CLINICAL STUDY PROTOCOL

Protocol Number:	LYR-210-2021-005
Current Version/Date:	4.0/ 29 March 2024
NCT/EUDRACT #:	NCT05295459/ 2021-006911-27
EU CT #:	2023-506268-15-00
Study Title:	ENLIGHTEN 2: A Phase III, Randomized, Blinded, Controlled, Parallel-Group Trial to Evaluate the Efficacy and Safety of LYR-210 for the Treatment of Chronic Rhinosinusitis (CRS) in Adults
Short Title:	Efficacy and Safety of LYR-210 for the Treatment of Chronic Rhinosinusitis (CRS)
Sponsor:	Lyra Therapeutics, Inc. 480 Arsenal Way Watertown, MA USA 02472 617-393-4600

GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), as defined by United States Food and Drug Administration (USFDA) and International Council for Harmonisation (ICH), Regulation EU # 536/2014, Declaration of Helsinki and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities

Confidentiality Statement

The information contained in this document, is the property of the Sponsor and is confidential. This information may not be disclosed, reproduced, or distributed to anyone other than personnel directly involved in the conduct of the study and in response to a relevant Institutional Review Board/Ethics Committee and Review by a Regulatory Authority as required by the applicable laws and regulations, without the written authorization of the Sponsor, except to the extent necessary to obtain written informed consent from those individuals to whom the study drug may be administered. These restrictions will continue to apply after the study has closed.

Sponsor Signature Page

Protocol Number:	LYR-210-2021-005
Current Version/Date:	4.0/ 29 March 2024
NCT/EUDRACT #:	NCT05295459/ 2021-006911-27
EU CT #:	2023-506268-15-00
Study Title:	ENLIGHTEN 2: A Phase III, Randomized, Blinded, Controlled, Parallel-Group Trial to Evaluate the Efficacy and Safety of LYR-210 for the Treatment of Chronic Rhinosinusitis (CRS) in Adults
Short Title:	Efficacy and Safety of LYR-210 for the Treatment of Chronic Rhinosinusitis (CRS)
Sponsor:	Lyra Therapeutics, Inc. 480 Arsenal Way Watertown, MA USA 02472

Co-Lead Investigator Signature Page

Protocol Number:	LYR-210-2021-005
Current Version/Date:	4.0/ 29 March 2024
NCT/EUDRACT #:	NCT05295459/2021-006911-27
EU CT #:	2023-506268-15-00
Study Title:	ENLIGHTEN 2: A Phase III, Randomized, Blinded, Controlled, Parallel-Group Trial to Evaluate the Efficacy and Safety of LYR-210 for the Treatment of Chronic Rhinosinusitis (CRS) in Adults
Short Title:	Efficacy and Safety of LYR-210 for the Treatment of Chronic Rhinosinusitis (CRS)
Sponsor:	Lyra Therapeutics, Inc. 480 Arsenal Way Watertown, MA USA 02472

Investigator Agreement Signature Page

I hereby agree to participate in this clinical investigation sponsored by Lyra Therapeutics, Inc., (hereinafter "Study Sponsor"). I agree to conduct this investigation in accordance with this version of the protocol. I agree to protect the rights, safety, and welfare of participants under my care. I agree that the study will be conducted according to the principles of the ICH E6 guideline for GCP, the ethical principles that have their origins in the World Medical Association Declaration of Helsinki, Regulation EU # 536/2014 and local regulatory authority or ethics committee requirements as appropriate. I agree to supervise all use of the investigational product and to ensure appropriate informed consent is obtained from all participants prior to inclusion in this study.

I understand that this investigation will be monitored by the Study Sponsor and/or a designee employed by the Study Sponsor. This monitoring will involve periodic inspection of my investigational site and ongoing review of the data that is submitted by me to the Study Sponsor. I am also aware that I may be inspected by a representative of the local regulatory authority or ethics committee to verify compliance with applicable federal regulations related to clinical research on human participants.

I am aware that the Study Sponsor reserves the right to discontinue this investigation at any time. If I decide to discontinue my participation as an Investigator in this study, I will notify the Study Sponsor with suitable written notice and in accordance with the Clinical Trial Agreement prior to discontinuing. I understand that I am obligated to complete the follow-up of the participants already participating in the investigation.

I agree to provide to the Study Sponsor my current curriculum vitae (CV) along with the current CV of those physicians at this institution who will be using this investigational product or participating in this study as Sub-Investigators under my supervision. These CVs include education, training, and the extent and type of our relevant experience with pertinent dates and locations. I certify that I have not been involved in an investigation that was terminated for noncompliance at the insistence of a Study Sponsor, or a local regulatory authority or ethics committee.

I understand that this investigation, protocol, and trial results are confidential, and I agree not to disclose any such information to any person other than a representative of Study Sponsor or local regulatory authority or ethics committee without the prior written consent of the Study Sponsor.

Investigator:

Name (Print): _____

Signature: _____ Date of Signature: _____
(DD MMM YYYY)

Site Number: _____

Clinical Study Protocol Synopsis

Short title:	ENLIGHTEN 2
Complete title:	ENLIGHTEN 2: A Phase III, Randomized, Blinded, Controlled, Parallel-Group Trial to Evaluate the Efficacy and Safety of LYR-210 for the Treatment of Chronic Rhinosinusitis (CRS) in Adults
Protocol number	LYR-210-2021-005
Study design:	Multicenter, phase III, randomized, blinded, controlled, parallel group
Investigational product:	LYR-210 System (7500 μg)
Active ingredient:	Mometasone furoate (MF)
Background Therapy	Nasal saline irrigation
Study locations	US and Europe
Number of sites	Approximately 60 sites
Enrollment:	Approximately 180 adult randomized participants with symptomatic CRS without nasal polyps or with grade 1 nasal polyps (limit of approximately 30 participants with nasal polyps)
Randomization	2 treatment:1 control
Treatment:	Bilateral LYR-210 in treatment participants vs sham procedure (no product) in control participants. All participants will continue daily saline irrigation.
Inclusion criteria:	A participant must meet **all** the following criteria to be eligible for this study: 1. Age ≥18. 2. Diagnosed as having CRS, defined by duration of 12 weeks or longer with 2 or more of the following symptoms: • nasal blockage/obstruction/congestion • nasal discharge (anterior, posterior, or both) • facial pain/pressure • reduction/loss of sense of smell 3. Bilateral ethmoid disease, defined as each side of anterior and/or posterior ethmoid sinus is ≥5% opacified upon the screening computed tomography (CT), as determined by the Central Imaging Core Lab/ Central Reviewer.

4. Mean 3 cardinal symptom (3CS) score over the preceding 7 days ≥5 (0-3 scale for each of the symptoms) as determined within 7 days of Day 1 (the determination for eligibility can be made on any day from Day -7 through Day 1).
5. Undergone at least 2 trials of medical treatments in the past, 1 of which must include intranasal corticosteroid sprays (INCS) for a minimum of 4 weeks with written medical record or confirmed via patient report and documented in the medical report record and are no longer using INCS at Screening.
6. Has been informed of the nature of the study and provided written informed consent as approved by the IRB/EC of the respective clinical site or regulatory authority, if applicable by national law.
7. Agrees to comply with all study requirements.
8. If currently on a waiting list for sinonasal surgery, willing to be removed from the waiting list or have preplanned surgery date cancelled for the duration of the study. [Note: this does not preclude a participant from receiving or being recommended for sinonasal surgery as rescue treatment during the study].

Exclusion criteria:

A participant who meets **any** of the following criteria will be excluded from this study:

1. Inability to tolerate topical anesthesia or endoscopic procedure.
2. Previous ethmoidectomy, or surgery of the middle meatus and/or middle turbinate preventing proper placement and retention of LYR-210. NOTE: any previous ethmoidectomy is exclusionary.
3. Previous nasal surgery or polypectomy within 3 months of Screening visit.
4. Presence of nasal polyp grade 2 or higher (ie, polyps extending outside the middle meatus) on either side.
5. Seasonal allergic rhinitis (SAR) with symptoms and/or, based on time of year, would anticipate onset of symptoms within 24 weeks of randomization. NOTE: mild SAR symptoms, as assessed by the Investigator, are not exclusionary.
6. Perennial rhinitis with symptoms that are well controlled by regular use of intranasal corticosteroids.
7. Severe asthma or experienced 1 or more exacerbations of asthma requiring systemic corticosteroid (SCS) use within the 6 months prior to the Screening visit. Participants with moderate or severe asthma will also be excluded if they have not been on a stable regimen of inhaled corticosteroids for asthma for a minimum of 3 months prior to the Screening visit.

8. Endoscopic exclusion criteria at Screening or Day 1 visit:
   a) Obstruction of middle meatus or degenerated middle turbinate preventing proper placement and retention of LYR-210.
   b) Evidence of mucosal erosion or ulceration.
   c) Acute nasal/sinus infection or purulence.
   d) Evidence of nasal septal perforation.
9. Screening CT exclusion criteria:
   a) Anatomic variation that, in the opinion of the investigator, would adversely impact placement of LYR-210.
   b) Structural, noninflammatory related CRS (eg, large concha bullosa preventing proper matrix placement, tumor).
   c) Sinus disease extended into orbital or intracranial space.
   d) Evidence of mycetoma/fungal ball, allergic fungal rhinosinusitis.
   e) Sinus mucocele.
10. History or clinical evidence or suspicion of invasive fungal sinusitis, allergic fungal rhinosinusitis, atrophic rhinitis, or odontogenic sinusitis.
11. Known history of hypersensitivity or intolerance to corticosteroids.
12. Oral steroid or monoclonal antibody (Xolair, Nucala, Dupixent, etc.) dependent condition, including biologics use within 3 months of screening and systemic steroids use within 1 month of screening. NOTE: monoclonal antibodies for this exclusion are limited to those that target T2 inflammatory pathways and/or are known to impact CRS-related inflammation and symptoms.
13. SCS administered within 1 month prior to Screening visit.
14. Known history of hypothalamic pituitary adrenal axial dysfunction.
15. Previous pituitary or adrenal surgery.
16. More than 1 episode of epistaxis with frank bleeding requiring medical attention within 2 months of Screening visit or more than 1 episode of epistaxis with frank bleeding within 1 month of Screening visit.
17. Acute exacerbation of nasal allergy or CRS, upper respiratory tract infection (URTI), or common cold within 4 weeks of the Screening visit or during the screening/run-in period. The infection/exacerbation must be resolved, and antibiotic or other medication use must be discontinued prior to screening.
18. Dental procedure/implant on maxillary dentition within 4 weeks of the Screening visit.

19. Past or present acute or chronic intracranial or orbital complications of CRS (eg, brain abscess, related problems with eyes or central nervous system).
20. History or diagnosis (in either eye) of glaucoma or ocular hypertension (IOP >21 mm Hg).
21. Presence (in either eye) of posterior subcapsular cataract of grade 2 or higher, nuclear sclerosis of grade 3 or higher, or cortical cataract of grade 2 or higher or involving a minimum of center optic zone of 3 mm diameter.
22. Loss of functional vision in 1 or both eyes.
23. Diagnosed with ongoing rhinitis medicamentosa.
24. Known history of immune dysfunction including immune deficiency (IgG subclass deficiency or IgA deficiency) or autoimmune disease (eg, Wegener's granulomatosis, sarcoidosis) that requires immunomodulatory therapy. NOTE: Autoimmune conditions that do not require immunomodulatory therapy are not exclusionary.
25. Currently positive for COVID-19 or residual sinonasal symptoms from a previous COVID-19 infection within the past 6 months.
26. Past, present, or planned organ transplant or chemotherapy with immunosuppression within the past 5 years.
27. History or diagnosis of ciliary dysfunction (eg, cystic fibrosis, primary ciliary dyskinesia [Kartagener syndrome]).
28. Past or present systemic vasculitis (eg, granulomatosis with polyangiitis).
29. Evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments.
30. Pregnant or breast feeding. Females of child-bearing potential must test negative for pregnancy at the time of screening based on a serum pregnancy test and reverified on Day 1 prior to randomization based on a urine pregnancy test. Both male and female participants of reproductive potential must agree to use highly effective methods of birth control throughout the study.
31. Previously received an experimental treatment in another clinical study within 5 half-lives or 30 days (whichever is longer) of Screening visit or prior participation in another LYR-210 clinical trial.
32. Currently participating in another drug or device study.

33. Determined by the investigator as not suitable for reasons not already specified if the health of the participant or the validity of the study outcomes may be compromised.

Objective: Evaluate the efficacy and safety of LYR-210 compared with sham control for treatment in adults with CRS.

Primary efficacy endpoint: Change from baseline (CFBL) in the 7-day average composite score of 3 cardinal symptoms (3CS) of nasal blockage/obstruction/congestion, anterior/posterior nasal discharge, and facial pain/pressure at Week 24 in participants without nasal polyps.

Key secondary efficacy endpoints:

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

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

Secondary endpoints

1. CFBL in 3CS score at Weeks 2, 4, 8, 12, 16, and 20
2. CFBL in the symptom score for individual cardinal symptoms of nasal blockage/obstruction/congestion, anterior/posterior nasal discharge, and facial pain/pressure at Weeks 2, 4, 8, 12, 16, 20 and 24
3. CFBL in loss of smell score at Weeks 4, 8, 12, 16, 20, and 24, for all participants and for participants with baseline score ≥2
4. Improvement of ≥1 point, ≥2 points, and ≥3 points from baseline in 3CS score at Week 24
5. CFBL in SNOT-22 total score at Weeks 4, 8, 12, 16, and 20
6. CFBL in SNOT-22 subdomain scores at Weeks 4, 8, 12, 16, 20, and 24
7. Improvement of ≥8.9 and ≥12 from baseline in SNOT-22 total score at Week 24

8. CFBL in the Zinreich score of the bilateral anterior and posterior ethmoids at Week 20
9. Time to first rescue treatment requirement through Week 24
10. Rescue medication use through Week 24
11. Sinonasal surgery requirement through Week 24
12. Total systemic corticosteroids (SCS) dose prescribed through Week 24
13. Number of days on SCS through Week 24
14. Acute exacerbation of CRS (AECRS), defined as a sudden worsening of CRS symptoms resulting in escalation of treatment by the Investigator, through Week 24
15. Conversion to a nonsurgical candidate through Week 24
16. CFBL in 36-Item short form health survey, version 2 (SF-36v2) physical health, mental health, and domain scores at Week 24
17. CFBL in EuroQoL 5-dimension, 5-level (EQ-5D-5L) score at Week 24
18. Improvement of ≥1 category and ≥2 categories from baseline in the severity of CRS-related symptoms as indicated by the PGIS at Week 24
19. Overall change of "very much better" or "much better" in the CRS-related symptom severity as indicated by the PGIC at Week 24
20. CFBL in Medical Outcomes Study Sleep Scale (MOS Sleep-R) score at Week 24
21. CFBL in Work Productivity and Activity Impairment-Specific Health Problem (WPAI-SHP), version 2.0 at Weeks 4, 12, and 24
22. CFBL in Fordyce Emotions Questionnaire (FEQ) at Weeks 4, 8, 12, 16, 20, and 24

Safety endpoints

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

Key study assessments	• Cardinal symptoms (CS) questionnaire • SNOT-22 • Work Productivity and Activity Impairment-Specific Health Problem (WPAI-SHP), version 2.0 • Fordyce Emotions Questionnaire (FEQ) • 36-Item short form health survey, version 2 (SF-36v2) • EuroQoL 5-dimension, 5-level (EQ-5D-5L) • Patient Global Impression of Severity (PGIS) • Patient Global Impression of Change (PGIC) • Medical Outcomes Study Sleep Scale (MOS Sleep-R) • Endoscopic nasal examination • Ocular examination (visual acuity [VA], intraocular pressure [IOP], and slit lamp) • 3-D volumetric (CT) score • Bilateral ethmoid Zinreich score • Adverse events (AEs)

Abbreviations and Acronyms

AE	Adverse event
AECRS	Acute exacerbation of CRS
ANCOVA	Analysis of covariance
CFBL	Change from baseline
CFR	Code of Federal Regulations (US)
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CRO	Clinical research organization
CRS	Chronic rhinosinusitis
CS	Cardinal symptoms
CT	Computed tomography
CTRA	Clinical trial research agreement
CV	Curriculum vitae
EC	Ethics Committee
EDC	Electronic data capture
EIU	Exposure in utero
EQ-5D-5L	EuroQoL 5-dimension, 5-level
EOS	End of study
EOT	End of treatment
ePRO	Electronic patient-reported outcomes questionnaire
ET	Early treatment termination
EU MDR	European Medical Device Regulations (2017/745)
FEQ	Fordyce Emotions Questionnaire
FESS	Functional endoscopic sinus surgery
FSH	Follicle stimulating hormone
GCP	Good clinical practices
HPLC	High performance liquid chromatography
ICF	Informed consent form
ICH	International Council on Harmonisation
INCS	Intranasal corticosteroid spray
IOP	Intraocular pressure
IRB	Institutional Review Board
IRT	Interactive response technology
ISE	Integrated summary of efficacy
ITT	Intention-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
Kg	Kilogram
K-M	Kaplan-Meier
LC-MS	Liquid chromatography mass spectrometry
MCID	Minimum clinically important difference

MedDRA	Medical Dictionary for Regulatory Activities
MF	Mometasone furoate
MOS Sleep-R	Medical Outcomes Study Sleep scale
MRM	Multiple repeated measures
OMC	Ostiomeatal complex
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PP	Per-protocol
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Seasonal allergic rhinitis
SCS	Systemic corticosteroids
SD	Standard deviation
SF-36v2	36-Item Short Form Health Survey, version 2
SNOT-22	22-item Sino-Nasal Outcome Test
SUSAR	Serious and unexpected suspected adverse reaction
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TMF	Trial master file
UADE	Unanticipated adverse device effect
URTI	Upper respiratory tract infection
VA	Visual acuity
WHO	World Health Organization
WPAI-SHP	Work Productivity and Activity Impairment -Specific Health Problem
WPS	Worst possible score

Table of Contents

Table of Tables and Figures

1. Background and Purpose

1.1 Background

Chronic rhinosinusitis (CRS) is a common condition defined by symptomatic inflammation of the paranasal sinuses lasting longer than 12 weeks. CRS affects approximately 10.9% of the European population[1] and 4.9% of the United States (US) population[2] and is the 5th most common condition in people under age 65 in the US.[3] CRS affects 6.95% of the population in south Korea[4] and is common in mainland China with an estimated prevalence of 8%, affecting approximately 107 million individuals.[5] CRS results in 18 million annual office visits,[6] and the economic implications are high in both the US[7] and Europe.[8] Common symptoms of CRS include nasal blockage/obstruction/congestion, facial pressure or pain, nasal discharge, and sense of smell dysfunction.[9,10] The underlying cause of CRS-related symptoms is inflammation of mucosal tissue, often leading to impairment of mucociliary clearance.

Currently there is no FDA-approved medical therapy for CRS without nasal polyps. A clinically proven anti-inflammatory treatment delivered directly to the sinonasal mucosal tissue that can reach deep in the nasal passageway and is not dependent upon patient compliance is needed as a treatment option to offer CRS patients.

Lyra Therapeutics, Inc. (Lyra) is developing the LYR-210 System, comprised of an implantable anti-inflammatory drug matrix (LYR-210 drug matrix) preloaded in a single-use applicator. The LYR-210 System is being studied in adult CRS patients who have failed previous medical management. The LYR-210 drug matrix is a miniaturized local drug implant designed to fit within the confined space of a patient's middle meatus. The LYR-210 drug matrix is comprised of the synthetic corticosteroid mometasone furoate (MF), embedded in a bioabsorbable polymer matrix that allows for gradual, sustained, and targeted release of MF for up to 24 weeks from a single administration. Therefore, the primary mode of action of the LYR-210 System is pharmacological (anti-inflammatory). The LYR-210 drug matrix is designed to dynamically adapt and conform to the irregular shape of the sinonasal passageway and maintain contact with the mucosa through the duration of drug delivery. LYR-210 drug matrices are intended to be administered bilaterally into the middle meatus by an otolaryngologist in the physician's office under endoscopic visualization using the provided single-use applicator. Administration of LYR-210 drug matrices is performed with topical anesthesia using minimally invasive techniques. Two dose strengths of LYR-210 (2500 ug and 7500 ug) were developed and evaluated in the early phase clinical studies; Lyra intends to proceed with the 7500 ug dose of LYR-210 for future development. At this dose, LYR-210 is designed to deliver a total dose of 15 000 µg of MF for up to 24 weeks with an average daily dose of 89 µg of MF per human patient (approximately 45 µg of MF per nostril). When treatment is complete, the LYR-210 drug matrices are removed using standard tools during an office visit.

1.2 Investigator information/report of prior investigations

Lyra's nonclinical rabbit matrices, representative of human matrices, were tested in the maxillary sinuses of New Zealand white (NWZ) rabbits and demonstrated local and systemic safety. The human cadaver study demonstrated ease of placement and satisfactory anatomic conformation of the LYR-210 drug matrix in the middle meatus.

Three clinical studies have been completed that evaluated the safety, tolerability, pharmacokinetics, and efficacy of the LYR-210 System in adult CRS patients. These studies have demonstrated the LYR-210 drug matrix to be safe with no treatment- or procedure-related serious adverse events (SAEs) reported to date. MF was detectable in the plasma of patients receiving the LYR-210 (7500 ug) drug matrices and systemic bioavailability of MF was within the limits of approved inhaled MF formulations for chronic use in adults and children. The LYR-210 matrix (7500 ug) dose also showed statistically significant symptom improvement compared to control in patients with CRS who had previously failed medical management. These study results support the safety of the LYR-210 System and its further evaluation in pivotal clinical trials.

For simplicity in this document, the product (matrix and/or system) is generally referred to as LYR-210.

1.3 Purpose

The purpose of this study is to evaluate the efficacy and safety of the LYR-210 compared with a sham procedure control for treatment in adults with CRS.

2. Study Objectives and Endpoints

2.1 Study objectives

2.1.1 Primary objective

The primary objective is to evaluate the efficacy of LYR-210, compared with a sham procedure control, in improving the 3 cardinal symptoms of CRS in CRS participants without nasal polyps, who had previously failed medical management. The 3CS are nasal blockage/obstruction/ congestion, anterior/posterior nasal discharge, and facial pain/pressure.

2.1.2 Secondary objective

The secondary objectives are to:

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

2.2 Study endpoints

2.2.1 Primary estimand/Primary efficacy endpoint

The primary estimand is a composite strategy. The attributes of the primary estimand are provided below in **Table 1**.

Table 1. Attributes of the Primary Estimand

Attribute	Specification
Treatment	LYR-210 7500 µg drug matrix over a 20-week period or sham procedure, with daily saline nasal irrigation
Population	Adults with CRS who do not have nasal polyps, have failed medical management (including treatment with intranasal corticosteroid sprays [INCS]), and have not had endoscopic sinus surgery (ESS)
Variable (Primary Endpoint)	The primary endpoint is change from baseline (CFBL) in the 7-day average composite score of the 3 cardinal symptoms (3CS) of nasal blockage/obstruction/congestion, anterior/posterior nasal discharge, and facial pain/pressure at Week 24 in participants without nasal polyps. The daily composite score is the sum of the 3 daily cardinal symptom scores. If less than 4 daily scores are available for a week, the 3CS score will be considered missing for the week.
Intercurrent Events	(1) Rescue with systemic corticosteroids (SCS) or ESS: a composite variable strategy will be implemented where the 3CS score post SCS use or ESS will be censored and imputed with the participant's worst observed score. (2) Decongestants use or INCS use or early termination of study treatment due to any reasons (e.g., spontaneous bilateral matrix dislodgement of LYR-210): a treatment policy strategy will be adopted in which the 3CS scores reported by the participants will be used regardless of whether the intercurrent event occurs. (3) Infection with COVID-19: a hypothetical strategy will be used in which the 3CS score reported by the participants post the intercurrent event will be censored as if the COVID-19 infection did not occur.
Population-level Summary for the Variable	Difference in the mean change from baseline in the 3CS score at Week 24

See Section 9 (Statistical Considerations) for the primary analysis method.

2.2.2 Key secondary efficacy endpoints

If the primary efficacy endpoint is met, the statistical significances of the key secondary endpoints will be evaluated, each at a 2-sided significance level of 0.05, using the hierarchical method in the following order:

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

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

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

2.2.3 Additional secondary endpoints

Additional secondary endpoints include:

1. CFBL in 3CS score at Weeks 2, 4, 8, 12, 16, and 20
2. CFBL in the symptom score for individual cardinal symptoms of nasal blockage/obstruction/congestion, anterior/posterior nasal discharge, and facial pain/pressure at Weeks 2, 4, 8, 12, 16, 20 and 24
3. CFBL in loss of smell score at Weeks 4, 8, 12, 16, 20, and 24, for all participants and for participants with baseline score ≥2
4. Improvement of ≥1 point, ≥2 points, and ≥3 points from baseline in 3CS score at Week 24
5. CFBL in SNOT-22 total score at Weeks 4, 8, 12, 16, and 20
6. CFBL in SNOT-22 subdomain scores at Weeks 4, 8, 12, 16, 20, and 24
7. Improvement of ≥8.9 and ≥12 from baseline in SNOT-22 total score at Week 24
8. CFBL in the Zinreich score of the bilateral anterior and posterior ethmoids at Week 20
9. Time to first rescue treatment requirement through Week 24
10. Sinonasal surgery requirement through Week 24
11. Rescue medication use through Week 24
12. Total systemic corticosteroid (SCS) dose prescribed through Week 24
13. Number of days on SCS through Week 24
14. Acute exacerbation of CRS (AECRS), defined as a sudden worsening of CRS symptoms resulting in escalation of treatment by the Investigator, through Week 24,
15. Conversion to a nonsurgical candidate through Week 24
16. CFBL in 36-Item short form health survey, version 2 (SF-36v2) physical health, mental health, and domain scores at Week 24
17. CFBL in EuroQoL 5-dimension, 5-level (EQ-5D-5L) score at Week 24
18. Improvement of ≥1 category and ≥2 categories in the severity of CRS-related symptoms, as indicated by the PGIS at Week 24
19. Overall change of ‘very much better” or much better’ in the CRS-related symptom severity, as indicated by the PGIC at Week 24
20. CFBL in Medical Outcomes Study Sleep Scale (MOS Sleep-R) score at Week 24
21. CFBL in Work Productivity and Activity Impairment-Specific Health Problem (WPAI-SHP), version 2.0 at Weeks 4, 12, and 24
22. CFBL in Fordyce Emotions Questionnaire (FEQ) at Weeks 4, 8, 12, 16, 20, and 24

2.2.4 Safety endpoints

Safety endpoints include:

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

3. Investigational Plan

3.1 Study design

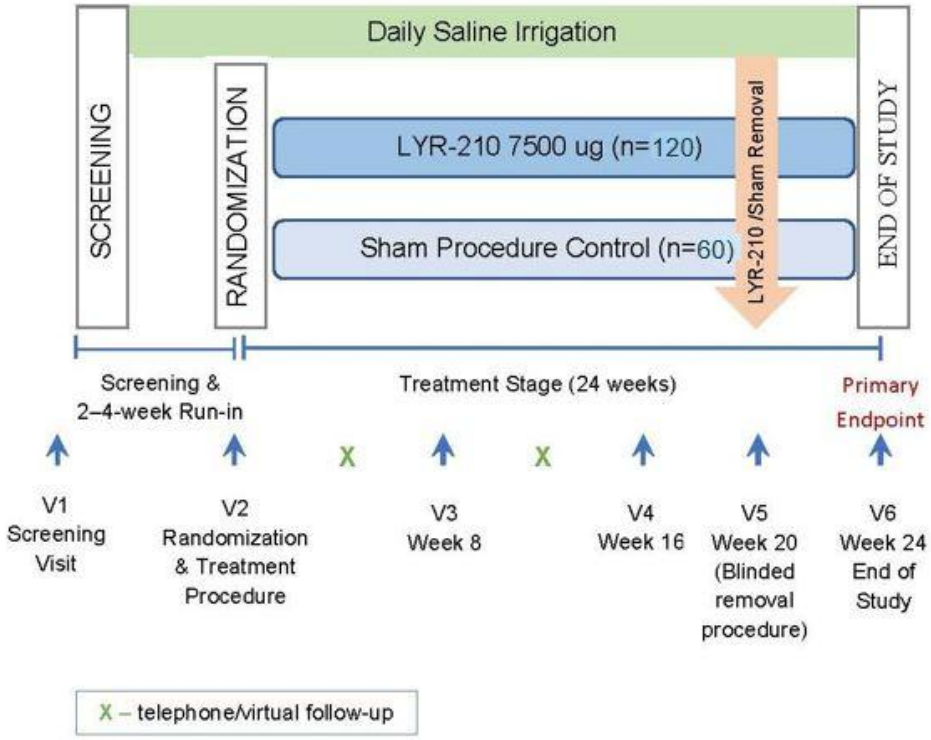
This global, multicenter study will be conducted in a randomized, controlled, parallel-group, blinded fashion in approximately 180 symptomatic adult CRS participants who have failed previous medical management. Participants enrolled in the study will include participants who have accessible and intact middle meatus. The efficacy and safety of LYR-210 matrix (7500 µg) versus a control group receiving a sham procedure will be assessed on a background therapy of daily saline irrigation. Participants will be randomized 2:1 to either treatment with LYR-210 or to control.

The study will consist of 2 stages:

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

The study design is depicted in **Figure 1**.

Figure 1. Study Design



3.1.1 Study Design Rationale

The proposed study aims at evaluating the efficacy of LYR-210 in the treatment of CRS in participants who have previously failed medical management, including INCS. Since participants must have already failed INCS and given that INCS do not have an approved indication for use in CRS without nasal polyps, use of INCS during the study is prohibited. Participants will use daily saline irrigation as background therapy.

The safety and efficacy of LYR-210 in treating CRS will be evaluated against a control group receiving sham procedure. [redacted] Furthermore, a drug-free matrix is likely to induce a foreign-body inflammatory reaction and potentially exacerbate the CRS symptoms.[11]

Inclusion of a sham procedure as a control is necessary for maintaining patient blinding and to ensure unbiased completion of the Patient Reported Outcome questionnaires as the primary and secondary efficacy endpoints of the study. Participants will be randomized 2:1 to either treatment with LYR-210 or to sham control. Since the participants must have previously failed medical management before entering the study, the impact of participants randomized to the sham control arm should be minimal. In addition, the protocol allows rescue treatment for any participant that experiences a worsening of CRS.

3.2 Study size and duration

Approximately 180 participants are planned to be enrolled in this study.

The total duration of study participation for all enrolled and treated participants is expected to be approximately 7 months (including the Screening/Run-in and Treatment stages). The end of the study (EOS) is defined as the date of the last EOS visit of the last participant of the study.

3.3 Study population

The study population will consist of approximately 180 adult participants with symptomatic CRS without nasal polyps or with grade 1 nasal polyps, who have failed previous medical management. Enrollment of participants with nasal polyps of grade 1 will be limited to approximately 30 participants.

3.3.1 Inclusion criteria

A participant must meet **all** the following criteria to be eligible for this study:

1. Age ≥18.
2. Diagnosed as having CRS, defined by duration of 12 weeks or longer with 2 or more of the following symptoms:
    - nasal blockage/obstruction/congestion
    - nasal discharge (anterior, posterior, or both)
    - facial pain/pressure
    - reduction/loss of sense of smell
3. Bilateral ethmoid disease, defined as each side of anterior and/or posterior ethmoid sinus is ≥5% opacified upon the screening computed tomography (CT), as determined by the Central Imaging Core Lab/ Central Reviewer.
4. Mean 3CS score over the preceding 7 days ≥5 (0-3 scale for each of the symptoms) determined within 7 days of Day 1 (the determination for eligibility can be made on any day from Day -7 through Day 1).
5. Undergone at least 2 trials of medical treatments in the past, 1 of which must include intranasal corticosteroid sprays (INCS) for a minimum of 4 weeks with written medical record or confirmed via patient report and documented in the medical report record and are no longer using INCS at Screening.
6. Has been informed of the nature of the study and has provided written informed consent as approved by the Institutional Review Board (IRB)/Ethics Committee (EC) of the respective clinical site or regulatory authority, if applicable by national law.
7. Agrees to comply with all study requirements.
8. If currently on a waiting list for sinonasal surgery, is willing to be removed from the waiting list or have a preplanned surgery date cancelled for the duration of the study. [Note: this does not preclude a participant from receiving or being recommended for sinonasal surgery as rescue treatment during the study].

3.3.2 Exclusion criteria

A participant who meets **any** of the following criteria will be excluded from this study:

1. Inability to tolerate topical anesthesia or endoscopic procedure.

2. Previous ethmoidectomy, or surgery of the middle meatus and/or middle turbinate preventing proper placement and retention of LYR-210. NOTE: any previous ethmoidectomy is exclusionary.
3. Previous nasal surgery or polypectomy within 3 months of Screening visit.
4. Presence of nasal polyps grade 2 or higher (ie, polyps extending outside the middle meatus) on either side.
5. Seasonal allergic rhinitis (SAR) with symptoms and/or, based on time of year, would anticipate onset of symptoms within 24 weeks of randomization. NOTE: mild SAR symptoms, as assessed by the Investigator, are not exclusionary.
6. Perennial rhinitis with symptoms that are well controlled by regular use of intranasal corticosteroids.
7. Severe asthma or experienced 1 or more exacerbations of asthma requiring SCS use within the 6 months prior to the Screening visit. Participants with moderate or severe asthma will also be excluded if they have not been on a stable regimen of inhaled corticosteroids for asthma for a minimum of 3 months prior to the Screening visit.
8. Endoscopic exclusion criteria at Screening or Day 1 visit:
    a) Obstruction of middle meatus or degenerated middle turbinate preventing proper placement and retention of LYR-210.
    b) Evidence of mucosal erosion or ulceration.
    c) Acute nasal/sinus infection or purulence.
    d) Evidence of nasal septal perforation.
9. Screening CT exclusion criteria:
    a) Anatomic variation that, in the opinion of the investigator, would adversely impact placement of LYR-210.
    b) Structural, noninflammatory related CRS (eg, large concha bullosa preventing proper matrix placement, tumor).
    c) Sinus disease extended into orbital or intracranial space.
    d) Evidence of mycetoma/fungal ball, allergic fungal rhinosinusitis.
    e) Sinus mucocele
10. History or clinical evidence or suspicion of invasive fungal sinusitis, allergic fungal rhinosinusitis, atrophic rhinitis, or odontogenic sinusitis.
11. Known history of hypersensitivity or intolerance to corticosteroids.
12. Oral steroid or monoclonal antibody (Xolair, Nucala, Dupixent, etc.) dependent condition, including biologics use within 3 months of screening and systemic steroid use within 1 month of screening. NOTE: monoclonal antibodies for this exclusion are limited to those that target T2 inflammatory pathway and/or are known to impact CRS-related inflammation and symptoms.
13. SCS administered within 1 month prior to Screening visit.
14. Known history of hypothalamic pituitary adrenal axial dysfunction.
15. Previous pituitary or adrenal surgery.

16. More than 1 episode of epistaxis with frank bleeding requiring medical attention within 2 months of Screening visit or more than 1 episode of epistaxis with frank bleeding within 1 month of Screening visit.
17. Acute exacerbation of nasal allergy or CRS, upper respiratory tract infection (URTI), or common cold within 4 weeks of the Screening visit or during the screening/run-in period. The infection/exacerbation must be resolved, and antibiotic or other medication use must be discontinued prior to screening.
18. Dental procedure/implant on maxillary dentition within 4 weeks of the Screening visit.
19. Past or present acute or chronic intracranial or orbital complications of CRS (eg, brain abscess, related problems with eyes or central nervous system).
20. History or diagnosis (in either eye) of glaucoma or ocular hypertension (IOP >21 mm Hg).
21. Presence (in either eye) of posterior subcapsular cataract of grade 2 or higher, nuclear sclerosis of grade 3 or higher, or cortical cataract of grade 2 or higher or involving a minimum of center optic zone of 3-mm diameter.
22. Loss of functional vision in 1 or both eyes.
23. Diagnosed with ongoing rhinitis medicamentosa.
24. Known history of immune dysfunction including immune deficiency (IgG subclass deficiency or IgA deficiency) or autoimmune disease (eg, Wegener's granulomatosis, sarcoidosis) that requires immunotherapy. NOTE: Autoimmune conditions that do not require immunomodulatory therapy are not exclusionary.
25. Currently positive for COVID-19 or residual sinonasal symptoms from a previous COVID-19 infection within the past 6 months.
26. Past, present, or planned organ transplant or chemotherapy with immunosuppression within the past 5 years.
27. History or diagnosis of ciliary dysfunction (eg, cystic fibrosis, primary ciliary dyskinesia [Kartagener syndrome]).
28. Past or present systemic vasculitis (eg, granulomatosis with polyangiitis).
29. Evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments.
30. Pregnant or breast feeding. Females of child-bearing potential must test negative for pregnancy at the time of screening based on a serum pregnancy test and reverified at the time of enrollment based on a urine pregnancy test. Both male and female participants of reproductive potential must agree to use highly effective methods of birth control, throughout the study. (See **Appendix 14.3** for further information on contraception and pregnancy.)
31. Previously received an experimental treatment in another clinical study within 5 half-lives or 30 days (whichever is longer) of Screening visit or prior participation in another LYR-210 clinical trial.

32. Currently participating in another drug or device study.
33. Determined by the investigator as not suitable to be enrolled for reasons not already specified if the health of the participant or the validity of the study outcomes may be compromised.

3.4 Concomitant medications

Participants in the study are free to use any appropriate concomitant medications if medically warranted per treating physician's discretion. However, a standardized concomitant medications regimen is recommended during the run-in and treatment stages to avoid confounding the efficacy or safety assessments of LYR-210. Effective treatment will not be withheld from study participants solely for entering the study.

3.4.1 Permitted medications

At the discretion of the investigator, the following concomitant medications may be used in accordance with the restrictions described for each treatment:

- All participants will be provided with saline and instructions for daily intranasal saline irrigation as background treatment starting from screening through Week 24/EOS.
- If acute sinus infection is suspected at any time during the study, treatment with antibiotics or macrolides (for a maximum of 14 days) will be allowed after a clinic visit and according to the investigator's judgment.
- For severe acute nasal blockage lasting a minimum of 3 consecutive days: a course of oxymetazoline nasal decongestant spray for a maximum of 3 consecutive days and a total maximum of 10 days during the treatment period. Oxymetazoline cannot be used within 24 hours before CT assessments.
- Nonsedating oral antihistamine including second (eg, loratadine, cetirizine), third (eg, fexofenadine), and fourth generation or equivalent.
- Participants who have been on a stable regimen of inhaled corticosteroids or leukotriene receptor antagonist for a minimum of 3 months prior to the Screening visit should remain on the same dosage throughout the study. Inhaled corticosteroid use must be limited to a stable low- or medium-dose as defined by guidelines established by the 2020 Global Initiative for Asthma Management and Prevention.[12]
- Perennial allergic rhinitis (PAR) participants who have been on a stable regimen of a nonsedating oral or intranasal antihistamine including second (eg, loratadine, cetirizine, azelastine), third (eg, fexofenadine), and fourth generation or equivalent for a minimum of 3 months prior to the Screening visit should remain on the same dosage throughout the study.

3.4.2 Prohibited medications

Use of the following medications is prohibited for the duration of the study:

- Oral/ocular/intramuscular/intravenous/intranasal corticosteroids (except for systemic corticosteroids permitted as rescue medication for CRS or sino-nasal symptoms only and

stable low or medium dose of inhaled corticosteroids for underlying respiratory diseases, eg, COPD, asthma).

- Certain anti-allergy medications, including: first generation antihistamines (eg, diphenhydramine, dimenhydrinate, chlorpheniramine); leukotriene receptor antagonists (except for a stable regimen for asthma or another non-CRS indication), nasal cromolyn sodium or sodium cromoglycate, nedocromil sodium, atropine, ipratropium bromide, or guaifenesin.
- Oral or intranasal decongestants (except for short course of intranasal decongestants permitted for severe acute nasal blockage or administration during endoscopic, insertion and removal procedures).
- Inhaled anticholinergic medications (except for a stable regimen defined as no changes in the 3 months prior to screening and throughout study participation).
- Any potent cytochrome P-450 3A4 (CYP3A4) inhibitors (eg, ketoconazole and ritonavir).
- Any monoclonal antibody.
- Any allergen immunotherapy (except for a stable dose and regimen defined as no changes in the 3 months prior to screening and throughout study participation).
- Oral antifungal medication.

Participants who received prohibited medications will be considered to have a protocol deviation and may require withdrawal from the study.

3.4.3 Rescue medications and treatment

Rescue treatment is defined as, after randomization, participant receives SCS and/or is recommended for sinonasal surgery to relieve CRS symptoms.

The following rescue medication is recommended for worsening or uncontrolled severe CRS symptoms that results in the participant contacting the investigator who determines an initiation of rescue treatment is necessary any time during the study:

- A course of systemic corticosteroids. Typical indications include persistent sinus infection after an initial course of antibiotics while starting another course of antibiotics, uncontrolled sinus inflammation, or a flare-up of asthma. The dose, duration of use, and rationale for the use of oral or systemic corticosteroid must be recorded. (NOTE: oral/systemic corticosteroids for rescue are not provided by the study sponsor. The Investigator may prescribe, per their clinical judgement, any brand of systemic or oral corticosteroid that is authorized for use within their respective country.)
- Sinonasal surgery as rescue treatment according to the investigator's recommendation. The type and rationale for sinonasal surgery must be recorded.

3.5 Methods and procedures

The study-required activities and assessments are detailed below and are presented in tabular form in **Appendix 14.1**.

3.5.1 Eligibility assessment

Participants are considered eligible for this study if they meet **all** the inclusion criteria and **none** of the exclusion criteria as defined in **Section 3.3**. The principal investigator or sub-investigator at each investigational site will determine participant eligibility based on the inclusion/exclusion criteria.

3.5.2 Screening visit and run-in stage

After providing written informed consent, participants who are qualified to participate in this study, have failed previous medical management and are no longer on oral or intranasal corticosteroids will have an initial Screening visit. Assessments at Screening will include demographics and medical history, a limited physical examination (head, neck, ear, nose, and throat) with vital signs, hematology and chemistry tests, SNOT-22 questionnaire, serum pregnancy test for women of childbearing potential, COVID-19 test, sinus CT (or within 1 month of Screening), nasal endoscopy, ocular examination (visual acuity [VA], IOP, and slit lamp), eligibility assessment, and concomitant medications/procedures.

Immediately following the initial Screening visit, participants will undergo a run-in period of 2-4 weeks. During this run-in period, if a patient requires rescue medication, he/she will not be enrolled into the study. In the event of difficulties in scheduling Day 1 visit (randomization), the run-in period can be extended up to day 35 with sponsor/medical monitor approval. If a participant fails the initial screening, they are permitted to be rescreened one time under a new participant ID.

Participants who fail screening due to administrative reasons (eg, visit window) or abnormal lab value(s) may be allowed to repeat certain screening assessment(s) and re-establish eligibility. To minimize patient burden, the sinus CT, ocular exam and /or endoscopy do not need to be repeated for rescreened participants if done within the preceding month. Medical Monitor approval is required in such cases. Documentation of the decision and Medical Monitor approval will be filed in the participant's file.

Participants will be provided with saline and instructions for daily intranasal saline irrigation starting from the Screening visit throughout the study. Participants will be instructed to stop use of saline rinse approximately 24 hours prior to the scheduled sinus CT. Daily saline irrigation should then continue following the sinus CT. Daily saline irrigation procedures should adhere to the Investigator's prescribing information and local standards, as applicable. Beginning at least 14 days prior to LYR-210 administration/sham procedure on Treatment Day (Day 1), participants will record daily scores for each of the 4 cardinal symptoms (4CS) of CRS (nasal blockage/obstruction/ congestion, nasal discharge, facial pain/pressure, reduction/loss of sense of smell) on the electronic patient-reported outcomes (ePRO) questionnaire.

3.5.3 Day 1 visit, pretreatment

On Day 1, before the LYR-210/sham insertion procedure, participants will undergo the following assessments: urine pregnancy test for women of childbearing potential, COVID-19 test,

eligibility assessment, nasal endoscopy, baseline ePRO questionnaires (4CS, SNOT-22, PGIS, WPAI-SHP, FEQ, SF-36v2, EQ-5D-5L, MOS Sleep R), current medication listing, and AE reporting.

3.5.4 Randomization and blinding

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

To maintain the participant blind to treatment assignment, each participant will wear an eye mask (ie, blindfold) and headphones at the time of the LYR-210 administration/sham procedure. Except for the cases of spontaneous matrix dislodgement, participants should remain blinded to their treatment assignment (LYR-210 or control) until the study is completed. Participants will complete blinding questionnaires at Week 4 and Week 24.

The Sponsor will be blinded to participants' study treatment assignments until database lock for the study.

Due to the nature of the procedure, the treating investigator/surgeon will not be blinded to the treatment assignment. Efforts will be made to keep the study coordinator and other study staff blinded. A Site Blinding Plan will be implemented at each site to document the site-specific blinded and unblinded role.

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

3.5.5 Treatment procedure (active and sham)

On Day 1, after completing all required pretreatment assessments and randomization, participants will receive local anesthetic in the middle meatus and undergo a baseline nasal endoscopic assessment in preparation for the insertion procedure.

Participants who are assigned to the active treatment arm will have the LYR-210 administered bilaterally into the middle meatus according to the Sponsor's instructions for use. Participants who are assigned to the control arm, will undergo mock administration (ie, sham procedure) consisting of bilateral insertion of an unloaded applicator (without LYR-210 loaded) into the

middle meatus until the applicator tip touches the ethmoid bulla for a minimum of 20 seconds, followed by withdrawal of the applicator.

After the procedure, all participants will be instructed to continue daily saline irrigation and completion of daily 4CS ePRO.

The investigator will be allowed up to 2 attempts at LYR-210 administration or at the sham procedure per side. A treatment attempt is defined as an applicator of a LYR-210 or sham article is inserted to a participant's left or right nostril for an attempt of investigational product administration. If the investigator is unable to administer LYR-210 bilaterally or perform sham procedure successfully into both middle meatuses of a participant, the investigator will remove any LYR-210 already administered and treat the participant with any appropriate therapy, if necessary. The participant will be considered a **treatment administration failure**. Treatment administration failure participants will be followed within 7 (±2) days by telephone for AE and concomitant medication assessments. Treatment administration failure participants may be replaced to ensure adequate study enrollment.

3.5.6 Telephone/virtual visits

Participants will receive telephone/virtual follow-ups at Weeks 4 and 12 to record AEs and concomitant medications/procedures that they have had since their last follow-up assessment. Participants will also complete 4CS, SNOT-22, FEQ, and WPAI-SHP at these visits and women of childbearing potential will undergo a urine home pregnancy test.

3.5.7 Clinic follow-up visits

All participants will return to clinic for the scheduled follow up assessments at Weeks 8, 16, 20, and 24. Assessments at these visits include a urine pregnancy test for women of childbearing potential, COVID-19 test, nasal endoscopy, 4CS, SNOT-22, FEQ, concomitant medications/ procedures, and AEs. PGIS will also be assessed at Week 8 and 16 visits. Ocular examinations are required at Weeks 8 and 16.

At the Week 20 visit, after the visit assessments, all participants will undergo a LYR-210 removal or sham removal procedure. Participants who receive LYR-210 will have bilateral matrix removal using standard surgical tools. Control participants will undergo a sham removal procedure to remain blinded.

If **spontaneous dislodgement of LYR-210** occurs before the scheduled Week 20 visit in participants who receive LYR-210, participants are required to call the study clinic immediately to report the event. If a participant experiences dislodgement of 1 LYR-210 matrix, the participant will continue in the treatment phase. Any participant who undergoes a dual dislodgement is required to complete the assessments scheduled for the Week 20/ET visit, and subsequently the Week 24/End of Study (EOS) visit within 25-31 days of the ET visit.

Opacification of ethmoid sinuses will be assessed by CT scans obtained during screening (or using a historical CT scan taken within 1 month of screening) and within 7-14 days after Week 20/ET visit, unless medically contraindicated. Participants will be instructed to stop use of saline

rinse approximately 24 hours prior to the scheduled sinus CT. Daily saline irrigation should then continue following the sinus CT. If a participant is experiencing or recovering from a cold, acute exacerbation of nasal allergy, or URTI at the timing of follow up CT, the CT should be performed 4 weeks after resolution of the AE. If a participant requires SCS or sinonasal surgery as rescue treatment, the follow-up CT should be performed before receiving the rescue treatment.

3.5.8 End of study (Week 24)

All participants will undergo a Week 24 visit. If medically warranted per the treating physician's discretion (for example, needing sinonasal surgery as rescue treatment), early matrix removal may be performed at an unscheduled **early treatment termination (ET)** visit. Any participant who undergoes an ET visit is required to complete the assessments scheduled for the Week 20/ET visit, and subsequently the Week 24/ EOS visit within 25-31 days of the ET visit. ET participants are encouraged to continue completing ePRO assessments through the Week 24/EOS visit.

Week 24/EOS assessments include a urine pregnancy test for women of childbearing potential, COVID-19 test, hematology and chemistry tests, nasal endoscopy, ocular examination (IOP and slit lamp), all ePRO (4CS, SNOT-22, WPAI-SHP, FEQ, SF-36v2, EQ-5D-5L, PGIS. PGIC, MOS Sleep R), concomitant medications/procedures, and AEs. Participants enrolled in Germany will also undergo physical exam and vital signs at Week 24 /EOS. All participants will complete the End of Treatment (EOT) and blinding questionnaires at this visit.

At the conclusion of their study participation, participants will be followed per the local standard of care.

3.6 Data collection

Study data will be collected according to good clinical practices (GCP). Data will be entered into the study database by investigational site staff using the Medpace ClinTrak® EDC system. The data will be reviewed by Lyra Therapeutics staff, or designee, and any queries will be submitted to the investigational site for clarification. Patient-reported outcome questionnaires will be entered into an ePRO device (eg, electronic tablet), smartphone application, or computer URL directly by study participants.

3.7 Study assessments, endpoints, and activities

The study assessments are described below. Frequency of each assessment is found in the Schedule of Assessments (**Appendix 14.1**).

3.7.1 CRS Cardinal Symptoms ePRO

Enrolled participants will be asked to complete a daily ePRO questionnaire to assess the severity of the 4 individual cardinal symptoms of CRS (nasal blockage/obstruction/congestion, facial pain/pressure, anterior/posterior nasal discharge, and reduction/loss of smell).[9,10] Each symptom is scored on a 0-3 scale as follows: 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

In addition, the 4CS ePRO will capture use of daily saline irrigation by the participants.

3.7.2 SNOT-22 questionnaire

The SNOT-22 questionnaire is a 22-item disease-specific quality of life instrument validated for use in CRS.[13] Each symptom is scored on a 6-point scale as follows: 0 = no problem, 1 = very mild problem, 2 = mild or slight problem, 3 = moderate problem, 4 = severe problem, 5 = problem as bad as it can be. The total SNOT-22 score is the sum of the 22 items and can range from 0 to 110 with higher scores indicating worse symptoms. The MCID for the total SNOT-22 score has been determined to be 8.9 units. Additionally, the SNOT-22 scores can be divided into subcategories of rhinologic symptoms, extra-nasal rhinologic symptoms, ear/facial symptoms, psychological dysfunction, and sleep dysfunction[14].

3.7.3 Patient Global Impression of Severity (PGIS)

Participants will be asked a single question to rate their severity of CRS-related symptoms over the past 7 days on a 5-point ordinal scale: none, mild, moderate, severe, very severe.

3.7.4 Patient Global Impression of Change (PGIC)

The PGIC is a self-assessment of the participant's overall change in CRS-related symptom severity compared to pretreatment. The PGIC 7-point scale range is as follows: very much better, much better, a little better, no change, a little worse, much worse, very much worse.

3.7.5 Work Productivity and Activity Impairment (WPAI-SHP) questionnaire

The WPAI-SHP is a questionnaire to measure the effect of a specific health problem on the participant's work productivity and normal daily activities.[15] Employed participants report absenteeism, (time absent from work) and presenteeism (time at work but not fully productive), which are calculated to a work productivity index. All participants report time away from normal activities.

3.7.6 General quality of life questionnaires (SF-36v2, EQ-5D-5L)

Participants will complete 2 general quality of life questionnaires, the SF-36v2 and EQ-5D-5L.

The SF-36v2 health survey captures participants' perceptions of their health and well-being in 8 dimensions: physical functioning, physical limitations, emotional limitations, social functioning, bodily pain, general health, and mental health.[16] The items of the SF-36v2 are transformed and summed to a norm-based scale (mean=50, SD=10) for each physical and mental component domain in which higher scores indicate a better health-related quality of life status.

The EQ-5D-5L descriptive system comprises the following 5 dimensions, each describing a different aspect of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/ depression.[17] Each dimension has 5 response levels of severity: no problems, slight problems, moderate problems, severe problems, 'unable to'/extreme problems. In addition, the EQ-VAS records the overall current health on a vertical visual analogue scale, where the anchors are labelled 'the best health you can imagine' and 'the worst health you can imagine'.

3.7.7 Sleep questionnaire (MOS Sleep-R)

MOS Sleep-R is a 12-item instrument with a 4-week recall designed to measure key aspects of sleep, such as disturbance, adequacy, somnolence, and quantity.[18] The score ranges from 0 to 100, lower scores indicating better sleep and higher scores indicating worse sleep. The scale yields a sleep problem index and scores on the following 6 subscales: sleep disturbance, snoring, shortness of breath or headache, sleep adequacy, sleep somnolence, and sleep quantity.

3.7.8 Happiness questionnaire (FEQ)

The Fordyce Emotions Questionnaire (FEQ)[19] asks participants to rate how happy or unhappy they are on a 0 (extremely unhappy) to 10 (extremely happy) scale. They also report the percentages of time that they feel happy, unhappy, and neutral.

3.7.9 End-of-treatment questionnaire

The EOT questionnaire is a Sponsor-specific questionnaire designed to evaluate participants' experience with the study treatments.

3.7.10 Blinding questionnaire

To assess the adequacy of the blinding procedures, participants will complete a participant blinding questionnaire at various timepoints in the study. The participant blinding questionnaire is a 5-category response scale: 1 = I strongly believe I received the new treatment (LYR-210), 2 = I somewhat believe I received the new treatment (LYR-210), 3 = I don't know which treatment I received, 4 = I somewhat believe I received the placebo (the sham procedure), 5 = I strongly believe I received the placebo (the sham procedure).

3.7.11 Nasal endoscopy

Nasal endoscopies will be performed to evaluate presence/absence of and grade of nasal polyps and to document presence of epistaxis, mucosal erosion or ulceration, perforation, and any other local adverse effects. The endoscopic assessment of nasal polyps for eligibility will be conducted at Screening. A central reviewer will evaluate the screening endoscopy to determine presence/ absence of polyps and polyp grading (see **Appendix 14.2** for the nasal polyp grading scale), if applicable. The central assessment will be used for randomization stratification. Participants are required to wear a blindfold and headphones during any endoscopy examination to maintain their blind to treatment assignment. All nasal endoscopies will be recorded and uploaded to the Central Imaging Core Lab's repository. Nasal endoscopies will also be reviewed at the Central Imaging Core Lab for evaluation of presence of epistaxis, mucosal erosion or ulceration, perforation, and any other local adverse effects.

3.7.12 SCS rescue

Systemic corticosteroids (SCS) for rescue treatment of CRS or for another reason that are prescribed to the participant are to be recorded in the eCRF. If possible, an endoscopy should be performed before starting treatment with SCS. The participant should continue with the study treatment and follow-up visits per protocol. The investigator (or designee) will record the dates and dosing information (dosage form, daily dose, duration, name of drug) on the appropriate

page(s) of the eCRF. Indication for SCS use will also be captured by selecting 1 or more of the following categories:

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

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

3.7.13 Sinonasal surgery (actual or planned) for CRS

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

If the surgery is to be performed during the study treatment period, the study treatment will be discontinued and all procedures/assessments for the ET and EOS visits will be completed prior to the surgery. The participant will be discontinued from the study.

3.7.14 Sinus CT scoring

Opacification of the ethmoid sinuses will be assessed using CT images. Two scoring methodologies will be employed to assess sinus opacification – Zinreich modified Lund-Mackay and 3-D volumetric analysis. The Zinreich modified Lund-Mackay scoring system uses a 0-5 scale for scoring each sinus.[20] The scoring is based on the percentage of sinus opacification as follows: 0 = 0%, 1 = 1% to 25%, 2 = 26% to 50%, 3 = 51% to 75%, 4 = 76% to 99%, and 5 = 100% or completely occluded. The left and right sides are graded, and the sum is the total score out of maximum of 20. 3-D volumetric scoring will involve evaluations of each slice of 3-D coronal CT sequences and summing of all the slices to create a volumetric score ranging from 0% to 100%. Sinus CT opacification scoring will be performed by Medical Metrics Inc. imaging core lab.

3.7.15 Conversion to nonsurgical candidacy

Participants will be deemed as having converted to a nonsurgical candidate if they do not undergo sinonasal surgery (planned or actual) during the treatment stage and if they meet the following criteria at Week 24:

- 3CS score ≤4, or
- No disease in ethmoid sinuses on CT (Zinreich score=0)

3.7.16 Physical examination

A limited physical examination including a careful assessment of the head, eyes, ears, nose and throat will be performed per the Schedule of Assessments (**Appendix 14.1**). Height (cm), weight (kg) and body mass index (BMI) will be measured at Screening.

3.7.17 Vital signs

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

3.7.18 Ocular examination

Ophthalmologic assessments will include measurement of corrected VA, IOP, and a slit-lamp examination of the anterior segment of the eyes to identify new or worsening cataract development. The cataract assessment will be conducted according to the Simplified Cataract Grading System authored by the World Health Organization Cataract Grading Group.[21] Participants will be dilated with mydriatics following the WHO guidance for cataract assessment. IOP may be measured using Goldmann applanation tonometer, noncontact tonometer, or tono-pen; however, it is recommended that the same method be used for consistency across serial assessments on a given participant. A clinically significant increase of IOP is defined as IOP in 1 or both eyes >23 mm Hg or an increase of IOP from baseline in 1 or both eyes ≥10 mm Hg. Assessments will be conducted by an ophthalmologist/optometrist who is blinded to the participant's treatment assignment.

3.7.19 Laboratory Evaluations

Hematology assessments will include a leukocyte count with differential (neutrophils, eosinophils, lymphocytes, monocytes, and basophils), erythrocytes, hematocrit, hemoglobin, and platelet count. Clinical blood chemistry laboratory analytes will include electrolytes (sodium, potassium, chloride, and bicarbonate), blood urea nitrogen, serum creatinine, glucose, total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, uric acid, total protein, albumin, calcium, magnesium, and phosphate. Testing will be performed at the central lab, [redacted].

Pregnancy testing is required for all female participants of childbearing potential. It will include a serum pregnancy test at Screening and a urine pregnancy test at all subsequent visits.

All biological samples will be collected and analyzed per protocol and no samples will be stored for future research not outlined in this study protocol.

4. Risk/Benefit Analysis

4.1 Benefits

Participation in this study is voluntary. The enrolled participants are adults with CRS who have failed previous medical management and have limited treatment options. Anticipated benefits over existing medical therapies for participants in this study are increased control of and local delivery of a known effective anti-inflammatory corticosteroid drug (MF) to a targeted area that is difficult to reach by intranasal sprays for an extended duration of time without the need for

daily use compliance. Participants are expected to experience decreased sinonasal symptoms with increased convenience, as well as improvement of their general physical and mental health.

4.2 Potential risks

4.2.1 COVID-19 exposure and infection

There is a potential risk for exposure to and infection with COVID-19 for participants during the procedures or when attending clinic visits. As specified in exclusion criterion 3, participants infected with COVID-19 will be excluded from participation. Participants who test positive for COVID-19 after enrollment will be followed remotely until they are able to resume office visits.

Additionally, constraints at a clinical site due to COVID-19 may cause a temporary halt to enrollment at a clinical site, which could increase the total study time.

Recent studies have shown that visiting the hospital does not appear to impose a risk of contracting COVID-19. In a recently published retrospective case-control study from 39 US emergency departments, it was reported that colocation with COVID-19 patients was not associated with acquisition of COVID-19.[22] These results showed that patients who visit the hospital are not likely to be at increased risk of contracting COVID-19. A similar concern is of acquiring COVID-19 from healthcare workers, especially in their presymptomatic phase. This risk was also shown to be low; in a recent study, less than 1% of patients exposed to an infected healthcare worker developed COVID-19.[23]

4.2.2 LYR-210 administration or removal procedures and endoscopy procedures

The risks associated with any general endoscopic procedures (within 24 hours of procedure) are relevant to the administration or removal of the LYR-210 drug matrix. The possible expected AEs and the highest incidence rates reported in clinical studies of similar products and/or Lyra clinical studies that are related to endoscopic procedures are summarized in **Table 2**. Refer to the LYR-210 Investigator's Brochure.

Table 2. Summary of Expected Adverse Events Associated with LYR-210 Administration or Removal Procedure and Endoscopy Procedures

Incidence rate >5% and ≤10% in LYR-210 procedures		
Procedural headache	Epistaxis	
Incidence rate >0% and ≤5% in LYR-210 procedures		
Dizziness	Ear discomfort	Facial discomfort
Facial pain	Nasal congestion	Nasal discomfort
Ocular discomfort	Oropharyngeal pain	Parosmia
Postprocedural discomfort	Postprocedural hemorrhage	Postprocedural swelling
Presyncope	Rhinalgia	Rhinorrhea
Sneezing	Upper respiratory tract infection	
Incidence rate >5% and ≤10% in endoscopy procedures		
Procedural headache		
Incidence rate >0% and ≤5% in endoscopy procedures		
Dizziness	Epistaxis (moderate)	Facial pain
Nasal congestion	Nasal discomfort	Parosmia
Postprocedural discomfort	Presyncope	
Rare events without incidence rates reported but potential to endoscopy procedures		

Nasopharyngitis	Pharyngitis

4.2.3 Exposure to mometasone furoate or bioabsorbable nasal implant

The possible expected adverse reactions and the highest incidence rates reported in randomized and controlled clinical studies of MF drug products (Nasonex®,[24] Asmanex® Twisthaler®,[25] Propel®,[26] and Sinuva®[27]) and/or Lyra clinical studies[28] are summarized in **Table 3**. Refer to the LYR-210 Investigator's Brochure.

Table 3. Summary of Adverse Reactions Associated with Mometasone Furoate or Bioabsorbable Nasal Implant

Incidence rate >40% and ≤60%		
Headache	Rhinitis	Upper respiratory tract infection
Viral infection		
Incidence rate >20% and ≤40%		
Candidiasis	Epistaxis/blood-tinged mucus	Musculoskeletal pain
Pharyngitis		
Incidence rate >10% and ≤20%		
Alteration of HPA axis/adrenal insufficiency (endocrine)	Arthralgia (joint pain)	Back pain
Coughing	Dysmenorrhea	Dyspepsia (indigestion)
Dysphonia	Earache	Fatigue
Flu-like symptoms	Nasal congestion	Nasal odor
Nasal pharyngitis	Sinusitis	
Incidence rate >5% and ≤10%		
Abdominal pain	Diarrhea	Facial pain
Flatulence	Lower respiratory tract infection	Menstrual disorder
Myalgia (muscle pain)	Nasal discomfort	Nausea
Pain	Rhinorrhea	Sinus congestion
Sneezing		
Incidence rate >0% and ≤5%		
Abnormal hepatic function	Adverse drug reaction (rash)	Catarrh
Chest pain	Conjunctivitis	Dizziness
Dry throat	Ear infection	Edema
Facial discomfort	Gastroenteritis	Hypertension
Increased viscosity of upper respiratory secretion	Insomnia	Nasal burning
Nasal dryness	Nasal irritation	Parosmia
Postprocedural hemorrhage	Postprocedural swelling	Presyncope
Pruritus	Pyrexia (fever)	Rhinalgia (nose pain)
Toothache	Urinary tract infection	Vomiting
Rare events without incidence rates reported but potential to MF or bioabsorbable nasal implants		
Anaphylactic reaction	Bone necrosis	Cardiovascular complications
Cataract	Cushing syndrome	Eosinopenia (reduction of eosinophils)
Glaucoma	Hyperglycemia/Type 2 diabetes	Hypokalemia
Hypogammaglobulinemia	Impaired local wound healing	Metabolic complications (high blood sugar, diabetes mellitus)
Myopathy	Nasal ulcer (mucosal erosion, ulceration, perforation)	Osteoporosis/Bone fracture
Pneumonia	Preterm birth	Psychiatric symptoms (mood changes, memory deficits)
Reduced bone mineral density	Septum perforation	Sinus perforation

Skin complications (acne)	Susceptibility to infection	Swallowing or aspiration of implant or fragments
Weight gain (obesity)		

CRS is primarily a quality-of-life disease (as opposed to a life-threatening disease).[29] The extensive clinical and nonclinical data from existing marketed medical devices and MF containing pharmaceutical products support the safety of the LYR-210 drug matrices. In addition, data from nonclinical studies with the Lyra's rabbit matrix and the clinical studies of the LYR-210 drug matrices support product safety. Therefore, fatal and life-threatening 'suspected' SAEs are not expected as a result of the use of the LYR-210 drug matrices.

4.3 Risk mitigation

The protocol has been developed to minimize the risks for the participant in several ways. Sample size was calculated to expose the smallest number of participants while still being able to adequately test the study hypothesis. The procedure will be performed by practicing otolaryngologists experienced in endoscopic procedures and trained on the administration and removal of the LYR-210. Investigators are expected to comply with the Sponsor's IFU for the LYR-210.

The safety of MF, the active ingredient in LYR-210, has been demonstrated across a range of commercially approved nasal and inhaled dosage forms for the treatment of allergic rhinitis, asthma, nasal polyps after ethmoid surgery, or to maintain patency after sinus surgery. The bioabsorbable polymers in the LYR-210 have a long history of use in bioabsorbable medical sutures such as Vicryl® (PLGA 10:90) and Monocryl® (PGCL 75:25) from Ethicon (Bridgewater, NJ, USA) and the PLCL suture from Catgut GmbH (Markneukirchen, Germany). These polymers are also used extensively as inactive ingredients for sustained release of parenteral drugs.[30]

The participant selection criteria have been designed to minimize risk by excluding participants who have comorbidities or conditions that may put the participant at higher risk for LYR-210 placement. Because there are no clinical data on the LYR-210 System in pregnant women, women of childbearing potential will be required to take a serum pregnancy test at the initial Screening visit and a urine pregnancy test at all subsequent visits during the treatment phase. If the participant shows a positive pregnancy test after randomization, please refer to Section 7.8 (Exposure in Utero). Concomitant medications/procedures that could increase risk and confound study results are not permitted during the study. Participants will be tested for COVID-19 at Screening and at each clinic visit. Participants testing positive at Screening will be excluded; participants testing positive during the study will be followed remotely until they are able to resume office visits. Finally, the participants will be closely monitored by frequent follow-up visits during the study.

Because the LYR-210 System is investigational, there may be other side effects that cannot be predicted or foreseen. Unknown side-effects could be potentially serious and long lasting,

permanent, or even fatal. It is the conclusion of this risk analysis that potential benefits to participants in the clinical study outweigh the identified risks. Participants will be informed of these risks and the potential benefits through the informed consent process as a condition of study enrollment.

5. Investigational Product Information

5.1 Investigational product description

The LYR-210 System is a combination product comprised of a single-use applicator, preloaded with an anti-inflammatory drug matrix. LYR-210 contains mometasone furoate (MF), an active ingredient in multiple FDA-approved products indicated for therapeutic and prophylactic management of seasonal and perennial allergic rhinitis (AR), nasal polyps, a phenotype of CRS disease, and asthma. LYR-210 is designed to gradually soften over time and is made of bioabsorbable polymers that have been used as components of approved pharmaceutical drugs and/or medical devices.

Each LYR-210 contains a total MF dose of 7500 µg. LYR-210 is intended to be administered bilaterally into the middle meatus by an otolaryngologist under endoscopic visualization using the provided single-use applicator. Once administered, each LYR-210 is designed to gradually deliver sustained doses of MF to the inflamed mucosal tissue over a 24-week resident time. Bilateral placement of LYR-210 is designed to deliver a total dose of 15,000 µg MF over the 24 weeks, or an average daily dose of 89 µg MF per human participant (or approximately 45 µg MF per nostril).

LYR-210 has a tubular braid configuration with a uniform diamond pattern throughout and an uncompressed dimension of 13 mm in diameter and 10 mm in length in its unconstrained state. It is designed to be self-retaining against the mucosal tissue to allow effective drug transfer for up to 24 weeks. The matrix is comprised of a base structure and a drug formulation layer. The base structure is composed of poly(L-lactide-co-glycolide) and poly(L-lactide-co-ε-caprolactone) elastomer to provide 3-dimensional structure and elasticity. The drug formulation layer consists of an active ingredient, MF, embedded in the inactive ingredients containing poly(L-lactide-co-ε-caprolactone) and poly(L-lactide) to control the release rate of MF.

5.2 Investigational product management

The Sponsor will supply quantities of LYR-210 and the sham procedure articles sufficient to allow completion of the study. The investigator or designee must maintain accurate records to document the disposition of all products received by the clinical site. Required information includes the kit numbers received, date received, date used, product description, and a participant identifier for product that has been administered. Investigational sites will use a form to document product disposition, which will be reviewed by the study monitor during routine monitoring visits. When all study procedures are complete, any unused investigational product will be returned to Sponsor or discarded per Sponsor's authorization along with a final

accountability log. The accountability log must document the disposition of all investigational product, including those that have been returned to the Sponsor.

5.3 Product return

All drug matrices administered to a participant are to be removed, as indicated in the Schedule of Assessments (**Appendix 14.1**). All study product that are not administered into a participant must be returned to the Sponsor or designee or discarded per Sponsor authorization. Applicators successfully used for administration may be disposed on site after the study procedure is complete.

The investigator will inform the Sponsor of any complaints or malfunctions during the study. The Sponsor will investigate all product complaints and malfunctions.

Instructions for returning product will be provided to the sites by the Sponsor.

5.4 Packaging, labeling, and storage

The investigational products (LYR-210 and Sham) will be packaged and labeled, as required by regional legislation and industry guidelines. The LYR-210 System and the Sham product are individually packaged in a foil pouch which is sterilized and placed within a shelf carton.

The investigational products should be kept in a locked storage and stored in the original packaging to protect from moisture and light and at controlled room temperature (15 °C to 25 °C [59 °F to 77 °F]), with excursions permitted up to 30 °C (86 °F, inclusive).

The Sponsor or designee will ship study products to the sites as needed. Specific instructions for ordering product will be provided to the sites. Traceability of LYR-210 or the sham procedure articles will be achieved by assigning each matrix and applicator a unique kit number.

6. Monitoring Procedures

Sponsor personnel or qualified designees will monitor the clinical study in a manner consistent with 21 CFR 312, Subpart D, Responsibilities of Sponsor and Investigators, and other applicable local or national regulations. Specific monitor contact information will be provided separately from the protocol.

6.1 Investigational site monitoring

An appropriate representative of the Sponsor or designee (study monitor) will verify participant data and ensure compliance with GCP, clinical protocol, and other study requirements, according to the guidelines set forth in the monitoring standard operating procedures (SOPs) and applicable regulatory requirements. The study monitor will ensure the investigator continues to have appropriate staff and facilities to conduct the clinical study safely and effectively. Monitoring will be performed in accordance with a prespecified monitoring plan that is in compliance with applicable SOPs. Upon reasonable notice, the investigator and institution agree to provide the Sponsor representatives or designees and applicable regulatory authorities with direct access to

source documents relevant to the study for Sponsor quality assurance audits or inspections by the regulatory authorities.

Completed CRFs will be verified by the study monitor at the investigational sites at regular intervals throughout the study. The investigator will allow the monitor and/or representative of the Sponsor, and any regulatory body to review and inspect the study files, participant CRFs, participant medical records and other study-related documents, as required.

All CRFs will be reviewed for completeness and clarity. Missing or unclear data will be investigated by the study monitor and will be retrieved, clarified, and completed by study personnel as necessary throughout the study. The Sponsor or their authorized representative may request additional documentation from the investigator such as physician procedure notes or physician written summaries when AEs are observed and reported.

6.2 Investigators

The Sponsor will select investigators with appropriate training and experience to participate in this clinical study. Sites will be selected based upon the qualifications of the principal investigator at the site as well as other parameters, including proven ability and infrastructure to perform clinical studies. The complete list of all site investigators and the relevant clinical sites will be maintained within the trial master file (TMF).

In addition to specific training relating to use of the investigational product, the training of the investigator and appropriate clinical site personnel will be the responsibility of the Sponsor (or designee) and may be conducted during an investigator meeting, a site initiation visit, or other appropriate venue. Training will include, but not be limited to, the clinical protocol, IB, CRF completion, GCP, and clinical study personnel responsibilities. All training will be documented prior to engaging in study-related activities.

The co-lead investigators for the study are:

[redacted]

7. Adverse Event Definitions and Reporting

7.1 Adverse events and treatment-emergent adverse events

An AE is any untoward medical occurrence (signs, symptoms, abnormal laboratory findings) in a participant regardless of relationship to the investigational product or procedure. Each AE is either expected or unexpected as described below. The site is required to report AEs that occur during the study. These events shall also be classified according to the suspected causality by the study investigator.

Throughout the course of the study, all efforts will be made to remain alert to possible AEs or untoward findings. If AEs occur, the first concern will be the safety and welfare of the participant. Appropriate medical intervention will be undertaken. Any AE observed by the investigator or reported by the participants, whether or not ascribed to the investigational procedure or product, will be recorded on the participant's AE case report form (CRF). A new AE CRF will be used for each AE. All on-going AEs that result in early termination (ET) from the study or are deemed to be study product- or procedure-related by the site investigator will be followed until resolution or stabilization of the AE.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, and relationship to study product, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the participant upon indirect questioning.

A **treatment emergent AE (TEAE)** is an AE that occurs or worsens on or after initiation of the LYR-210 administration/sham procedure.

7.2 Serious adverse events

An AE or adverse reaction is considered a serious adverse event (SAE) if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE (Note: an AE or adverse reaction is considered "life-threatening" if, in view of either the investigator or Sponsor, its occurrence places the participant at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.)
- Requires hospitalization or prolongation of existing hospitalizations (Note: any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons, eg, no place to stay, live too far away to come for hospital visits, respite care, will not be considered inpatient hospitalization.)
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event (Note: important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above [eg, anaphylaxis]).

The investigator will assess each AE for its seriousness. Please note the term "serious" AE is not synonymous with a "severe" AE, which may be used to describe the intensity of an event experienced by the participant (**Section 7.4**). Any treatment-related SAE (**Section 7.3**) will be followed until resolution of the event, or until the participant withdraws from the study.

7.3 Relationship to investigational product or study procedure

The relationship between an AE and the LYR-210 study drug product or LYR-210 administration/sham procedure (within 24 hours) will be determined by the investigator based on his or her clinical judgment and the following definitions:

- **Definitely related**: The AE follows a reasonable temporal sequence from administration of the investigational product or the study procedure and the AE follows a known or expected response pattern to the investigational product or study procedure.
- **Probably related**: The AE follows a reasonable temporal sequence from administration of the investigational product or the study procedure and is unlikely to have been produced by other factors (eg, disease, concomitant medications).
- **Possibly related**: The AE follows a reasonable temporal sequence from administration of the investigational product or the study procedure and the AE follows a known or expected response pattern to the investigational product or study procedure but could readily have been produced by several other factors.
- **Unlikely related**: The AE is temporally distant from administration of the investigational product or the study procedure that makes a relationship improbable and the AE could readily have been produced by several other factors.
- **Not related**: An AE for which sufficient information exists to indicate that the etiology is unrelated to the investigational product or study procedure. One or more of the following variables apply:
    - The AE does not follow a reasonable temporal sequence following administration of the investigational product or study procedure
    - The AE is readily explained by the participant's clinical state or other therapies

The following factors should be considered when evaluating relatedness:

- The temporal sequence from study drug administration – the event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases – each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the participant may have.
- Concomitant drug – the other drugs the participant is taking or the treatment the participant receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug – clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses – the exposure to stress might induce adverse changes in the participant and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug – the known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

7.4 Severity of adverse events

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the investigator or reported to him/her by the participant. The assessment of severity is made irrespective of relationship to study procedure or product or seriousness of the event and should be evaluated according to the following scale:

- **Mild**: Event is noticeable to the participant but is easily tolerated and does not interfere with the participant's daily activities.
- **Moderate**: Event is bothersome, possibly requiring additional therapy, and may interfere with the participant's daily activities.
- **Severe**: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the participant's daily activities.

7.5 Expectedness of serious adverse events

The expectedness of a product or procedure-related SAE should be determined by the Sponsor based upon existing safety information about the investigational product or study procedure using these explanations:

- **Unexpected**: An SAE that is not listed in the study protocol, investigator's brochure (IB), or prescribing information for the registered formulation of MF or is not listed at the specificity or severity that has been observed.
- **Expected**: An SAE that is listed in the IB or prescribing information for the registered formulation of MF or is listed at the specificity and severity that has been observed.

7.6 Reporting adverse events

AEs are to be collected from the time a participant signs the informed consent form (ICF) until the completion of all follow-up visits. At each office or telephone/virtual visit during the study, AEs that have occurred since the previous office visit must be recorded. All participants will be evaluated for AEs or complications associated with the study procedure or the investigational product. The investigator will determine the severity and relationship of each event, as defined above. AEs observed during this study, regardless of severity or relationship to the study procedure or investigational product, will be recorded on the appropriate CRF.

Documentation of all new AEs or changes in previously reported AEs will be recorded. Pre-existing diseases or conditions will not be reported as AEs unless there has been a substantial increase in severity or frequency of the problem, which cannot be attributed to the expected progression of the disease or condition.

The investigator will review the results of all clinical and laboratory tests as they become available. For each laboratory test result, the investigator will ascertain whether the result represents an abnormal (ie, clinically significant) CFBL for that individual participant. If this laboratory test result is determined to be a clinically significant abnormal CFBL for that participant, the value will be considered to constitute an AE.

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) throughout the study.

7.7 Reporting serious adverse events

7.7.1 Initial reports

All SAEs occurring from the time of informed consent until the completion of all follow-up visits must be reported to the Sponsor or designee within 24 hours of the knowledge of the occurrence. After the completion of each follow-up visit, any SAE that the investigator considers related to study drug must be reported to the Sponsor or designee.

To report the SAE, the investigator or designee must complete the AE form with the SAE information electronically in the electronic data capture (EDC) system for the study. When the form is completed, safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets seriousness criteria and it is not possible to access the EDC system, the investigator or designee should send an email to the safety contact (as indicated by the Sponsor) and fax/email the completed paper SAE form to the safety contact within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered as soon as possible.

[redacted]

7.7.2 Follow-up reports

For participants with an SAE, the investigator must continue to follow the participant until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the participant dies.

Within 24 hours of receipt of follow-up information, the investigator or designee must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to the safety contact by fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

7.8 Exposure in utero

If a participant becomes pregnant during the treatment phase, the matrix will be removed (or sham removal) and the participant will continue study follow-up through Week 24. However, the investigator must continue to follow the participant until the completion of the pregnancy, including the outcome and the condition of the newborn at 8 weeks postpartum (if applicable).

A pregnancy is not considered to be an AE or SAE; however, it must be reported within 24 hours of knowledge of the event. Sponsor or designee will then provide the Exposure In Utero (EIU) form to the investigator/site for completion and return.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to Sponsor or designee. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

7.9 Expedited reporting

Any serious and unexpected suspected adverse reactions (SUSARs) and unexpected adverse device effect (UADE) will be reported by the Sponsor or designee to the appropriate regulatory authorities, including the Eudravigilance database, in accordance with applicable local guidelines.

The SUSARs meet all the following criteria:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

A UADE is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants. Device deficiency reporting will be performed if applicable per regulations.

7.10 Safety monitoring

Participants will be closely monitored throughout the trial with high priority for participant safety. The Sponsor will establish a Safety/Medical Monitoring team early in the study. The team will be responsible for developing a Safety/Medical Monitoring Plan (MMP), which will define in detail the objectives, scope, and roles and responsibilities of each team member involved.

Participant safety monitoring encompasses, but is not limited to, providing advice to sites and the project team for protocol-related issues, providing input into decisions requiring medical advice and routine safety monitoring of the study, review of serious and nonserious AEs, various data

listings, lab results, vital signs, and other clinical data. Reviews of blinded aggregate data as well as individual participant data may be undertaken to identify outliers and trends that may impact safety of the participant and consistency of data.

7.11 Stopping rules for individual participants

Dosing for an individual participant will be stopped and drug matrices removed if the Sponsor and/or Investigator determine that either of the following have occurred in that participant:

- An unexpected product-related SAE per causality and SAE definitions in Sections 7.2 and 7.4 that warrants matrix removal.
- Development of cataract where other potential factors (such as age) are not likely to have played a role or persistent clinically significant increase in IOP that, in the opinion of the Sponsor or Investigator, represent a safety concern.
- If a participant becomes pregnant during the treatment phase, the matrix will be removed (or sham removal)

8. Protocol Deviations

The investigator agrees to conduct the study according to the clinical protocol, local regulatory authority regulations, GCP, and any conditions of approval imposed by their IRB/EC and agrees that all persons delegated to perform study procedures will do so as well.

A protocol deviation is a failure to comply with the requirements specified within this clinical study protocol. Examples of protocol deviations may include enrollment of a study participant who does not meet all the inclusion/exclusion criteria specified in the protocol, use of prohibited medications or therapies, visits performed outside of the protocol-specified visit window and missed study assessments or visits. All protocol deviations should be documented and explained. Major/CSR reportable protocol violations are defined as those that could impact the performance evaluation such as enrollment of an ineligible participant, missing key data, administration of an unauthorized treatment. All participants with protocol deviations will continue to be followed for safety and performance assessments unless the Sponsor determines that the participant should be discontinued from the study.

An investigator is not permitted to deviate from the protocol unless there are concerns of participant's safety. Under emergency circumstances, deviations from the protocol to protect the rights, safety, and well-being of human participants may proceed, but such deviations must be documented and reported to the Sponsor and the IRB/EC (as required) as soon as possible and **within 24 hours**.

If an investigator is found to be repeatedly noncompliant with the Clinical Trial Research Agreement (CTRA), study protocol, or any other conditions of the clinical study, the Sponsor at their sole discretion, will either undertake remedial measures to secure compliance or terminate the investigator's participation in the study.

9. Statistical Considerations

9.1 Study hypothesis

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

H_0: $\mu L = \mu C$

vs

H_1: $\mu L \neq \mu C$

where μL and μC are true mean CFBL in 3CS at Week 24 for participants without nasal polyps receiving the LYR-210 (7500 μg) treatment and the control (sham) treatment, respectively.

9.2 Sample size estimation

Per the null and alternative hypotheses described above, 2:1 randomization (LYR-210:control), in the participants without polyps, the residual standard deviation (SD) from the ANCOVA model (adjusted for baseline severity and using worst possible score imputation for treatment with SCS or sinonasal surgery [actual or planned]) is 2.08 and an observed mean difference of 1.61 (3.89 unit decrease from baseline for treated and 2.28 unit difference from baseline for control). The observed effect size is therefore 0.77 SD units. With a sample size of 150 participants (n=50 control and n=100 LYR-210), alpha = 0.05, and power of 0.95, we will be able to detect an effect size of 0.63, which represents a mean difference of 1.31. This effect size is 18% smaller than the observed difference in the Phase 2 study (1.61 versus 1.31 3CS mean change scores). For the first key secondary endpoint (an analysis of the primary endpoint in all participants; n=60 control and n=120 LYR-210), the study will have 95% power to detect an effect size of 0.57, which represents a mean difference of 1.19.

9.3 Statistical analysis

This section provides a summary of the statistical methods. Detailed specifications of the statistical methods will be described in the SAP.

9.3.1 Analysis sets

- Safety analysis set: all randomized participants who successfully received the study treatment (LYR-210 or control) on Day 1. Participants will be analyzed according to the treatment received. This is the primary analysis set for assessment of safety.
- Intention-to-treat (ITT) analysis set: all randomized participants who successfully received the study treatment (LYR-210 or control) on Day 1. The primary analysis will be conducted for ITT Analysis Set without nasal polyp while the remaining efficacy analyses will be conducted for ITT Analysis Set. Participants will be analyzed according to the treatment they were assigned to at randomization.
- Per-protocol (PP) analysis set: all randomized participants who successfully received the study treatment on Day 1, have post-Day 1 efficacy assessments, and are without any matrix dislodgement before Week 13 or important protocol deviations that might affect the accuracy and/or reliability of efficacy assessments.

9.3.2 Analysis methods

Data collected in this study will be presented using listings, summary tables, and figures. Continuous data will be summarized by treatment group using the following descriptive statistics: the number of observations (n), mean, SD, median, minimum, and maximum. Categorical data will be summarized by treatment group as number and percentage of participants in each category. Individual participant's data will be presented in listings.

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

Unless otherwise specified, all hypothesis tests will be conducted at a 2-sided significance level of 0.05 and all confidence intervals will be constructed 2-sided with a confidence level of 95%.

The primary analysis method for the primary endpoint will be mixed models repeated measures analysis of covariance (MMRM) with treatment group, and week as factors, with baseline measurement as covariate, an interaction of treatment by week and an interaction of baseline measurement by week. The primary analysis will be conducted according to the primary estimand that is specified in Table 1. Sensitivity analysis will be conducted to assess the impact of the missing at random assumption in the MMRM. Additionally, supplement analyses will be conducted to assess the robustness of the primary analysis according to the prespecified plan in the SAP. The LS mean change for each treatment group, the LS mean difference between treatment groups, as well as the corresponding 95% confidence intervals and p-values will be reported.

Changes from baseline to continuous endpoints will be analyzed using an MMRM or ANCOVA as appropriate which will be prespecified in the SAP.

Time-to-event endpoints will be analyzed using the Kaplan-Meier (K-M) method. The K-M curves will be compared between treatment groups using the log-rank test.

Responder endpoints (eg, improvement of ≥8.9 in SNOT-22 and improvement of ≥1 point, ≥2 points, ≥3 points in 3CS) will be analyzed using the CMH test controlling for geographic region and nasal polyp status. Participants who receive SCS for any reason and/or are indicated for sinonasal surgery will be considered nonresponders for time points after SCS use or surgery. Unless otherwise specified, participants with missing data will be included as nonresponders.

9.3.3 Methods for handling missing data

All efforts will be made to minimize missing data. Participants who discontinued treatment early are encouraged to continue completing ePRO assessments through Week 24. Data collected after treatment discontinuation will be included in the analysis. Details will be specified in the SAP.

9.3.4 Participant disposition and demographic characteristics

Participant disposition, including analysis set assignment and reason for discontinuation, will be summarized for all randomized participants. Demographics, other baseline characteristics, and study drug exposure will be summarized for the ITT set and safety analysis set if these two sets are different.

9.3.5 Safety analyses

Safety will be assessed through adverse events (AEs) and changes in laboratory tests and nasal endoscopy assessment. AEs will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

The number and percentage of participants with incidence of the safety endpoints will be presented by treatment group, where participants will be classified according to the treatment received. There will be no formal statistical tests comparing treatments on safety endpoints and there will be no imputation of missing data.

9.3.6 Efficacy analyses

Hypothesis testing for all efficacy endpoints will be conducted on the ITT population. The study level type-1 error for the family of primary and key secondary efficacy hypotheses will be controlled at alpha of 0.05. Unless otherwise noted, all analyses of efficacy outcome measures will be adjusted for baseline score, geographic region, and nasal polyp status. Adjustment by additional covariates, if any, will be described in the SAP.

All efficacy analyses will be carried out after the last participant completes the blinded Week 24 visit or withdraws prematurely before Week 24, and all data from the 24-week study period have been entered into the study database, cleaned, verified, and locked.

9.3.7 Interim analyses

No interim analysis is planned to be performed.

10. Administrative Information

10.1 Statements of compliance

This clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) GCP, Regulation EU # 536/2014, United States Food and Drug Administration (US FDA) Guidelines, and all applicable regulatory requirements. The Sponsor will not commence the clinical study until all required approval is obtained from the relevant IRB/ECs and, if applicable, regulatory authorities. All required study documentation will be archived as required by regulatory authorities.

Prior to initiating the trial, the investigator will provide the Sponsor or designee all required documents according to ICH GCP guidelines.

10.2 Protocol amendments

The clinical protocol, eCRFs, ICF and other participant information, or other clinical investigation documents may be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of a document. The amendments to the protocol and the participants' ICF (if required) will be provided to and approved by, the local regulatory authorities and IRB/ECs, as required. For nonsubstantial changes (eg, minor logistical or administrative changes, change of monitor[s], telephone numbers, renewal of insurance) not affecting the rights, safety, and well-being of human participants, or not related to the clinical investigation objectives or endpoints, a simple notification to the IRB/EC and, where appropriate, local regulatory authority can be sufficient. The version number and date of amendments will be documented.

10.3 Data quality assurance

The investigator/designee(s) will maintain accurate source documentation as part of participant case histories. Electronic data capture (EDC) will be utilized for collecting participant data in the clinical database. Each site is required to have a computer and internet connection available for entry of clinical data in to the eCRF. Only authorized users will get access to the eCRF as appropriate to their study responsibilities. Site users must have successfully undergone EDC training prior to entering data into the eCRF. The Sponsor and delegated clinical research organization (CRO) personnel will ensure that an appropriate eCRF is developed to capture the data accurately. The database will allow users to enter data and manage modifications documented by an audit trail. Appropriate queries will be raised to resolve any missing or inconsistent data within the clinical database. Data management will ensure that all data has been entered, cleaned, closed, and signed by the investigator prior to database lock.

Data management procedures will be completed in accordance with the CRO's SOPs. The details will be provided in the Data Management Plan for the study.

The Sponsor will also ensure that AE data collected in the eCRF are consistent with information provided to the service provider's pharmacovigilance department. The coding of an AE, medical history, and concomitant medication terms will be performed by the service provider. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and AEs/medical history terms will be coded using MedDRA.

10.4 Investigational site selection

The study will be conducted at up to 60 investigational sites worldwide. The primary regions of investigation are the United States and Europe. Sites will be evaluated to ensure they have the capacity and capability to obtain informed consent and comply with all protocol requirements. The investigators and investigational site personnel are required to comply with the principles of GCP and all local and national regulations.

10.5 Training

The Sponsor will select investigators with appropriate training and experience to participate in this clinical study. Sites will be selected based upon the qualifications of the principal investigator at the site as well as other parameters including proven ability and infrastructure to perform clinical studies. The complete list of all site investigators and the relevant clinical sites will be maintained within the TMF.

In addition to specific training relating to use of the investigational product, the training of the investigator and appropriate clinical site personnel will be the responsibility of the Sponsor (or designee) and may be conducted during an investigator meeting, a site initiation visit, or other appropriate venue. Training will include, but not be limited to, the clinical protocol, IB, CRF completion, GCP, and clinical study personnel responsibilities. All training will be documented prior to engaging in study-related activities.

10.6 Informed consent process

The investigators have both an ethical and legal responsibility to ensure that each participant being considered for inclusion in this study is given a full explanation of the clinical protocol.

All foreseeable risks and potential benefits which might occur with the use of the investigational product will be discussed with the participant. The participant will be informed that, should an unexpected adverse product-related or study procedure-related AE occur, which presents an unreasonable risk to participating participants, he/she will be notified.

The participant will be informed that the information obtained during the study will be used to evaluate the safety and performance of the investigational product. The participant will be informed that his/her medical records are available for review by representatives of the Sponsor or designee, the IRB/EC, and the appropriate regulatory authority, as necessary. However, his/her confidentiality will be maintained at all times and personal information will not publicly available. As part of the informed consent process, the investigator will obtain participants' permission for the Sponsor personnel or designees, IRB/EC, and regulatory authority to review, in confidence, any pertinent records relating to the participants in this clinical investigation. The participant will be told that he/she is free to refuse study participation or to withdraw from the study at any time without compromising future medical care.

A sample participant ICF template with standard wording suggested for this study will be provided to each investigator. A copy of the ICF from each site must be forwarded to the Sponsor for review and approval to assure compliance with the ICH requirements prior to submitting it to the IRB/EC.

The IEB/EC-approved written consent form is to be reviewed with the participant by the investigator or designee and will be signed by each participant prior to enrolling in the study. The investigator or designee is responsible for maintaining each participant's ICF in the study file and providing each participant with a copy of their signed ICF.

If new information becomes available that can significantly affect a participant's future health and medical care, that information shall be provided to the affected participant in written form. If relevant, all affected participants will be asked to confirm their continuing informed consent in writing.

10.7 Confidentiality and Data Protection

The conduct of this study and the processing of any personal data collected from each participant (or from a subject's healthcare professional or other relevant third-party sources) by the Sponsor or its designee, the site and the Investigator for use in the study will fully adhere to the requirements set out in applicable data protection and medical privacy laws or regulations, including, without limitation, the GDPR EU 2016/679, its subsequent amendments and any additional national laws on Data Protection.

All study data will be stored and archived in line with national and local laws and regulations on the protection of personal data including the General Data Protection Regulation (GDPR) EU 2016/679.

The Sponsor or its designee shall ensure that at all times it has an appropriate legal basis for processing personal data under applicable data protection law. The Sponsor and its vendors have implemented and maintain a number of measures, including but not limited to appropriate database security, appropriate and restricted user access, pseudonymisation and encryption of personal data, as appropriate to maintain the confidentiality of personal data.

The investigator has a responsibility to ensure that participant anonymity is protected and maintained. He or she must also ensure that the participants' identities are protected from any unauthorized parties. All study data will be stored and archived in line with national and local laws and regulations on the protection of personal data. Site-based organizational and technical arrangements to avoid unauthorized access vary by site but all include access-controlled/access-limited document control and technical solutions (i.e., including passwords and security control measures) to protect study-specific data, both in paper and electronic format.

Participation in the study will be treated as confidential and participants will not be referred to by name in any report of the study. Participant confidentiality will be maintained throughout the clinical study in a manner that ensures the information can always be tracked back to the source data. For this purpose, a unique participant identification code will be used that allows identification of all data reported for each participant. The investigators shall provide coded data to the Sponsor or its designee, which does not reveal the patient's name and full date of birth. All personal information shall be replaced with a unique participant code before any information leaves the investigator's sites. The identity of the participants will not be disclosed in any study records and participants' data will be described using the unique participant identifier. Participant data will be processed electronically to determine the outcome of this study and will be provided to health authorities as applicable.

Participants will be informed that the Sponsor or designee will have access to their medical records. Data relating to the study may be made available to third parties (eg, in the case of an audit performed by a regulatory authority) provided the data are treated confidentially and that the participant's privacy is guaranteed. Participants will be advised that their data may be transferred to other countries.

The Investigator shall report any data breaches that might occur to the Sponsor or its designee, without undue delay. The Sponsor has implemented a process to address Data Breaches that complies with the requirements of applicable laws and regulations including the GDPR. If applicable, the authorities and the data subjects shall be notified of a data breach, within the required timeframes of the applicable laws and regulations, including those of the GDPR. In case of the occurrence of a data breach, the Sponsor will immediately apply relevant measures to mitigate the risks to data subjects. Any data breach presenting risks to the rights and freedoms of data subjects will be reported to the relevant supervisory data protection authority, as applicable.

10.8 Institutional Review Board/Ethics Committee

The clinical protocol and ICF must have the approval of a properly constituted IRB/EC responsible for approving clinical studies prior to commencing the study at that site. Any additional approval requirement(s) of the IRB/EC will be followed. Any advertisements used to recruit participants or any participant-facing documents will also be reviewed and approved by the IRB/EC before use.

No investigative procedures other than those defined in this clinical protocol will be undertaken on the enrolled participants without the written agreement of the IEB/EC and Sponsor. Each site principal investigator will advise their IRB/EC of the progress of this clinical investigation on a regular basis, according to IRB/EC reporting requirements. Approvals for the continuation of the study at each investigational site must be kept current and notifications forwarded to the Sponsor.

The Sponsor or designee will submit reports as required by IRB/ECs and local and national regulations. These reports may include SAEs, withdrawal of IRB/EC or regulatory authority's approval, annual progress reports, recall information, and final reports.

10.9 Investigator responsibilities

The investigator for each investigational site is responsible for ensuring the study is conducted according to:

- All signed agreements
- The study protocol
- IRB/EC guidelines
- Applicable local and federal regulations

The investigator for each site may not begin enrollment until the Sponsor has provided written approval to do so. The Sponsor will not provide approval until they have received and approved

(when necessary) all required documents, including the IRB/EC approvals of the investigational plan and ICF.

It is acceptable for the investigator to delegate one or more of the above functions to a subinvestigator or trained study coordinator; however, the investigator remains responsible for the proper conduct of the clinical investigation, including obtaining informed consent, collecting all required data, and submitting accurate and complete eCRFs.

The study is not transferable to other sites/facilities attended by the investigator unless preapproval is obtained from the applicable IRB/EC and the Sponsor.

10.10 Sponsor responsibilities

The Sponsor's responsibilities for this study are to:

- Select all clinical investigators, investigational sites, and other consultants, including study monitors, who participate in the study
- Provide sufficient training to participating investigational sites to support study activities according to the agreements executed with the sites
- Provide financial support to each site according to the agreements executed with each site
- Follow/promote all regulatory standards according to local/federal regulations for the investigational sites, core laboratories, and other participants, and ensure regular investigational site monitoring to assure compliance with the regulations
- Retain ownership of all clinical data generated in this study and control the use of the data for appropriate purposes only
- Review and approve publication of study results in the literature
- Ensure timely and appropriate study registration and results posting in a public clinical trial database (eg, www.clinicaltrials.gov), if applicable

10.11 Early study termination

The Sponsor reserves the right to discontinue the clinical study at any stage, with suitable written notice to the investigator. The investigator may also discontinue participation in the clinical study with suitable written notice to the Sponsor.

Specific instances that may precipitate site termination include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to the study participants
- A decision by the Sponsor to suspend or discontinue testing, evaluation, or development of the investigational product
- Failure of the investigator to enroll participants into the study at an acceptable rate
- Failure of the investigator to comply with pertinent regulations of IRB/EC or appropriate regulatory authority
- Failure of the investigator to comply with the protocol
- Submission of knowingly false information from the research facility to the Sponsor, the study monitor, IRB/EC, or regulatory authority

- Insufficient adherence to protocol requirements consistent with the US Code of Federal Regulations (CFR) 21 CFR 312, European Medical Device Regulation (EU MDR) 2017/745, European Directive 2001/83/EC, or other relevant national regulations, as appropriate.

Study termination and follow-up will be performed in compliance with the conditions set forth in ICH E6(R2) on GCP as well as 21 CFR 312.56b, the EU MDR 2017/745, 2011/83/EC, and other relevant national regulations, as appropriate, which require the Sponsor to ensure an investigator's compliance with these requirements and to promptly secure a plan for compliance or discontinue shipments of the study drug to the investigator and end the investigator's participation in the study.

If the study is discontinued for any reason, the Sponsor will provide guidelines to the institutions on how to safely exit participants and appropriately close the study. Additionally, if the study is suspended, the Sponsor will promptly work with the investigators/institutions to inform the local regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The investigator should also notify the IRB/EC promptly and provide the reason(s) for the termination or suspension by the Sponsor or by the investigator/institution. An appropriate schedule for termination will be instituted.

11. Reports and Records

11.1 Records

Each investigator will maintain all records pertaining to this clinical study as required by local regulations, the relevant IRB/EC, and the institution. The investigator will maintain all study-related documentation, including all correspondence, records of financial interest, individual participant records, ICFs, all investigational product accountability records, the protocol with any/all amendments, all correspondence with and approval from all regulatory agencies, the budget agreement, the investigator agreement, and copies of CRFs.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained. No study document will be destroyed without prior written agreement between the Sponsor and the investigator. In addition, in accordance with the CTRA, the Sponsor should be contacted if the investigator plans to leave the investigational site so that appropriate arrangements can be made for the transfer of the records to the appropriate designee at the study site.

11.2 Reporting requirements

Investigators are responsible for the following reporting requirements to the applicable IRB/EC and the Sponsor:

- Reporting failure to obtain informed consent before study procedures
- Progress reports
- Protocol deviations due to emergency or participant safety

In addition to this list, each individual IRB/EC may add additional reporting requirements. The principal investigator at each investigational site is responsible for ensuring any additional local IRB/EC reporting requirements are met, if applicable.

Investigators are also responsible for the following reporting requirements to the Sponsor:

- Withdrawal of IRB/EC approval
- Participant withdrawal

The Sponsor will be responsible for reporting any investigational product recalls to the IRB/EC within 30 days of the request. Additionally, the Sponsor will develop a final study report upon study completion or termination. The Sponsor will also be responsible for registration and posting results on www.clinicaltrials.gov.

12. Publications

All unpublished documentation (such as the clinical protocol, CRFs, IFU, and IB) given to the investigator is strictly confidential. All recipients must agree not to disclose the information herein contained to any person without the prior written authorization of the Sponsor. The submission of these documents to the IRB/EC is expressly permitted. The investigator agrees that the Sponsor maintains the right to use the results of this study in their original form and/or in a global report for submission to governmental and regulatory authority of any country.

The data and results from the clinical study are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical study. An investigator may only publish data generated by this clinical study in accordance with the terms of the CTRA.

Results of the study will be posted by the Sponsor on a publicly available clinical study registration website(s) (eg, www.clinicaltrials.gov) in accordance with the applicable regulations.

13. References

[1] Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in Europe – an underestimated disease. A GA^{2}LEN study. *Allergy*. 2011;66(9):1216-1223.

[2] Bhattacharyya N. Incremental health care utilization and expenditures for chronic rhinosinusitis in the United States. *Ann Otol Rhinol Laryngol*. 2011;120(7):423-427.

[3] Office of the Assistant Secretary for Planning & Evaluation. United States Department of Health and Human Services. Individuals living in the community with chronic conditions and functional limitations: A closer look. Created January 2021. Accessed August 17, 2021. Available at: https://aspe.hhs.gov/system/files/pdf/75961/closerlook.pdf

[4] Kim YS, Kim NH, Seong SY, Kim KR, Lee GB, Kim KS. Prevalence and risk factors of chronic rhinosinusitis in Korea. Am J Rhinol Allergy. 2011;25(3):117-121.

[5] Shi JB, Fu QL, Zhang H, et al. Epidemiology of chronic rhinosinusitis: results from a cross-sectional survey in seven Chinese cities. *Allergy*. 2015;70(5):533-539.

[6] Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg*. 2003;129(3Suppl):S1-S32.

[7] Smith KA, Orlandi RR, Rudmik L. Cost of adult chronic rhinosinusitis: a systematic review. *Laryngoscope*. 2015;125(7):1547-1556.

[8] van Agthoven M, Uyl-de Groot CA, Fokkens WJ, van de Merwe JP, Busschbach JJV. Cost analysis of regular and filgrastim treatment in patients with refractory chronic rhinosinusitis. *Rhinology*. 2002;40(2):69-74.

[9] Fokkens WJ, Lund VJ, Hopkins C, et al. European position paper on rhinosinusitis and nasal polyps 2020. *Rhinology*. 2020;58(Suppl S29):1-464.

[10] Orlandi RR, Kingdom TT, Smith TL, et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. *Int Forum Allergy Rhinol*. 2021;11(3):213-739.

[11] Ramot Y, Haim-Zada M, Domb AJ, Nyska A. Biocompatability and safety of PLA and its polymers. *Adv Drug Deliv Rev*. 2016;107:153-162.

[12] Global Initiative for Asthma. Global initiative for asthma management and prevention (2020 update). Accessed August 17, 2021. Available at: https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf

[13] Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol*. 2009;34(5):447-454.

[14] DeConde AS, Mace JC, Bodner T, et al. SNOT-22 quality of life domains differentially predict treatment modality selection in chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2014;4(12):972–979.

[15] Reilly MC, Zbrozek AS, Dukes E. The validity and reproducibility of a work productivity and activity impairment measure. *PharmacoEconomics*. 1993;4(5):353-365.

[16] Brazier JE, Harper NM, Jones A, et al. Validating the SF-36 health questionnaire: A new outcome measure for primary care. *BMJ*. 1992;305(6846):160-164.

[17] Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727-1736.

[18] Hays RD, Martin SA, Sesti AM, Spritzer KL. Psychometric properties of the Medical Outcomes Study Sleep measure. *Sleep Med*. 2005;6(1):41-44.

[19] Fordyce MW. Adapted from Seligman MEP. *Authentic Happiness: Using the New Positive Psychology to Realize Your Potential for Lasting Fulfillment*. Free Press, a division of Simon & Schuster, Inc. 2002.

[20] Zinreich SJ. Imaging for staging of rhinosinusitis. *Ann Otol Rhinol Laryngol Suppl*. 2004;193:19-23.

[21] WHO Cataract Grading Group. *A Simplified Cataract Grading System*. World Health Organization; 2002.

[22] Ridgway JP, Robicsek AA. Risk of coronavirus disease 2019 (COVID-19) acquisition among emergency department patients: A retrospective case control study. *Infect Control Hosp Epidemiol*. 2021;42(1):105-107.

[23] Baker MA, Fiumara K, Rhee C, et al. Low risk of coronavirus disease 2019 (COVID-19) among patients exposed to infected healthcare workers. *Clin Infect Dis*. 2021;73(7):e1878-e1880.

[24] Merck & Co., Inc. NDA 20762 Drug Approval Package, NASONEX® (mometasone furoate monohydrate) Nasal Spray, 50 mcg. Approval date October 1, 1997. Accessed August 17, 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020762_nasonex_toc.cfm

[25] Merck & Co., Inc. NDA 21067 Drug Approval Package, ASMANEX® TWISTHALER® 110 mcg, 220 mcg (mometasone furoate inhalation powder). Approval date March 30, 2005. Accessed August 17, 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021067s000_AsmanexTOC.cfm

[26] Intersect ENT, Inc. PMA P100044 Summary of Safety and Effectiveness, PROPEL™ (mometasone furoate implant, 370 µg) . Approval date March 23, 2016. Accessed September 08, 2021. Available at: www.accessdata.fda.gov/cdrh_docs/pdf10/P100044B.pdf

[27] Intersect ENT, Inc. NDA 209310 Drug Approval Package, SINUVA™ (mometasone furoate) sinus implant. Approval date December 8, 2017. Accessed August 17, 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209310Orig1s000TOC.cfm

[28] Douglas RG, Psaltis AJ, Rimmer J, Kuruvilla T, Cervin A, Kuang Y. Phase 1 clinical study to assess the safety of a novel drug delivery system providing long-term topical steroid therapy for chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2019;9(4):378-387.

[29] Metson RB, Gliklich RE. Clinical outcomes in patients with chronic sinusitis. *Laryngoscope*. 2000;110(3 Pt 3):24-28.

[30] Chaubal M. Polylactides/glycolides - excipients for injectable drug delivery and beyond. *Drug Deliv Technol*. 2002;2:34-36.

14. Appendices

14.1
14.2
14.3
14.4
14.5
14.6
14.7
14.8
14.9
14.10
14.11
14.12
14.13
14.14
14.15

Appendices 14.1-14.15 have been redacted