ Day = date\ of\ event - reference\ start\ date + 1$$

- If the date of the event is prior to the reference start date, then:

$$Study\ Day\ = date\ of\ event - reference\ start\ date$$

In the situation where the event date is partial or missing, the event date will appear partial or missing in the listings and any corresponding Study Day and durations will appear missing in the listings.

6.2. POST-TREATMENT DAY

The Post-Treatment Day will be calculated for data collected after the Week 24/EOT visit as follows:

$$Post\ Treatment\ Day = date\ of\ event - date\ of\ Week\ 24/EOT\ visit$$

6.3. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to LYR-210 administration/Sham procedure or treatment attempt (including screening and unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide (and time is not collected), that measurement will be considered baseline, but AE and medications commencing on the reference start date will be considered post-baseline.

The baseline CS7DA4S score is the average of the 7 days leading up to and including Day 1, that is Day -6 to Day 1 (refer to Section 15.1.1 for further details on the calculation of the CS7DA4S scores).

6.4. UNSCHEDULED VISITS, RETESTS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries if a nominal visit is performed in the same visit window but will contribute to the Last Observation Carried Forward (LOCF) value, and the worst-case value where required (e.g. overall post-baseline abnormal summaries).

In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early termination data.

6.5. DERIVED TIMEPOINT

An EOT timepoint will be derived and presented in the by-visit summaries. Data collected at the Week 24 visit or EOT visit will be pooled together under this EOT timepoint. This derived timepoint is for information purpose only and will not be included in any statistical models. That is, only descriptive statistics will be presented for this timepoint.

6.6. WINDOWING CONVENTIONS

All assessments (scheduled, unscheduled, and early termination visits), excluding daily diary data (refer to Section 6.6.1), will be windowed as per Table 1: Scheduled Visit Windows to ensure all assessments fall into a scheduled visit in order to ensure all data are presented.

If more than one assessment is mapped to the same analysis visit, the following rules for selection of the assessment to use in the analysis will be applied:

- If a nominal and an unscheduled/early termination assessment are mapped to the same analysis visit, the nominal assessment will be selected over the unscheduled/early termination assessment. However, if the nominal assessment result is missing and the unscheduled or early termination assessment result is non-missing, the unscheduled/early termination assessment will be selected.
- In all other scenarios the visit closest to the target day will be selected. If two assessments were performed equally close to an analysis visit's target day, one prior to and one after, the assessment before the analysis visit's target day will be assigned to that analysis visit (except for the follow-up MRI assessment which is scheduled to be performed within 7 days after the Week 24/EOT visit).

Table 1: Scheduled Visit Windows

Assigned Visit	Target Day	Visit Windowing	
		Lower Limit	Upper Limit
Screening		-28	-1
Baseline[a]	1	-28	1
Week 2[b]	15	2	22
Week 4[b]	29	23	43
Week 8[b]	57	44	71
Week 12[b]	85	72	99
Week 16[b]	113	100	127
Week 20[b]	141	128	155
Week 24[b]	169	156	183
4 weeks post-treatment[c]	28	14	42
8 weeks post-treatment[c]	56	43	70
12 weeks post-treatment[c]	84	71	98
16 weeks post-treatment[c]	112	99	126
20 weeks post-treatment[c]	140	127	154
24 weeks post-treatment[c]	168	155	182

[a] See Section 6.3, the planned timepoint for Baseline is Day 1.
[b] For Weeks 2 to 24, target day is calculated relative to the reference start date (refer to Section 6.1).
[c] For post-treatment visits, target day is calculated relative to end of treatment date (refer to Section 6.2).

6.6.1. Daily Diary Visit Assignment

The daily diary data do not associate assessments with visits. The date of assessment is collected and will be used to assign the ePRO data to specific visits as required for the definition of various endpoints. The CS7DA4S score is the average of the total daily scores for the 4 CS cardinal symptoms over the 7 days leading up to and including a visit (refer to Section 15.1.1).

The selection of the total daily scores to use to derive CS7DA4S and the 7-day average CS score for the 4 symptoms

for a respective visit is displayed in Table 2: Daily Diary Visit Assignment. For example, in order to derive the Week 2 CS7DA4S, the average of the 7 total daily scores for relative days 9 to 15 will be used.

Table 2: Daily Diary Visit Assignment

Assigned Visit	Target Day	CS7DA4S Range	
		Lower Limit	Upper Limit
Baseline[a]	1	-6	1
Week 1[b]	8	2	8
Week 2[b]	15	9	15
Week 3[b]	22	16	22
Week 4[b]	29	23	29
Week 8[b]	57	51	57
Week 12[b]	85	78	85
Week 16[b]	113	107	113
Week 20[b]	141	135	141
Week 24	169	163	169
4 weeks post-treatment[c]	28	21	28
8 weeks post-treatment[c]	56	49	56
12 weeks post-treatment[c]	84	77	84
16 weeks post-treatment[b]	112	105	112
20 weeks post-treatment[c]	140	133	140
24 weeks post-treatment[c]	168	161	168

[a] See Section 6.3, the planned timepoint for Baseline is Day 1.
[b] For Weeks 2 to 24, target day is calculated relative to the reference start date (refer to Section 6.1)
[c] For post-treatment visits, target day is calculated relative to end of treatment date (refer to Section 6.2).

6.7. COMMON CALCULATIONS

The following common calculations will be applicable:

- For quantitative measurements, change from baseline at visit X will be calculated as:

$$Change\ from\ baseline = result\ value\ at\ visit\ X - baseline\ value$$

- For quantitative measurements, percent change from baseline at visit X will be calculated as:

$$\%\ Change\ from\ baseline = 100\% \times \frac{result\ value\ at\ visit\ X - baseline\ value}{baseline\ value}$$

- The duration of the bilateral insertion/sham procedure in minutes will be calculated as the difference between the beginning time of the first study article preparation and the time of completion of the procedure, as captured on the LYR-210 Administration/Sham Procedure eCRF:

$$Duration\ of\ insertion\ or\ sham\ procedure\ in\ minutes = time\ of\ completion\ of\ procedure - beginning\ time\ of\ article\ preparation$$

- The duration of the depot/sham removal procedure in minutes will be calculated as the difference between the start and end times of the removal procedure, as captured on the End of Treatment eCRF:

$$Duration\ of\ removal\ procedure\ in\ minutes = end\ time\ of\ removal\ procedure - start\ time\ of\ procedure$$

7. STATISTICAL CONSIDERATIONS

7.1. SAMPLE SIZE

Per the null and alternative hypotheses described in Section 7.8 and under the assumption that μC = -1.30 and μL_{2500} and/or μL_{7500}=-3.00 (conservatively set, based on the mean of this endpoint for LYR-210 in Phase I study, and approximately 130% larger decrease than the assumed control mean of -1.30) and that the true standard deviation (SD) of the primary endpoint within each treatment group is at most 2.4, then an evaluable sample size of 63 subjects (21 per treatment group) yields 73% power to reject at least one null hypothesis in favor of the alternative at a one-sided 0.05 level of significance. An additional 6-9 subjects will be enrolled to account for potential subject dropout.

7.2. SUMMARY STATISTICS

For continuous data, descriptive statistics (i.e., n [number of subjects with available data], mean, SD, median, minimum, and maximum values) will be presented by treatment group and visit, when applicable.

For categorical data, the number and percentages of subjects in each category will be presented by treatment group and visit, when applicable.

7.3. MISSING DATA

Missing efficacy data for the primary and secondary endpoints will be handled as described in Sections 15.1.2 and 15.2.3, respectively. No missing data methods will apply for exploratory endpoints.

Missing safety data will not be imputed.

7.4. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following covariates and factors will be used in the primary and secondary analyses when an analysis of

covariance (ANCOVA) is performed. For details of their inclusion in the models please refer to Section 15.

- Covariates:
  - Baseline value of the concerned endpoint
- Factors:
  - Treatment group (fixed effect)
  - Randomization stratification variables
    - Nasal allergy (Yes/No)
    - Nasal polyps (Yes/No)

7.5. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally. Randomization to treatment arms is not stratified by country, region or center. Approximately 25 sites will participate in the study. Data from all centers will be pooled together in the analyses.

In order to assess the treatment effect across regions, descriptive statistics for the primary endpoint will be presented for each treatment for each region. Geographic region will be categorized as follows:

Geographic Region	**Identifier Code in Subject ID**
Australasia	Australia (036) and New Zealand (554)
Europe	Czech (203) and Poland (616)

In addition, an exploratory ANCOVA on the primary endpoint will include region and treatment-by-region interaction as factors (fixed effects). Please refer to Section 15.1.5 for more details. It is to be noted that should data be too sparse for at least one treatment group in at least one region (i.e. less than 5 ITT subjects for at least one treatment group in at least one region), only descriptive statistics by region will be provided.

7.6. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in the exploratory analysis sections to assess the consistency of treatment difference across the subgroups. It should be noted that the study was not designed to detect treatment differences with high statistical power within subgroups.

The following subgroups will be relevant to the exploratory analysis for this study:

- Nasal allergy:
  - Yes.
  - No.
- Nasal polyps:
  - Yes.
  - No.
- Baseline CS7DA4S:
  - Below median.
  - At or above median.
- Sex:
  - Male.
  - Female.
- Age:
  - Below median.
  - At or above median.
- Region:
  - See Section 7.5.
- Baseline Total Bilateral Zinreich Score as assessed by MRI:
  - Below median.
  - At or above median.

In the subgroups above, median is referencing the overall median for the ITT analysis set, regardless of the treatment group.

If data are too sparse for at least one treatment group in a subgroup (i.e. less than 5 ITT subjects for at least one

treatment group in a subgroup), only descriptive statistics by treatment group will be provided for that subgroup. That is, no statistical inferences will be performed for that subgroup.

7.7. STATISTICAL TESTS

The default significance level will be 5% and all tests will be one-sided, unless otherwise specified in the description of the analyses. Two-sided 90% CIs will be presented for all outputs were relevant.

7.8. MULTIPLE COMPARISONS/MULTIPLICITY

The primary objective of this study is to test the following null and alternative hypotheses:

$$H_0: \mu L_{2500} = \mu C \text{ vs. } H_1: \mu L_{2500} < \mu C$$

$$H_0: \mu L_{7500} = \mu C \text{ vs. } H_1: \mu L_{7500} < \mu C$$

where μL_{2500}, μL_{7500} and μC are the true mean values of the CFBL in the CS7DA4S score at Week 4 for the LYR-210 2500 µg, LYR-210 7500 µg, and control (Sham procedure) treatment groups, respectively.

Given the exploratory nature of the study, no adjustment to the overall alpha-level of the study will be made for multiple comparisons and multiplicity. That is, only nominal p-values will be provided for the primary efficacy endpoint, key secondary endpoints, non-key secondary endpoints, and exploratory efficacy endpoints.

7.9. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.

The table, figure and listing (TFL) shells provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by [redacted] Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

Subject disposition will be summarized for the CONS analysis set overall and by randomized treatment group. The number of patients screened, and screen failed will be presented. The number and percentage of subjects randomized into the study, treated and had a treatment attempt, who completed/discontinued early from the study treatment (including reasons for discontinuation) and who completed/discontinued early from the study (including reasons for discontinuation) will be presented.

Subjects' randomization details, end of treatment status, removal procedure and end of study status will be listed.

Analysis set assignment will be summarized for the CONS analysis set overall and by randomized treatment. The reasons for exclusion from each analysis set will be listed and summarized overall and by randomized treatment group.

9.1. PROTOCOL DEVIATIONS

All protocol deviations will be recorded in the CTMS log for the duration of the study. Deviations will be assessed and categorized as critical, major or minor. Site level IDs will be replicated for all subjects at that site and presented in the summary outputs as subject level deviations.

A table will be produced summarizing the type and severity of each protocol deviation overall and by randomized treatment group for the ITT analysis set. The summary will be presented on the number and percentage of subjects with each type and severity of deviation. All reported PDs will be listed.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be listed and summarized by treatment group for the ITT analysis set. No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and other baseline subject characteristics will be reported for this study:

- Age (years) – as reported on the Demography eCRF page
- Sex (Female/Male) and female childbearing potential
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islanders, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Region (Australasia, Europe)

- Height (cm)
- Weight (kg) at Baseline
- BMI (kg/m^2) at Baseline – refer to Section 10.1
- The baseline symptom scores for the 4 individual cardinal CS symptoms and total CS7DA4S
- Time since CS onset
- Characteristics of subjects' CS disease relevant medical history, as captured on the Chronic Sinusitis disease relevant medical history eCRF, including chronic sinusitis, asthma, perennial allergic rhinitis, seasonal allergic rhinitis, sensitivity to non-steroidal anti-inflammatory drugs (NSAID), chronic obstructive pulmonary disease (COPD) and smoking status.
- Characteristics of CS disease relevant surgical history
- Time since disease relevant surgery.

10.1. DERIVATIONS

- Time since onset of CS:

$$Time\ since\ CS\ onset\ (years) = \frac{date\ of\ informed\ consent - date\ of\ CS\ onset}{365.25}$$

- Time since disease relevant surgery will be calculated as:

$$Time\ since\ surgery\ (years) = \frac{date\ of\ informed\ consent - date\ of\ surgery}{365.25}$$

For all the above calculations if the start and/or end date is/are partial, only the available segment(s) of the date that appear in both dates will be used in the calculation. For example, if only the year of the start date is available, and the month and year of the end date are available, the calculation will only be between the start and end years. If only month level is used the calculation should be divided by 12 to obtain the duration in years. No division will occur if only year is available.

- BMI (kg/m^2) will be derived as follows:

$$BMI = \frac{Weight\ in\ kg}{(Height\ in\ m)^2}$$

11. SURGICAL AND MEDICAL HISTORY

CS disease relevant medical/surgical history will be listed and summarized for the ITT analysis set as per Section 10. All other Medical and Surgical History will be listed only for the SAF analysis set.

Medical and Surgical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later.

12. MEDICATIONS

Medications other than CS medical treatment history (see Section 10) will be coded World Health Organization Drug Dictionary (WHO-DD) version March 2020 or later. No Anatomical Therapeutic Class (ATC) coding will be performed for this study.

See APPENDIX 2 for handling of partial dates for medications. In the case where it is not possible to define a medication as prior, concomitant, or post-treatment, the medication will be classified by the worst case; i.e. concomitant.

- 'Prior' medications are medications which started and stopped prior to the bilateral insertion/Sham procedure or treatment attempt.
- 'Concomitant' medications are medications which:
    - started prior to the bilateral insertion/Sham procedure/treatment attempt AND were ongoing or ended after the bilateral insertion/Sham procedure/treatment attempt;
    - started on the day of the bilateral insertion/Sham procedure/treatment attempt;
    - started after the bilateral insertion/Sham procedure/treatment attempt but before or on the removal/Sham removal + 28 days.
- 'Post-treatment' medications are medications which started after the bilateral removal/Sham procedure + 28 days.

Prior, Concomitant and Post Medications will be listed by WHO drug name concatenated with base name for the SAF analysis set.

13. STUDY TREATMENT EXPOSURE

Descriptive statistics of exposure to study treatment in weeks will be presented for each treatment group in the ITT

analysis set.

The duration of exposure will be based on the difference of the date of successful bilateral insertion procedure taken from the LYR-210 Administration/Sham Procedure eCRF and the relevant event date. The event date is defined by whichever of the following events occurs first for a subject:

- Date of end of treatment (date collected on the End of Treatment eCRF) for subjects completing or early discontinuing treatment
- Depot dislodgement (date collected by the randomization vendor). If only one depot was dislodged, this will not be considered as an event. If both depots dislodged, but not simultaneously, the date of the second dislodgement will be considered as the event date.

Duration of exposure will not be calculated for subjects with an unsuccessful treatment attempt.

13.1. DERIVATIONS

Duration of exposure is calculated as below and will be rounded to 1 decimal place:

$$Duration\ of\ exposure\ (weeks)\ = \frac{date\ of\ event - date\ of\ insertion\ procedure + 1}{7}$$

14. SALINE IRRIGATION COMPLIANCE

Compliance to daily saline irrigation will be presented descriptively by treatment group for the ITT analysis sets as collected in the ePRO.

Compliance will be presented as a percentage of the days saline irrigation was done relative to the duration of the washout and treatment periods (days). The washout period information is collected on the Washout Period eCRF.

14.1. DERIVATIONS

Compliance is calculated as below and will be rounded to 1 decimal place:

$$Compliance\ per\ period\ (\%) = \frac{Number\ of\ days\ saline\ irrigation\ was\ completed\ during\ washout/treatment\ period}{Duration\ of\ washout/treatment\ period\ (days)} \times 100$$

- Duration of washout period is defined as:

$$Duration\ of\ washout\ period\ (days) = washout\ stop\ date - washout\ start\ date + 1$$

- Duration of treatment period is the same as the duration of exposure as noted in Section 13.1 but will be converted from weeks to days (multiply by 7).

15. EFFICACY OUTCOMES

15.1. PRIMARY EFFICACY

15.1.1. PRIMARY EFFICACY ENDPOINT AND DERIVATION

The primary efficacy endpoint is CFBL in CS7DA4S score at Week 4. The 4 CS cardinal symptoms are:

- nasal blockage/obstruction/congestion
- facial pain/pressure
- reduction/loss of sense of smell
- anterior/posterior nasal discharge.

Each symptom is scored on a 4-point scale and is collected on ePRO:

- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe

The CS7DA4S score is calculated as:

- Add together the four individual symptom scores per day as recorded by the subject to derive the total daily score
  - Total daily scores will only be calculated in cases where all four individual symptom scores are available
- Calculate the average of the total daily scores across the 7 days leading up to and including this visit. This is the CS7DA4S score at the relevant visit
  - Subject is considered to have sufficient data available to calculate the CS7DA4S score at any given

timepoint if the total daily score is available for at least 5 of the total 7 days

- CS7DA4S scores will be rounded to 1 decimal place

The change from baseline in CS7DA4S at Week 4 will be calculated as detailed in Section 6.7.

15.1.2. Missing Data Imputation Methods for Primary Efficacy Endpoint

The primary analysis will not include any missing data imputation methods. The primary analysis of the primary efficacy endpoint will include subjects in the ITT analysis set with available CS7DA4S data at Baseline and Week 4 visit.

15.1.3. Primary Analysis of Primary Efficacy Endpoint

The CFBL for CS7DA4S at Week 4 will be analyzed using the ITT analysis set. The following analysis will be performed for the CFBL CS7DA4S score at Week 4:

- Summary statistics for the Baseline CS7DA4S score, the Week 4 CS7DA4S score and the CFBL at Week 4
- An ANCOVA model for CFBL at Week 4. The ANCOVA model will include the baseline CSD7A4S score as a covariate, treatment group and the randomization stratification variables (nasal allergy, nasal polyps) as fixed effects.

Each hypothesis as described in Section 7.8 will be tested at a one sided 0.05 alpha level of significance by the ANCOVA model. The LS means and SE of each treatment group, the LS mean difference of each LYR-210 procedure against the Sham procedure and their SEs, 90% CIs, and p-values estimated by the model will also be provided.

15.1.4. Sensitivity Analysis of Primary Efficacy Endpoint

The following sensitivity analyses to the primary analysis of the primary endpoint will be performed:

Sensitivity to the analysis set

The primary analysis of the primary efficacy endpoint will be repeated for the PPAS.

Sensitivity analyses to missing data

- LOCF single imputation method:
  - The CS7DA4S will be calculated as described in Section 15.1.1 for baseline, Week 1, Week 2, Week 3

and Week 4

- If Week 4 CS7DA4S score is missing, then the last available post baseline CS7DA4S prior to Week 4 will be carried forward and will be used as the Week 4 CS7DA4S score and the same analysis as for the primary analysis of the primary efficacy endpoint will be repeated (refer to Section 15.1.3).

- Multiple imputation will be implemented using 3 steps:

  - First, intermittent missing CS7DA4S data will be imputed under the missing at random (MAR) assumption using a multivariate joint Gaussian imputation model and the Monte Carlo Markov Chain (MCMC) method. A separate imputation model will be estimated for each treatment group separately. The imputation models will include the baseline CS7DA4S values as a covariate and the stratification variables and weekly CS7DA4S (Weeks 1 to 4) as factors. The MAR mechanism assumed that subjects have unobserved values in line with similar subjects with available data in their treatment group, taking into account their values observed prior to the weeks with missing data. The MAR assumption is reasonable for the Sham patients as it accounts for the trial effect while no active treatment is taken. It is also a reasonable assumption for the LYR-210 subjects as subjects will remain on randomized treatment while intermittent missing data may occur and thus, may be modeled based on similar subjects from their randomized treatment group. The MCMC method will be used with a random seed number of 2575, multiple chains, a burn-in of 200 iterations, and non-informative prior. During this step, 50 imputed datasets will be created.

  - Second, for each of these 50 imputed datasets, monotone missing weekly CS7DA4S data will be imputed using sequential linear regression multiple imputation approach also using a MAR approach, where a separate regression model will be estimated for imputation of each post-baseline timepoint (i.e., Weeks 1, 2, 3, and 4). Each regression model will include the treatment group, region, the two stratification variables, and all previous weekly CS7DA4S scores (Baseline and Weeks 1 to Week 4), as appropriate. In other words, to impute Week 1, the model will include the treatment group, region, the two stratification variables and baseline CS7DA4S scores. Similarly, to impute Week 2, the model will include the treatment group, region, the two stratification variables, baseline CS7DA4S scores, and CS7DA4S scores at Week 1 (observed and imputed values). Missing CS7DA4S scores at Weeks 3 and 4 will be similarly imputed, one after the other. The random seed number for this step will be 210. No rounding or range restrictions will be applied to imputed weekly average values.

  - Finally, each of the 50 imputed datasets will be analyzed using the following method: change from baseline in CS7DA4S score at Week 4 will be calculated based on the observed and imputed data and analyzed using the ANCOVA model as described in Section 15.1.3. For each LYR-210 dose group, results from the analysis of each imputed dataset i.e., LS mean differences between treatment groups and their SEs, will be combined using PROC MIANALYZE in SAS as per Rubin's rule (Rubin, 1987) to produce a

pooled estimate of the LS mean difference between treatment groups and a pooled estimate of its SE. From these pooled estimates, one t-test statistic and its p-value, assessing whether the null hypotheses in Section 7.8 can be rejected, will be calculated and presented for each LYR-210 dose vs. Sham.

15.1.5. Supportive Analysis of Primary Efficacy Endpoint

Supportive analyses to the primary analysis of the primary efficacy endpoint will be performed using the ANCOVA model specified in Section 15.1.3 for the following:

15.1.5.1. Assessment of Consistency of Treatment Effect Across Region

To assess the consistency of treatment difference across region, descriptive statistics of the primary endpoint will be presented by treatment group within each region. The primary analysis of the primary efficacy endpoint will be repeated but will also include the region and treatment-by-region interaction as fixed effect. Should this interaction be statistically significant at the 0.15 level of significance, LS means and SE of each treatment group by region will be provided as well as the LS mean difference of each LYR-210 procedure against the Sham procedure and their SEs, 90% CIs, and p-values by region.

It is to be noted that should data be too sparse for at least one treatment group in at least one region (i.e., less than 5 ITT subjects for at least one treatment group in at least one region), only description statistics by region will be provided.

15.1.5.2. Assessment of Treatment Effect Across Subgroups Described in Section 7.6

To assess the consistency of treatment difference across subgroups, descriptive statistics of the primary endpoint will be presented by treatment group within each subgroup. An exploratory analysis of covariance on the CFBL of CS7DA4S score at Week 4 will be carried out on the ITT analysis set for subjects with available data. The ANCOVA model will include the baseline CS7DA4S score as a covariate, the stratification variables, and treatment group as a fixed effect and will be repeated for each subgroup of interest.

If data is too sparse for at least one treatment group in at least one subgroup (i.e., less than 5 ITT subjects for at least one treatment group in at least one subgroup), only descriptive statistics by subgroup will be provided.

15.2. Secondary Efficacy

15.2.1. Key Secondary Efficacy Endpoints and Derivation

15.2.1.1. CFBL in CS7DA4S at Week 24

CFBL at Week 24 will be derived as described in Section 15.1.1.

15.2.1.2. Proportion of Subjects with at Least 1-point Decrease in Bilateral Zinreich Score in at Least One Pair of Anterior Ethmoid, Maxillary, Posterior Ethmoid, Frontal or Sphenoid Sinuses at Week 24

Sinus inflammation will be assessed by MRI at time points specified in the schedule of events in Section 8.1 of the protocol. The sinus inflammation will be assessed using the Zinreich modified Lund-Mackay scoring system (Likness, et al., 2014). The Zinreich score for each sinus will be assessed by Medical Metrics, Inc. (MMI) and all analysis will use the data collected by MMI. Six areas of each sinus (left and right) will be assessed:

- Anterior ethmoid
- Maxillary
- Posterior Ethmoid
- Frontal
- Sphenoid
- Ostiomeatal Complex (OMC)

Each area will be assigned a score based on the percentage of opacification as follows:

- 0=0%
- 1=1%-25%
- 2=26%-50%
- 3=51% to 75%
- 4=76% to 99%
- 5=100% or completely occluded

The OMC is given a score of 0 to 2 as follows:

- 0=completely patent
- 1=partially occluded
- 2=completely occluded

The bilateral Zinreich score for each area will be derived by [redacted] Biostatistics by adding the score for both sinuses together. The range of the score will be 0-10 except for OMC which will have a range of 0-4. The bilateral Zinreich score for each area will only be calculated if both sinus scores are non-missing. The total bilateral score

will be the sum of all 6 areas and will have a range of 0-54. The total bilateral score will only be calculated when all bilateral scores for each of the 6 areas are present. The baseline bilateral Zinreich score for each area and baseline total score will be the value recorded at screening. The individual and total Zinreich scores for all areas at all visits will be summarized and listed.

The key secondary endpoint will be the proportion of subjects with at least 1-point decrease from baseline in the Zinreich score in at least 1 pair of the anterior ethmoid, maxillary, posterior ethmoid, frontal or sphenoid sinuses at Week 24.

15.2.1.3. Time-to-Treatment Failure

Time-to-treatment failure, in days, will be derived as:

$$Time\ (days) = date\ of\ treatment\ failure - treatment\ start\ date + 1$$

Where treatment failure is defined as:

- after subject enrollment, the subject being recommended by treating physician for oral corticosteroid or ESS due to worsening of CS symptoms as collected on the Follow-up eCRF

OR

- the subject complaining of persistent CS symptoms, i.e., has an average CS7DA4S score over the preceding 30 days greater than or equal to the baseline CS7DA4S score as defined by [redacted] Biostatistics.
    - The earliest timepoint at which to calculate this score is Day 31. For each day post-Day 30, the average CS7DA4S over the preceding 30 days will be derived and compared to the baseline CS7DA4S score
    - The average CS7DA4S for at least 21 of the preceding 30 days should be available for this derivation.

Subjects without the event will be censored at their follow-up period. That is, should a subject reach Week 24 without having met the criteria for the time-to-treatment failure, the subject will be censored at the date of the Week 24 visit; should a subject discontinue early from the study before Week 24 without having met the criteria for the time-to-treatment failure, the subject will be censored at the date of discontinuation from study.

Time-to-treatment failure will be derived at different timepoints: Weeks 2 (15 days), 4 (29 days), 8 (57 days), 12 (85 days), 16 (113 days), 20 (141 days) and 24 (169 days). These timepoints are independent of the scheduled visits.

15.2.2. Other Secondary Efficacy Endpoints and Derivations

15.2.2.1. Time-to-Onset of Action

Onset of action is defined as, within the first 30 days of treatment, the time when all subsequent mean CFBL in the

CS7DA4S score of the LYR-210 is statistically significantly greater than that for the Sham procedure.

For this endpoint, the CS7DA4S will be calculated daily from Days 8 to 30. That is, the CS7DA4S at Day 8 will be the average of the total daily scores for the 4 CS cardinal symptoms over Days 2 to 8, the CS7DA4S at Day 9 will be the average of the total daily scores for the 4 CS cardinal symptoms over Days 3 to 9, and so on up to Day 30 which will be the average of the total daily scores for the 4 CS cardinal symptoms over Days 24 to 30.

Then, the CFBL to each of these daily CS7DA4S values will be calculated.

15.2.2.2. CFBL in CS7DA4S and 7-day Average Score of Individual Symptoms at Additional Timepoints

CFBL in CS7DA4S will be derived for Weeks 8, 12, 16 and 20 as per Section 6.7.

In addition, the 7-average score of each individual symptom will be calculated at each visit only if at least 5 of the previous 7 days have available scores. Then, the CFBL in the 7-day average score of each individual cardinal CS symptom score will be calculated for Weeks 1, 2, 3, 4, 8, 12, 16, 20 and 24 as per Section 6.7.

15.2.2.3. 22-Item Sino-Nasal Outcome Test (SNOT-22) Questionnaire

SNOT-22 questionnaire data will be collected in ePRO. Subjects score the severity of their symptoms and social/emotional consequences of CS over the past two weeks on a 6-point scale:

- 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 scores are summed within each domain as per Table 3: Categorized Survey Items for Separate Domains of the SNOT-22 Instrument (DeConde, Bodner, Mace, & Smith, 2014), where higher scores indicate a higher severity of symptoms or social/emotional consequences of CS. For each domain, if less than 50% of the domain items are missing at a visit for a subject, the missing items will be imputed with the mean of subject's non-missing items at that visit prior to the domain score calculation. Otherwise if 50% or more of a domain items are missing at a visit for a subject, the subject's domain score will be set to missing at that visit.

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

The total SNOT-22 score will also be calculated as the sum of all 22 questions and will have a range of 0-110. For the total score, if less than 50% of the items are missing at a visit for a subject, the missing items will be imputed with the mean of the subject's non-missing items at that visit prior to the total score calculation. Otherwise if 50% or more of the questionnaire items are missing at a visit for a subject, the total score will be set to missing at that visit for that subject.

CFBL in the total and subdomain SNOT-22 scores will be derived for Weeks 2, 4, 8, 12, 16, 20 and 24 as per Section 6.7. If a subject's CFBL in total SNOT-22 score is greater than 8.9 (i.e. the score decreased by more than 8.9), the subject is considered to have achieved a minimally important clinical difference.

15.2.2.4. Change from Baseline in Bilateral Zinreich Anterior Ethmoid, Maxillary, Posterior Ethmoid, Frontal, Sphenoid and OMC Sinus Scores, and Total Score at Week 24

The bilateral Zinreich anterior ethmoid, maxillary, posterior ethmoid, frontal, and sphenoid scores at Week 24 will be calculated as defined in Section 15.2.1.2. The bilateral Zinreich OMC and total Zinreich scores will also be calculated as defined in Section 15.2.1.2.

Then, the CFBL in each of these endpoints will be calculated at Week 24 as per Section 6.7.

15.2.2.5. 36-Item Short Form Health Survey Version 2 (SF-36v2) Questionnaire

The SF-36v2 questionnaire is a multi-purpose, short-form health survey with 36 questions/items. It yields 8 functional health and well-being domains as well as 2 psychometrically-based physical and mental overall component summary measures, where lower scores imply higher disability (i.e., a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability).

The 8 domains of the SF-36 are (refer to Table 4: SF-36v2® Health Survey Measurement Model):

- Physical Functioning (PF)
- Role-Physical (RP)
- Bodily Pain (BP)
- General Health (GH)

- Vitality (VT)
- Social Functioning (SF)
- Role-Emotional (RE)
- Mental Health (MH)

The two overall component summary measures are (refer to Table 4: SF-36v2® Health Survey Measurement Model):

- Physical Component Summary (PCS)
- Mental Component Summary (MCS)

Table 4: SF-36v2® Health Survey Measurement Model

SF-36v2 Components and Domains	Survey Items
Physical Component Summary (PCS)	
Physical Functioning (PF)	#3a, #3b, #3c, #3d, #3e, #3f, #3g, #3h, #3i, #3j
Role -Physical (RP)	#4a, #4b, #4c, #4d
Bodily Pain (BP)	#7, #8
General Health (GH)	#1, #11a, #11b, #11c, #11d
Mental Component Summary (MCS)	
Vitality (VT)	#9a, #9e, #9g, #9i
Social Functioning (SF)	#6, #10
Role-Emotional (RE)	#5a, #5b, #5c
Mental Health (MH)	#9b, #9c, #9d, #9f, #9h

There is also a single item (item #2) that assesses health transition, which is not included in the scoring of the scales and overall component summary measures. Scoring will be performed with the Optum™ software as follows:

- First, 10 items are reverse-coded (Questions #1, #6, #7, #8, #9a, #9d, #9e, #9h, #11b and #11d) to ensure that across all questions, a higher score will indicate a better health state. An algorithm for an algebraic summation of the item scores is applied to produce domain-specific raw scale scores that account for missing item responses i.e., when calculating the raw domain scores, if at least half the item scores for a domain are non-missing, the missing item scores are replaced by the average of the non-missing item scores for the domain before applying the algorithm for an algebraic summation. Otherwise if 50% or more of the item scores for a domain are missing, the raw domain score is set to missing.

- Domain-specific raw scale scores are then transformed to a 0 to 100 range, after which a norm-based (T-score) transformation is applied so that each scale ranges from 0 to 100, with a mean of 50 and a standard

deviation of 10. The norm-based transformation is applied so that domain-specific scale scores can be meaningfully compared between each other.

The PCS and MCS are computed by aggregating domain scores using factor score coefficients. The aggregated component summary scores are also standardized to have a mean of 50 with a standard deviation of 10.

The Eight domain scores and the two summary scores will be calculated using software provided by the publisher, Optum™. The CFBL in the 8 domains and 2 overall component summary measures will be calculated at each visit as per Section 6.7.

15.2.2.6. University of Pennsylvania Smell Identification Test (UPSIT™)

The UPSIT™ is composed of 40 odorants embedded on scent strips that are released when scratched with a sharply tipped object (Doty, Shaman, & Dann, 1984). The UPSIT™ is comprised of 4 booklets, each containing 10 microencapsulated (scratch & sniff) odours. The UPSIT™ is a forced-choice test, and subjects will be instructed to identify each odorant with alternatives accompanying each test item. The total olfaction score using the UPSIT™ is defined as the number of odorants correctly identified out of the 40 odours tested, with higher scores designating better olfactory performance.

The total olfaction score will be collected on the UPSIT eCRF page. The change from baseline in UPSIT™ total score will be calculated at each post-baseline visit as per Section 6.7.

15.2.3. Missing Data Imputation Methods for Secondary Efficacy Endpoints

15.2.3.1. Missing Data Imputation Methods for Key Secondary Efficacy Endpoints

For the primary analysis of the CFBL in CS7DA4S score at Week 24 key secondary efficacy endpoint, LOCF and multiple imputation will also be used to impute missing data for sensitivity analyses (refer to Section 15.1.4).

For bilateral Zinreich score and time-to-treatment failure, no imputation for missing data will be performed.

15.2.3.2. Missing Data Imputation Methods for Other Secondary Efficacy Endpoints

The primary analysis of the other secondary efficacy endpoints will be performed based on the observed-case. That is, no missing data will be imputed.

Additionally, LOCF will be used to impute missing data of endpoints based on CS7DA4S and SNOT-22 for sensitivity analyses. Multiple imputation will also be performed for endpoints based on CS7DA4A as sensitivity analysis, but not for the endpoints based on SNOT-22. No sensitivity analyses to the missing data imputation method will be performed for any other non-key secondary efficacy endpoint.

15.2.4. Analysis of Key and Other Secondary Efficacy Endpoints

15.2.4.1. Analysis of CFBL in CS7DA4S Individual and Total Scores at Weeks 8, 12, 16, 20 and 24

The analysis of the CFBL in CS7DAS total score will be conducted using an ANCOVA model as per Section 15.1.3. Week 24 is considered a key secondary endpoint, while Weeks 8, 12, 16, and 20 are considered as non-key secondary endpoints and all other visits as exploratory endpoints.

Additionally, the 7-day average score of nasal blockage/obstruction/congestion, reduction/loss of sense of smell, facial pain/pressure and anterior/posterior nasal discharge at Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24 will be analyzed as per Section 15.1.3.

This analysis will be repeated for the ITT and PP analysis sets.

The same three sensitivity and supportive subgroup analyses as for the primary endpoint as detailed in Sections 15.1.4 and 15.1.5.2 will be repeated for the CS7DA4S total scores at all Weeks. Furthermore, the analysis of the CS7DA4S total score at all Weeks by CSsNP and CSwNP subgroups will be repeated with missing data imputed as per Section 15.1.2.

For all other endpoints, the sensitivity analyses based on the PP analysis set and based on the ITT analysis set but with missing data imputed based on LOCF will be performed. That is, no sensitivity analysis based on the ITT analysis set with missing data imputed based on the multiple imputation method will be performed for the other secondary efficacy endpoints.

Additionally, a plot of the LS means and SE for CFBL for CS7DA4S total and individual symptom scores at each timepoint up to Week 24 and Week 48 will be provided for the primary and final data analysis, respectively.

15.2.4.2. Analysis of Zinreich Score

The number and percentage of subjects at Week 24 in the ITT analysis set with and without at least a 1-point decrease in one of the six bilateral Zinreich sinuses score as defined in Section 15.2.1.2 will be provided by treatment group.

A logistic regression adjusting for the baseline total bilateral Zinreich score and stratification variables (nasal allergy and nasal polyps) will be used to compare treatment groups. The responder indicator will be set to 1 for subjects who achieve at least a 1-point decrease in any score at Week 24 compared to baseline. Subjects for whom the decrease cannot be calculated, for example due to early termination, will be excluded from the analysis.

Odds ratios together with the 90% CI will be presented to compare treatment groups. This analysis will be repeated for the PP analysis set.

As non-key secondary analyses, the CFBL in each of the 5 bilateral Zinreich sinuses score, Zinreich OMC score and total Zinreich score at Week 24 will be analyzed using an ANCOVA model as specified in Section 15.1.3 replacing the baseline CS7DA4S with the appropriate baseline bilateral Zinreich sinuses score, Zinreich OMC score or baseline Zinreich total score. This analysis will be repeated for the PP analysis set.

Additionally, the logistic regression and ANCOVA models will be repeated on the subgroups as per baseline median total bilateral Zinreich score, for the ITT analysis set.

15.2.4.3. Analysis of Time-to-Treatment Failure

The number and percentage of subjects with and without treatment failure will be presented based on the ITT analysis set. For subjects without treatment failure, the censoring reason will be summarized. Time-to-treatment failure (days) will be analyzed for the ITT analysis set using a Cox proportional hazards model with fixed effects for baseline CS7DA4S score, treatment group and the stratification variables (nasal allergy and nasal polyps). The Hazard ratio of each LYR-210 treatment group vs. the Sham treatment group, its 90% CI and p-values will be presented.

Additionally, Kaplan-Meier results will be displayed for the 25%, 50% and 75% quartiles, along with Kaplan-Meier estimates of probability of treatment failure at different timepoints: Weeks 2, 4, 8, 12, 16, 20 and 24. These timepoints are independent of the scheduled visits. Kaplan-Meier plots of time-to-treatment failure will be produced for each treatment group.

15.2.4.4. Analysis of Time-to-Onset of Action

Each daily CFBL in CS7DA4S values will be summarized and analyzed as the primary efficacy endpoint (see to Section 15.1.3).

The daily LS mean CFBL (+/- SE) in CS7DA4S up to Day 30 will be presented graphically for each treatment group in the ITT analysis set with an indicator as to when the LYR-210 treatment groups are statistically significantly greater than the Sham group.

For each LYR-210 group, the time-to-onset action will be the earliest day at which statistical significance is reached in comparison with the Sham group, when statistical significance is also reached for all subsequent visits. For example, if Days 10, 13, 14 and all subsequent days reached statistical significance for a LYR-210 group against the Sham group, time-to-onset of action will be Day 13 even if statistical significance was reached at Day 10 because statistical significance was not reached at Days 11 and 12.

15.2.4.5. Analysis of SNOT-22 and SF-36v2 Domain and Total Scores

For each post-Day 1 visit, the questionnaires will be compared between treatments using an ANCOVA model as described for the primary endpoint in Section 15.1.3 for the ITT analysis set. The CS7DA4S baseline score in

Section 15.1.3 will be replaced by the baseline score for the domain/total score of interest in the ANCOVA model. The summary of SNOT-22 will include the proportion of subjects who have achieved a minimally clinical important difference.

Additionally, a plot of the biweekly LS means and SE for CFBL for SNOT-22 total score over time up to Week 24 and Week 48 by treatment group will be provided for the primary and final data analyses, respectively.

The analysis for SNOT-22 will be repeated for the PP analysis set. In addition, analysis for SNOT-22 in the ITT analysis set will be repeated where missing data will be imputed using the LOCF method outlined in Section 15.1.4.

15.2.4.6. Analysis of UPSIT™

The UPSIT™ score at Week 24 will be analyzed for the ITT analysis set using an ANCOVA model outlined in Section 15.1.3. The Baseline CS7DA4S score will be replaced by the baseline UPSIT™ score in the model.

15.3. EXPLORATORY EFFICACY

15.3.1. EXPLORATORY EFFICACY ENDPOINTS AND DERIVATIONS

15.3.1.1. Acute Exacerbation of Chronic Sinusitis

The percentages of subjects reporting acute exacerbation of CS (AECS) at Weeks 4, 8, 12, 16, 20 and 24 are exploratory endpoints, where AECS will be assessed by the investigator. AECS is defined as a sudden worsening of symptoms in a subject resulting in the treating physician reporting an escalation of treatment. This will be reported by the investigator on the Follow-up eCRF.

15.3.1.2. Improvement from Baseline in Nasal Polyp Severity Within Middle Meatus

The percentage of subjects with improvement from baseline in nasal polyp severity within the middle meatus in CSwNP subjects at Week 24 will be analyzed. Investigators will evaluate the severity of nasal polyps in the middle meatus using endoscopy at the Week 24/EOT visit by grading polyp severity as “better,” “worse,” or “the same” in comparison to the Baseline severity evaluated at Day 1 before the insertion procedure. A subject will be considered to have an improvement from baseline if both sinuses are assessed to be “better” than baseline or one side is assessed to be “better” than baseline and the other side to be “the same” as baseline.

15.3.1.3. CFBL in Endpoints by Absence or Prescence of Nasal Polyps

The secondary endpoints analysis will be repeated using the subgroups of subjects without nasal polyps (CSsNP), and subjects with nasal polyps (CSwNP). The endpoints to be summarized by these subgroups are:

- CFBL in CS7DA4S score at Weeks 1, 2, 3, 4, 8, 12, 16, 20 and 24

- CFBL in 7-day average score of individual cardinal CS symptoms at Weeks 1, 2, 3, 4, 8, 12, 16, 20 and 24
- CFBL in SNOT-22 domain and total scores at Weeks 2, 4, 8, 12, 16, 20 and 24
- CFBL in SF-36 domain and overall component summary measure scores at Week 24
- Percentage of subjects with at least 1-point decrease in any area for the bilateral Zinreich score at Week 24
- CFBL in each of the 5 bilateral Zinreich sinus scores, Zinreich OMC score and Zinreich total score at Week 24
- CFBL in USPIT™ total olfaction score at Week 24

15.3.1.4. CFBL in Endpoints at Post-Treatment Visits

The secondary endpoint analysis will be repeated for the post-treatment visits. The endpoints to be explored for these visits are:

- Proportion of subjects with improvement from baseline in nasal polyp severity within the middle meatus at Week 28
- CFBL in CS7DA4S total score at Weeks 28, 32, 36, 40, 44 and 48
- CFBL in 7-day average score of individual cardinal CS symptoms at Weeks 28, 32, 36, 40, 44 and 48
- CFBL in SNOT-22 domain and total scores at Weeks 28, 32, 36, 40, 44 and 48
- CFBL in SF-36 domain and overall component summary measure scores at Week 48
- CFBL in UPSIT at Week 28.

15.3.2. Missing Data Imputation Methods for Exploratory Efficacy Endpoints

No missing data methods will be used for exploratory analysis.

15.3.3. Analysis of Exploratory Efficacy Endpoints

The exploratory efficacy endpoints that are continuous will be compared between treatments at each post-baseline timepoint in the same manner as the primary efficacy analysis in Section 15.1.3 for the ITT analysis set. For the efficacy endpoints to be analyzed by CSsNP and CSwNP subgroups, the analysis will be a repeat of Section 15.1.3, however the model will not include the presence of nasal polyps as a fixed effect.

For dichotomous exploratory efficacy endpoints, treatments will be compared in the same manner as the proportion

of subjects with at least 1-point decrease from baseline in the Zinreich score in at least 1 pair of the anterior ethmoid, maxillary, posterior ethmoid, frontal or sphenoid sinuses key secondary endpoint in Section 15.2.4.2, replacing the baseline bilateral Zinreich score with the baseline CS7DA4S score. This analysis will be carried out for the ITT analysis set.

In addition, for all endpoints measured longitudinally at various visits during the study, a generalized estimating equation (GEE) linear regression and logistic regression will be used to compare treatments over time for continuous and dichotomous endpoints, respectively. The estimates, SE, 90% CIs and p-values will be presented for each visit. In the GEE, only treatment stage timepoints will be analyzed; assessments with only one follow-up timepoint will not be analyzed.

The assumed within-subject correlation matrix structure will be unstructured. If the unstructured model does not converge, then an autoregressive (1) structure will be assumed. Included as independent variables for each outcome endpoint will be treatment group, visit, treatment-by-visit, stratification variables, and the baseline value of the endpoint being analyzed. This will be carried out on ITT subjects with available data for the below endpoints:

- CFBL in CS7DA4S total score
- CFBL in 7-day average score of individual cardinal CS symptoms
- CFBL in SNOT-22 domain and total scores

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

16.1. ADVERSE EVENTS

AEs will be coded using MedDRA version 23.0 or later.

- Prior AEs are defined as any AE starting before the bilateral insertion/Sham procedure.
- Treatment emergent adverse events (TEAEs) are defined as any AE starting or worsening on or after the bilateral insertion/Sham procedure, but before or on 28 days after the removal/Sham procedure.
- Post-treatment AEs are defined as any AE starting or worsening more than 28 days after the removal/Sham procedure.

See APPENDIX 2 for the handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case (i.e. treatment emergent).

An overall summary of the number and percentage of subjects as well as the number of events within each of the categories below will be provided:

- TEAEs
- TEAEs by maximum severity
- TEAEs by highest relationship to study treatment
- TEAEs by highest relationship to study procedure
- Serious TEAE
- Serious TEAEs by maximum severity
- Serious TEAEs by highest relationship to study treatment
- Serious TEAEs by highest relationship to study procedure
- TEAE leading to treatment discontinuation
- TEAE leading to study discontinuation
- TEAE leading to death
- Post-treatment AEs
- Post-treatment AEs by maximum severity
- Post-treatment SAEs
- Post-treatment SAEs by maximum severity
- Post-treatment SAEs leading to study discontinuation
- Post-treatment SAEs leading to death.

Listings will include all AEs regardless of whether they are treatment emergent.

16.1.1. ALL TEAES AND POST-TREATMENT AES

Incidence of TEAEs and post-treatment AEs will be presented by System Organ Class (SOC) and Preferred Term

(PT). If a subject reports a TEAE or post-treatment AE more than once within that SOC/PT, the subject will be counted only once for that SOC/PT.

In the summary tables, TEAEs and post-treatment AEs will be presented by decreasing frequency of total events overall within each SOC and then similarly by decreasing frequency of total events overall within each PT. System organ class or PTs with equal frequencies will be sorted alphabetically.

Summaries will present TEAEs and post-treatment AEs broken down further by maximum severity. Summaries will also present TEAEs by relationship to study treatment and relationship to study procedure.

16.1.1.1. Severity

Severity is classified as mild, moderate or severe (increasing severity). TEAEs starting on or after the bilateral insertion/Sham procedure, and post-treatment AEs starting 28 days after removal procedure with a missing severity will be classified as severe for analysis purposes. If a subject reports an AE more than once within that SOC/PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

16.1.1.2. TEAE Relationship to Study Treatment

Relationship, as indicated by the Investigator, is classified as "Not Related", "Possible Related" or "Definitely Related" (increasing severity of relationship). A "related" TEAE is defined as a TEAE with a relationship to study treatment as "Possibly Related" or "Definitely Related". TEAEs starting on or after the bilateral insertion/Sham procedure with a missing relationship to study treatment will be regarded as "Related". If a subject reports the same AE more than once within that SOC/PT, the AE with the worst-case relationship to study treatment will be used in the corresponding relationship summaries.

16.1.1.3. TEAE Relationship to Study Procedure

The same conventions as noted in Section 16.1.1.2 will be applied to the relationship to study procedure for Day 1 insertion procedure and Week 24 removal procedure as indicated by the investigator. A TEAE related to the insertion/removal procedure is an AE that occurred within one day after the insertion/removal procedure.

16.1.2. SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events eCRF. A summary of serious TEAEs and post-treatment SAEs by SOC and PT will be prepared, including events leading to death. If a subject reports a serious TEAE/post-treatment SAE more than once within that SOC/PT, the subject will be counted only once for that SOC/PT.

Additionally, a listing of all SAEs will be provided, including events leading to death.

16.1.3. TEAEs Leading to Discontinuation of Study Treatment

TEAEs leading to early discontinuation of study treatment will be identified as an AE for which the "Action taken" is reported as "Study treatment discontinuation" on the Adverse Event eCRF. A summary of TEAEs leading to early discontinuation of study treatment by SOC and PT will be prepared.

Additionally, a listing of all TEAEs leading to permanent discontinuation of study treatment will be provided.

16.1.4. TEAEs and Post-Treatment AEs Leading to Discontinuation of Study

TEAEs and post-treatment AEs leading to study discontinuation will be identified as an AE for which the question "Did the AE cause the subject to discontinue from the study?" is reported as "Yes" on the Adverse Events eCRF. A summary of TEAEs leading to study discontinuation by SOC and PT will be prepared. If a subject reports a TEAE leading to study discontinuation more than once within that SOC/PT, the subject will be counted only once for that SOC/PT.

Additionally, a listing of all AEs leading to study discontinuation will be provided.

16.1.5. Adverse Events Leading to Death

TEAEs and post-treatment AEs leading to death are those events for which "Outcome" is reported as "Death" on the Adverse Events eCRF, or the seriousness criteria is indicated as "Death". A summary of TEAEs and post-treatment AEs leading to death by SOC and PT will be prepared.

Additionally, a listing of all AEs leading to death will be provided.

16.2. Laboratory Evaluations

Results from the local and central laboratories will be included in the reporting for this study.

- Local Laboratories:
  - Hematology
  - Chemistry
  - Serum cortisol levels at screening
- Central laboratories:

- Morning Serum cortisol after screening

The local laboratory results will be converted to standard units by data management and transferred to biostatistics for use in the analysis.

Quantitative laboratory measurements reported as "< X", that is below the lower limit of quantification, or "> X", that is above the upper limit of quantification, will be converted to X for quantitative summaries.

The following summaries will be provided for laboratory data:

- Observed values and change from baseline by visit for quantitative measurements.
- Shift from baseline according to investigator assessment (abnormal CS, abnormal NCS, or normal as indicated by the investigator on the Hematology, Blood Chemistry, and Adverse Events eCRFs).

Since the results are originating from various local laboratories, a single set of reference ranges is not available for use in the analysis. Prior to summarizing, the lab results will be normalized as described in Section 16.2.1.

The laboratory tests to be presented in the analysis tables are listed in the protocol Sections 8.4.3.1 to 3. Any other lab test will be listed only.

16.2.1. LABORATORY STANDARDIZATION

As the results are from local laboratories, laboratory parameters will have different normal ranges in the database. Prior to the analysis, observed values of all subjects will be standardized to a unique set of normal range using the location-scale standardization formula (Chuang-Stein, 1992):

$$s = LS + (x - LX)\frac{US - LS}{UX - LX}$$

where:

s = standardized observed value;

x = original observed value;

LS = Lower Limit of the normal range chosen to be the standard normal range;

US = Upper Limit of the normal range chosen to be the standard normal range;

LX = Lower Limit of the normal range associated with the original observed value;

UX = Upper Limit of the normal range associated with the original observed value;

It is to be noted that the choice of the standard normal range is arbitrary for all laboratory parameters except serum cortisol. Serum cortisol is collected by both central and local laboratories and for analysis purposes the central laboratory ranges will be used as the standard normal range.

16.2.2. PREGNANCIES

A serum pregnancy test will be conducted on females of child bearing potential at screening and prior to randomization on day 1. Urine pregnancy tests will be conducted thereafter at the time points specified in the schedule of assessments in Section 8.1 of the protocol. These data will be listed only.

16.3. VITAL SIGNS

The following vital signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Respiration Rate (breaths/min)
- Weight (kg)
- Body Mass Index (kg/m^2)
- Temperature (^0C) (to be listed only)

The following summaries will be provided for vital signs data:

- Observed, change from baseline by visit for quantitative measurements
- Incidence of abnormal values according to investigator criteria
- Shift from baseline according to investigator assessment (abnormal CS, abnormal NCS, or normal as indicated by the investigator on the eCRF).

16.4. PHYSICAL EXAMINATION

A physical examination will be conducted at Screening, Day 1, and Weeks 4, 12, 24, 28 and 48. This will consist of an assessment of all body systems including the skin, eyes, ears, nose and throat. These data will be listed only.

16.5. OTHER SAFETY ASSESSMENTS

16.5.1. OPHTHALMOLOGY ASSESSMENT

Ophthalmologic assessments will be performed at the site and result reported on the Ophthalmology Examination eCRF.

- Intraocular pressure (IOP) results will be summarized as follows:
  - Observed values and change from baseline in IOP by visit
  - Incidence of elevated IOP in one or both eyes
  - Clinically significant increase of IOP in one or both eyes
  - Shift from baseline according to investigator assessment (abnormal or normal as indicated by the investigator on the eCRF)
- In addition, the slit-lamp examination results will be reported in a descriptive summary table.
  - The summary will include the number and percentage of subjects with newly identified or worsened cataracts in one or both eyes as assessed per the protocol schedule of events.
  - A further classification between abnormal not affecting vision and abnormal affecting vision will also be presented.
  - For subjects with different results for left and right eyes, the worst-case result will be reported for the relevant visit, that is abnormal affecting vision.

16.5.2. OPHTHALMOLOGY SPECIFIC DERIVATIONS

- Elevated IOP is defined as results > 21 mmHg in one or both eyes.
- A clinically significant increase of IOP is defined as IOP in one or both eyes > 28 mmHg or an increase of IOP from Baseline in one or both eyes >= 10 mmHg.
- Newly identified or worsened cataracts will be identified as follows:
  - Mature or Morgagnian cataract present reported as “Yes”

- Nuclear cataract reported at a higher grade than the Screening result
- Cortical cataract reported at a higher grade than the Screening result
- Central Optical zone involvement reported as "Yes"
- Posterior subcapsular cataract reported at a higher grade than the Screening result.

16.6. NASAL ENDOSCOPY ASSESSMENT

Nasal cavities will be assessed by endoscopy procedure as per the schedule of events in Section 8.1 of the protocol. The severity and percentage of subjects with adverse nasal endoscopic findings in one or both nostrils will be summarized by visit and by treatment group.

17. PHARMACOKINETIC ANALYSES

The PK analyses will be performed based on subjects in the PK analysis set with available data by treatment group as follows:

- Concentrations, nominal times post-dose, and actual times will be listed.
    - In listings, concentrations below the lower limit of quantification (LLOQ) will be reported as "<LLOQ", where LLOQ will be the actual value of LLOQ.
- A separate listing will present deviations from the nominal times per protocol.
- Descriptive statistics will be presented for concentrations by dose and nominal time post-dose including number (n), mean, SE, standard deviation, coefficient of variation (CV), median, minimum, maximum, geometric mean, geometric CV%, and the number of concentrations greater than or equal to LLOQ.
    - The "<LLOQ" values will be set to zero based on the Beal's method M7 (Beal, 2001).

18. REFERENCES

Beal, S. (2001). Ways to Fit a PK Model with Some Data Below the Quantification Limit. *Journal of Pharmacokinetics and Pharmacodynamics*, 481-504.

Chuang-Stein, C. (1992). Summarizing laboratory data with different reference ranges in multi-center clinical trials. *Drug Information Journal*, 26(1);77-84.

DeConde, A. S., Bodner, T. E., Mace, J. C., & Smith, T. L. (2014). Response Shift in Quality of Life After Endoscopic Sinus Surgery for Chronic Rhinosinusitis. *JAMA Otolaryngol Head Neck Surgery*, 140:712-719.

Doty, R. L., Shaman, P., & Dann, M. (1984). Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. *Physiology & Behavior*, 32:489-502.

Hopkins, C., Gillett, S., Slack , R., Lund, V., & Browne, J. (2009). Psychometric validity of the 22-item Sinonasal Outcome Test. *Clinical Otolaryngology*, 34: 447-454.

Likness, M. M., Pallanch, J. F., Sherris, D. A., Kita, H., Mashtare Jr., T. L., & Ponikau, J. U. (2014). Computed tomography scans as an objective measure of disease severity in chronic rhinosinusitis. *Otolaryngology Head and Neck Surgery*, 150:305-311.

O'Kelly, M., & Ratitch, B. (2104). *Clinical Trials with Missing Data: A Guide for Practitioners.* Chichester: John Wiley & Sons, Ltd.

Optum. (n.d.). *PSF-36v2® Health Survey Measurement Model.* Retrieved from https://www.optum.com/content/dam/optum/resources/Manual%20Excerpts/SF-36v2-Health-Survey-Measurement-Model.pdf.

Rubin, D. B. (1987). *Multiple Imputation for Nonresponse in Surveys.* New York: John Wiley and Sons.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

PAPER SIZE, ORIENTATION AND MARGINS

The size of paper will be Letter. and the page orientation will be landscape. Margins will provide 1 inch (2.54 cm) of white space all around the page.

DATES AND TIMES

Depending on data available, dates and times will take the form DDMMMYYYY HH:MM.

SPELLING FORMAT

United States English.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in the given order:

- LYR-210 2500µg
- LYR-210 7500µg
- Sham

PRESENTATION OF VISITS

For tables and figures, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening	Scr
Baseline	BL
Week 2	WK 2
Week 4	WK 4
Week 8	WK 8
Week 12	WK 12
Week 16	WK 16
Week 20	WK 20
Week 24	WK 24

Long Name (default)	Short Name
Week 28	WK 28
Week 32	WK 32
Week 36	WK 36
Week 40	WK 40
Week 44	WK 44
Week 48	WK 48

For Listings the visit will be presented as derived in Section 6.6.

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Randomized treatment group (or treatment received if it's a safety output) in order of LYR-210 2500 µg, LYR-210 7500 µg and Sham procedure.
  - For listings where non-randomized subjects are included, these will appear in a category after the randomized treatment groups labeled "Randomized, Not Treated" and "Screen Failure".
- Subject ID
- Parameter (where applicable)
- Date (where applicable)

GENERAL CONVENTIONS

- Decimal precision:
  - If the original data has N decimal places, then the summary statistics should have the following decimal places:
    - Minimum and maximum: N
    - Mean and median: N + 1
    - SD: N + 2
  - Percentages will be presented to 1 decimal place
  - Zero count will not have percentage reported
  - Odd ratios will be presented to 2 decimal places
- Ordering of footnotes:

- Abbreviations
- Definitions
- Formulae
- P-value significance footnote
- Symbols. They will appear in the same order as they are defined in the table or listing, from left to right.
- Specific notes
- Common notes from table to table should appear in the same order.

APPENDIX 2. PARTIAL DATE CONVENTIONS

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS

Start Date	Stop Date	Action
Known	Known/Partial/ Missing	If start date < insertion procedure, then Prior If insertion procedure <= start date <= removal procedure + 28 days , then TEAE If start date > removal procedure + 28 days, then Post-Treatment AE
Partial, but known components show that AE started before insertion procedure	Known/Partial/ Missing	Assumed Prior
Partial, known components show that AE started on/after insertion procedure but before/on removal procedure + 28 days OR Missing	Known/Partial/ Missing	Assumed TEAE
Partial, known components show that AE started after removal procedure + 28 days	Known/Partial/ Missing	Assumed Post-Treatment AE

ALGORITHM FOR PRIOR/CONCOMITANT MEDICATIONS

Start Date	Stop Date	Action
Known	Known	If stop date < insertion procedure, assign as Prior If stop date >= insertion procedure and start date <= removal procedure+28 days, assign as Concomitant If start date > removal procedure+28 days, assign as Post-Treatment.

Start Date	Stop Date	Action
	Partial	If known date parts of stop date < insertion procedure, assign as Prior If known date parts of stop date >= insertion procedure and start date <= removal procedure+28 days, assign as Concomitant If start date > removal procedure+28 days, assign as Post-Treatment
	Missing	If stop date is missing could never be assumed a Prior medication If start date <= removal procedure+28 days, assign as Concomitant If start date > removal procedure+28 days, assign as Post-Treatment
Partial	Known	If stop date < insertion procedure, assign as Prior If stop date >= insertion procedure and known date parts of start date <= removal procedure+28 days, assign as Concomitant If known date parts of start date > removal procedure+28 days, assign as Post-Treatment
	Partial	If known date parts of stop date < insertion procedure, assign as Prior If known date parts of stop date >= insertion procedure and known date parts start date <= removal procedure+28 days assign as Concomitant If known date parts of start date > removal procedure+28 days, assign as Post-Treatment
	Missing	If stop date is missing could never be assumed a Prior medication If known date parts of start date <= removal procedure+28 days, assign as Concomitant If known date parts of start date > removal procedure+28 days, assign as Post-Treatment
Missing	Known	If stop date < insertion procedure, assign as Prior If stop date >= insertion procedure, assign as Concomitant Cannot be assigned as Post-Treatment
	Partial	If known date parts of stop date < removal procedure+28 days, assign as Prior If known date parts of stop date >= removal procedure+28 days, assign as Concomitant Cannot be assigned as 'Post-Treatment'
	Missing	Assign as Concomitant