CLINICAL STUDY PROTOCOL

Protocol Number: LYR-220-2021-001

Study Title: BEACON: A Phase II, Patient-blinded, Two-part, Randomized, Parallel-group Trial to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of LYR-220 in Chronic Rhinosinusitis (CRS) Patients Who Have Had a Prior Ethmoidectomy

Version: 4.0

Effective Date: 30 August 2022

NCT# NCT05035654

Confidentiality Statement

SPONSOR SIGNATURE PAGE

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Sponsor: Lyra Therapeutics, Inc.
480 Arsenal Way
Watertown, MA USA 02472

Version: 4.0

Signed: [redacted]

Signed: [redacted]

COORDINATING INVESTIGATOR SIGNATURE PAGE

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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 subjects 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, 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 subjects 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 subjects.

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 subjects 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 Subinvestigators 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: _____

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Abbreviation / Term	Definition
AE	Adverse event
AR	Allergic rhinitis (seasonal or perennial)
ARS	American Rhinologic Society
ANCOVA	Analysis of covariance
CFBL	Change from baseline
CFR	Code of Federal Regulations
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
COPD	Chronic obstructive pulmonary disorder
CRF	Case report form
CRO	Contract research organization
CRS	Chronic rhinosinusitis
CRS-PRO	Patient-reported outcome measure for chronic rhinosinusitis
CS	Cardinal symptoms of CRS
CT	Computed tomography
CTRA	Clinical trial research agreement
CV	Curriculum vitae
CYP3A4	Cytochrome P-450 3A4
EC	Ethics Committee
EDC	Electronic data capture
EOS	End-of-study
EOT	End-of-treatment
ePRO	Electronic patient-reported outcome
ET	Early termination
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FESS	Functional endoscopic sinus surgery
GCP	Good clinical practice
HEENT	Head, ears, eyes, nose, and throat
IB	Investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IFU	Instructions for use
IgA	Immunoglobulin A
IgG	Immunoglobulin G
INCS	Intranasal corticosteroid spray
IOP	Intraocular pressure
IRB	Institutional Review Board

Abbreviation / Term	Definition
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
kg	kilogram
K-M	Kaplan-Meier
LOCF	Last observation carried forward
µg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
MF	Mometasone furoate
mg	milligram
mL	milliliter
mm Hg	Millimeters of mercury
MMP	Medical monitoring plan
MMRM	Mixed model of repeated measures
mRNA	Messenger ribonucleic acid
NSAID	Nonsteroidal anti-inflammatory drug
pg	picogram
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetics
SAE	Serious adverse event
SAR	Seasonal allergic rhinitis
SCS	Systemic corticosteroid
SD	Standard deviation
SNOT-22	Sino-Nasal Outcome Test (22-item)
SOP	Standard operating procedure
SUSAR	Serious unexpected suspected adverse reaction
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
UADE	Unexpected adverse device effect
URTI	Upper respiratory tract infection
US	United States

1. SYNOPSIS

Sponsor	Lyra Therapeutics, Inc. 480 Arsenal Way Watertown, MA 02472, USA
Protocol Title	BEACON: A Phase II, Patient-blinded, Two-part, Randomized, Parallel-group Trial to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of LYR-220 in Chronic Rhinosinusitis (CRS) Patients Who Have Had a Prior Ethmoidectomy
Protocol Number	LYR-220-2021-001
Phase of Development	Phase II
Investigational Product	LYR-220-32 System (7500 µg) and LYR-220-16 System (7500 µg)
Active Ingredient	Mometasone furoate (MF)
Trial Location	Worldwide
Number of Sites	Up to 25 sites
Study Population	Adult CRS patients who have had a prior bilateral total ethmoidectomy
Estimated Number of Subjects	Approximately 50 subjects
Study Endpoints	
Primary	
- Product-related unexpected serious adverse events	
Pharmacokinetics	
- Plasma MF concentrations at 1 hour post study treatment administration and at Days 2 or 3, Days 5 or 8, and Weeks 4, 12, 16 or 20, 24, and 25	
Secondary – Safety	
- Treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) through Week 28 - Clinically significant abnormal laboratory values (hematology and chemistry) through Week 25 - Newly identified or worsened endoscopic findings (epistaxis and mucosal injury) in ethmoid cavity through Week 25	

- Clinically significant increase of IOP through Week 25 *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.* - Newly identified or worsened cataract in 1 or both eyes by slit-lamp examination through Week 25
Secondary – Efficacy
- Change from baseline (CFBL) in SNOT-22 total and subdomain scores at Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28 *The SNOT-22 questionnaire is a 22-item disease-specific quality of life instrument validated for use in CRS. Each symptom is scored as it has been over the past 2 weeks 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.*
- CFBL in the average composite score over the preceding 7 days of 3 cardinal symptoms (3CS) and individual cardinal symptom scores at Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28 *The 3 cardinal symptoms include nasal blockage/obstruction/congestion, facial pain/ pressure, and anterior/posterior nasal discharge. Each symptom is scored on a 0-3 scale as follows: 0 = none, 1 = mild, 2 = moderate, and 3 = severe.*
- CFBL in average loss of smell score over the preceding 7 days for all subjects and for subjects with baseline score ≥2 at Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28
- Change from baseline (CFBL) in Patient-Reported Outcome Measure for Chronic Rhinosinusitis (CRS-PRO) total and subdomain scores at Day 8 and Weeks 2, 3, 4, 6, 8, 12, 16, 20, 24, and 28 *The CRS-PRO questionnaire is a 12-item disease-specific health-related impairment for use in CRS. Each symptom is scored as it has been over the past 7 days on a 5-point scale as follows: 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much.*
- Time to first use of rescue treatment recommendation through Week 28 *Rescue treatment is defined as, after subject enrollment, worsening or acute exacerbation of CRS in a subject resulting in the treating physician reporting an escalation of treatment, including systemic corticosteroids (SCS) and/or sinonasal surgery. Rescue treatment is not recommended if worsening of symptoms is less than 3 days duration.*
- Oral steroids use or sinonasal surgery through Week 28
- CFBL in bilateral percent ethmoid cavity opacification by CT at Week 25
- CFBL in Patient Global Impression of Severity (PGIS) score at Weeks 8, 16, and 24
- Patient Global Impression of Change (PGIC) score at Week 24

- No longer a candidate for revision surgery

  Subjects will be deemed as having converted if they do not undergo revision sinonasal surgery (planned or actual) during the study and if they meet the following criteria:
  - *3CS score ≤4 at Week 24, or*
  - *No disease in ethmoid cavities on Week 25 CT*

- CFBL in nasal inflammatory marker levels at Week 25

Study Design

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

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

Each subject will undergo 3 stages during the study:

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

Screening and Run-in Stage

After providing written informed consent, subjects who are qualified to participate in this study will have an initial Screening visit. Immediately following the initial Screening visit, subjects will undergo a 2–4-week run-in period. During this run-in period, except for a background therapy of daily saline irrigation, subjects will receive no other active treatment for CRS or any prohibited or rescue medications specified in the study protocol. Beginning at least 14 days prior to LYR-220 insertion procedure on Treatment Day (Day 1), subjects will record daily cardinal symptoms (CS) of CRS on the electronic patient-reported outcomes (ePRO) system. At Screening, the SNOT-22 and CRS-PRO will also be collected.

Treatment Stage

The total duration of the Treatment Stage will be approximately 24 weeks.

In part 1 of the study, on Day 1, subjects will be treated with any design of LYR-220 bilaterally. The LYR-220 insertion procedure will be assessed and optimized, if necessary, before the randomized part 2 stage.

In part 2 of the study, on Day 1, before any treatment, subjects will be randomized in a 1:1ratio to 1 of the 2 study arms:

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

Subjects in part 2 of the study will be stratified for treatment assignment according to the following criteria:

- Nasal polyps (Yes vs No)

No more than 10 subjects with polyps will be enrolled in each treatment arm

Subjects enrolled in either part of the study will undergo the same study procedures and assessments. On Day 1, after completing any required pretreatment baseline assessments, subjects will receive local anesthetic and may receive decongestants in the ethmoid cavity for endoscopic assessment and in preparation for the insertion procedure.

All subjects will return to clinic for the scheduled follow-up assessments at Day 2 or 3, Day 5 or 8, and Week 4, Week 12, Week 16 or 20, and Week 24 visits. Subjects will receive telephone follow-ups at Week 8 and Week 16 or 20 (ie, the week they are not scheduled to attend in-clinic visit for PK blood draw) to record AEs and concomitant medications/procedures that they have had since their last follow-up assessment.

At the Week 24 visit, all subjects will return to clinic for the **end-of-treatment (EOT)** visit assessments. Subjects who have been treated with LYR-220 will have the bilateral matrices removed using standard surgical tools and control group subjects will undergo a sham removal procedure.

If **spontaneous dislodgement of LYR-220** occurs before the scheduled Week 24/EOT visit, subjects are required to call the study clinic immediately to report the event. If a subject experiences dislodgement of 1 of the bilateral matrices, the subject will continue in the treatment phase unless an early treatment discontinuation is recommended by the treating physician or subject requests matrix removal from the remaining side of the nose. If matrices spontaneously dislodge from both sides of the nose, the subject will complete an Unscheduled **early-termination (ET)** visit within 7 days of the second matrix dislodgement, and complete the assessments scheduled for the Week 24/EOT visit. Spontaneously dislodged LYR-220 should be retained, if available, and returned to the clinic at subject's next visit.

If medically warranted, according to the treating physician's discretion (for example, needing sinonasal surgery as rescue treatment), early matrix removal may be performed at an unscheduled ET visit.

Any subject who undergoes an ET visit is required to complete the assessments scheduled for the Week 24/EOT visit and should stay in the study and complete the assessments scheduled for the Week 25 visit within 5-9 days after the ET visit.

Post-treatment Follow-Up Stage

All subjects will undergo a 1-week post-treatment follow-up visit (Week 25 visit). AEs, concomitant medications/procedures, endoscopy, nasal swabs, ophthalmologic assessments, CT, and other scheduled assessments will be performed at the Week 25 visit. In addition, subjects will complete a 4-week post-treatment follow-up by telephone or in-clinic visit [Week 28/**end-of-study (EOS)**]. End of study assessments include AEs, concomitant medications/procedures, and final ePROs (4CS, SNOT-22, CRS-PRO, and End-of-Study Questionnaire).

Assessments

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events (AEs) or untoward findings. Any AEs observed by the Investigator or reported by the subjects, whether or not attributed to the investigational procedure or product, will be monitored and evaluated throughout the study. If AEs occur, the first concern will be the safety and welfare of the subject. Appropriate medical intervention will be undertaken per the treating physician's discretion.

Routine safety assessments will be performed during the screening visit including vital signs and limited physical exams of head, eyes, ears, nose, and throat (HEENT). Samples for hematology and chemistry will be collected at Screening and Week 25 visits.

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

Ophthalmologic assessments will include IOP and slit-lamp examination during Screening and at Week 25 visit. IOP assessment will also be performed at Week 4 and 12 visits.

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

Plasma samples for PK will be collected from all subjects on 9 occasions:

- Day 1 pre-procedure
- 1 hour (±10 min) post procedure on Day 1
- Day 2 or 3*
- Day 5 or 8*
- Week 4
- Week 12

- Week 16 or 20*
- Week 24/EOT
- Week 25

[*Note: Subjects will be asked to come to the clinic on either one of the 2 visit options.]

Enrolled subjects will be asked to complete a daily ePRO questionnaire to assess the severity of the 4 cardinal symptoms (CS) of CRS including nasal blockage/obstruction/congestion, facial pain/pressure, anterior/posterior nasal discharge, and loss of smell. In addition, the ePRO will capture use of daily saline irrigation by the subjects. Subjects will also complete 2 validated CRS-specific quality of life questionnaires, the SNOT-22 and CRS-PRO, at Screening, on Day 1 before treatment, and at Weeks 2, 4, 6, 8, 12, 16, and 20, at Week 24 before matrix removal, and at Week 28/EOS. CRS-PRO will also be assessed at Day 8 and Week 3. The PGIS will be assessed at Day 1 and at Weeks 8, 16, and 24/EOT. The PGIC will be assessed at Week 24/EOT. At Week 28/EOS visit, an End-of-Study questionnaire will be administered.

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

Concomitant Medications: Prohibited, Permitted, and Rescue
Subjects participating 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 safety, pharmacokinetic, and efficacy assessments of LYR-220.

Prohibited Concomitant Medications:
Use of the following medications is prohibited for the duration of the study:

- Any drug or product containing mometasone furoate (MF).
- Oral/ocular/intramuscular/intravenous/intranasal corticosteroids (except for oral corticosteroids permitted as rescue medication only).
- Antiallergy medications, including: first generation antihistamines (eg, diphenhydramine, dimenhydrinate, chlorpheniramine), leukotriene receptor antagonists (except for a stable regimen for asthma), nasal cromolyn sodium or sodium cromoglycate, nedocromil sodium, atropine, ipratropium bromide, or guaifenesin.
- Oral/intranasal decongestants (except for short course of intranasal decongestants permitted for severe acute nasal blockage or during endoscopic procedures).

- Inhaled anticholinergic medications (except for a stable regimen for subjects with chronic obstructive pulmonary disease [COPD]).
- 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).
- Oral antifungal medication.

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

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

- All subjects will be instructed to use daily intranasal saline irrigation as background treatment starting from Screening through the study duration.
- Subjects who have been on a stable regimen of inhaled corticosteroids (not containing MF) or leukotriene receptor antagonists for asthma 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.[1]
- 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 sprays for a maximum of 3 consecutive days and a total maximum of 10 days during the treatment period. [NOTE: Oxymetazoline cannot be used within 24 hours before CT assessments.]
- Nonsedating oral antihistamine such as loratadine (10 mg per day) or equivalent for acute allergic symptoms.
- Perennial allergic rhinitis subjects who have been on a stable regimen of a nonsedating oral antihistamine for a minimum of 3 months prior to the Screening visit should remain on the same dosage throughout the study.

Rescue Medications and Treatment:
The following rescue medication is recommended for worsening or uncontrolled severe CRS symptoms that last for a minimum of 3 days and result in the subject contacting the Investigator who determines an initiation of rescue treatment is necessary at any time during the study:

- A course of oral 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 corticosteroid must be recorded.
- Sinonasal surgery as rescue treatment according to the Investigator's recommendation. The type and rationale for sinonasal surgery must be recorded.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

A subject must meet <u>all</u> the following criteria to be eligible for this study:

1. Age ≥18 years.
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. Has had a prior bilateral ethmoidectomy involving both anterior and posterior ethmoids (>3 months ago). NOTE: The postsurgical ethmoid cavity should be large enough to accommodate the LYR-220 matrix.
4. Has ≥5% opacification in the ethmoid cavity on each side on CT.
5. SNOT-22 ≥20 at Screening visit.
6. Mean 3CS score over the preceding 7 days of ≥4.5 (on a 0-9 scale for the total 3CS symptoms score) determined within 7 days of Day 1 (the determination for eligibility can be made on any day from Day -7 through Day 1).
7. Not currently using INCS or decongestants at Screening or able to cease use of INCS and decongestants from Screening through the duration of the study.
8. Ability to tolerate local anesthesia.
9. 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.
10. Agrees to comply with all study requirements.

Exclusion Criteria:

A subject who meets <u>any</u> of the following criteria will be excluded from this study:

1. Ethmoidectomy that was unilateral.
2. Presence of nasal polyp grade 2 or higher, (ie, extending outside of the middle meatus) on either side.
3. Endoscopic exclusion criteria at Screening and Day 1 visit:
    a. Obstructing the nasal cavity for proper placement or retention of LYR-220.

   b. Dense and obstructing adhesion/synechiae of ethmoid cavity that is difficult to separate or complete adhesion of the middle turbinate to the lateral nasal wall
   c. Severe scarring or residual ethmoid cells within ethmoid cavity preventing proper placement of LYR-220.
   d. Resected or degenerated middle turbinate that could interfere with retention of LYR-220.
   e. Evidence of mucosal erosion or ulceration within nasal cavity.
   f. Acute nasal/sinus infection or purulence.
   g. Evidence of nasal septal perforation.

4. Screening CT exclusion criteria:
   a. Anatomic variation which, in the opinion of the Investigator, would adversely impact placement or retention of LYR-220.
   b. Structural, noninflammatory related CRS (eg, large concha bullosa, tumor).
   c. Sinus disease extended into orbital or intracranial space.
   d. Evidence of mycetoma/fungal ball, allergic fungal rhinosinusitis.
   e. Sinus mucocele.
5. Seasonal allergic rhinitis (SAR) subjects with symptoms and/or, based on time of year, would anticipate onset of symptoms within 24 weeks of Day 1 procedure.
6. Perennial rhinitis subjects whose symptoms are well controlled by regular use of INCS.
7. With severe asthma or with 1 or more exacerbations of asthma requiring SCS use within the 3 months prior to the Screening visit. Subjects 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. History or clinical evidence or suspicion of invasive fungal sinusitis, allergic fungal rhinosinusitis, or atrophic rhinitis.
9. Known history of hypersensitivity or intolerance to corticosteroids.
10. Oral steroid or monoclonal antibody (Xolair, Nucala, Dupixent) dependent condition, including biologics use within 3 months of screening, per protocol clarification letter.
11. SCS administered within 1 month prior to Screening visit.
12. Known history of hypothalamic pituitary adrenal axial dysfunction.
13. Previous pituitary or adrenal surgery.
14. 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.
15. Acute exacerbation of nasal allergy, CRS, upper respiratory tract infection (URTI), common cold, or clear worsening or acute change in symptoms within 4 weeks of the Screening visit. The infection/exacerbation must be resolved, and antibiotic or other medication use must be discontinued prior to screening per protocol clarification letter.
16. Dental procedure/implant on maxillary dentition within 4 weeks of the Screening visit.

17. Past or present acute or chronic intracranial or orbital complications of CRS (eg, brain abscess, related problems with eyes or central nervous system).
18. History or diagnosis (in either eye) of glaucoma or ocular hypertension (IOP >21 mm Hg).
19. Presence (in either eye) of posterior subcapsular cataract of grade 2 or higher, nuclear cataract 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.
20. Loss of functional vision in 1 or both eyes.
21. Diagnosed with ongoing rhinitis medicamentosa.
22. 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.
23. Past, present, or planned organ transplant or chemotherapy with immunosuppression.
24. History or diagnosis of ciliary dysfunction (eg, cystic fibrosis, primary ciliary dyskinesia [Kartagener syndrome]).
25. Past or present systemic vasculitis (eg, granulomatosis with polyangiitis).
26. Evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments.
27. 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 the time of treatment based on a urine pregnancy test. Both male and female subjects of reproductive potential must agree to use highly effective methods of birth control, throughout the study.
28. Previously received an experimental treatment in another clinical study within 5 half-lives or 30 days (whichever is longer) of Screening visit.
29. Currently participating in another drug or device study.
30. Currently positive for COVID-19 or residual sinonasal symptoms from a previous COVID-19 infection.
31. Determined by the Investigator as not suitable to be enrolled for reasons not already specified if the health of the subject or the validity of the study outcomes may be compromised.

Investigational Product, Dosage and Mode of Administration:

The LYR-220 System is a combination product comprised of a single-use applicator, preloaded with an anti-inflammatory LYR-220 drug matrix [referred to as LYR-220 in this document]. LYR-220 contains mometasone furoate (MF), an FDA-approved drug indicated for therapeutic and prophylactic management of seasonal and perennial allergic rhinitis (AR), nasal polyps, a phenotype of CRS disease, as well as asthma. LYR-220 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-220 contains a total MF dose of 7500 µg. LYR-220 is intended to be administered bilaterally into the ethmoid cavity, in which ethmoid sinuses have been removed previously by ethmoidectomy, by an otolaryngologist under endoscopic visualization using the provided single-use applicator. Once administered, each LYR-220 is designed to gradually deliver sustained doses of MF to the inflamed mucosal tissue over a 24-week resident time. Bilateral placement of LYR-220 is designed to deliver a total dose of 15,000 µg MF over the 24 weeks, or an average daily dose of 89 µg MF per person (or 45 µg MF per nostril).

The LYR-220 drug matrix has a tubular braid configuration with a uniform diamond pattern throughout. 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 a 3-dimensional structure and elasticity. The drug formulation layer consists of the active ingredient, MF, embedded in the inactive ingredients containing poly(L-lactide-co-ε-caprolactone) and poly(L-lactide) to control the release rate of MF. Two designs of LYR-220, LYR-220-32 drug matrix and LYR-220-16 drug matrix, manufactured with 32 and 16 woven fibers, respectively, will be assessed in Part 1 of this study. Both designs have the same nominal dimensions of 20 mm in diameter and 16 mm in length in the unconstrained state.

For the sham treatment, a single-use LYR-220 sham applicator is introduced to the sinus cavity. The sham applicator does not contain a preloaded LYR-220 drug matrix.

Duration of Study:

The total duration of the study, including the enrollment period, is approximately 14 months. Each enrolled subject is planned to participate in the study for a total duration of approximately 8 months, which includes the Screening/Run-in, Treatment, and Posttreatment Follow-up stages. The active treatment period will be 24 weeks. The end of the trial is defined as the date of the last EOS visit of the last subject of the study.

Statistical Methods:

Sample Size:

Because the primary objective of this study is to evaluate the safety, tolerability, and pharmacokinetics of LYR-220, the sample size determination is not based on statistical power considerations. Up to 10 subjects will be treated during the part 1 phase and approximately 20 subjects per treatment arm will be enrolled during the part 2 randomized phase (40 total).

Analysis Sets:

- Safety analysis set: All subjects who received the study treatment. Subjects will be analyzed according to the treatment received. This is the primary analysis set for assessment of safety.
- Efficacy analysis set: All subjects who received the study treatment. This is the primary analysis set for assessment of efficacy. Subjects will be analyzed according to the treatment they actually received.

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

Subject Disposition and Demographic Characteristics:
Subject disposition will be summarized for all consented subjects. Analysis set assignment will be summarized for all enrolled subjects by treatment group. Demographics and other baseline characteristics and study drug exposure will be summarized for the Efficacy analysis set.

PK Analyses:
The PK analyses will be performed based on subjects with available plasma MF concentration data post Day 1 LYR-220 administration procedure. A summary table will be used to present descriptive statistics (number, mean, SD, coefficient of variation, median, minimum, and maximum) of these PK parameters by treatment group. If plasma MF levels are detectable, PK parameters of MF will be estimated using a standard noncompartmental PK approach based on individual plasma concentration-time data. Maximum concentration (C_{max}) and time to reach maximum concentration (T_{max}) will be taken directly from the observed data. Actual PK sampling times will be used in the derivation of PK parameters. There will be no imputation of missing data.

Safety Analyses:
Safety will be assessed through AEs and changes in laboratory tests, vital signs, nasal endoscopy assessment, IOP and slit-lamp examination using the safety analysis set. AEs will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

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

Efficacy Analyses:

All efficacy analyses will be carried out after the last subject completes the Week 28 visit or withdraws prematurely prior to Week 28.

A mixed model repeated measures (MMRM) approach will be used to compare changes from baseline (CFBL) between LYR-220 group and the sham procedure group in SNOT-22, CRS-PRO, PGIS, and CS scores. An analysis of covariance (ANCOVA) model will be used to analyze the CT score and biomarker levels.

Efficacy data collected after early termination will be included in the analysis. A last observation carried forward (LOCF) method will be used to impute post rescue treatment and missing data. Rescue treatment include SCS and/or sinonasal surgery for any reason. There will be no imputation for missing follow-up CT or biomarker assessments.

2. INTRODUCTION

2.1 Chronic Rhinosinusitis

Chronic rhinosinusitis (CRS) is a common condition that is defined by symptomatic inflammation of the paranasal sinuses lasting longer than 12 weeks. CRS affects approximately 4.9% of the US population, which is about 14 million people[2], and 10.9% of the European population.[3] In the US, approximately 8 million people are treated for CRS by physicians each year,[4] of which approximately 4 million fail medical management.[5] Moreover, CRS results in 18 million annual office visits[6] and direct treatment costs of more than $60 billion annually in the US,[7] including approximately $5 billion on sinus surgeries.

CRS has 2 main phenotypes, CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP), with CRSsNP representing 70-90% of patients. The cardinal symptoms of CRS include nasal blockage/obstruction/congestion, facial pressure/pain, nasal discharge (anterior/posterior nasal drip), and reduction or loss of smell.[8, 9] The underlying cause of CRS-related symptoms is inflammation of mucosal tissues leading to impairment of mucociliary clearance.

Medical and surgical interventions are directed toward managing the symptoms of CRS. Currently, there are no FDA-approved drug therapies for CRSsNP, although evidence-based medical management supports the off-label use of an oral or topical corticosteroid therapy with or without antibiotics. The most common first-line therapy is topical corticosteroids with adjunctive use of daily nasal saline irrigation.[10] However, inefficient drug delivery to the inflamed mucosal tissues[11] and poor patient compliance limit the effectiveness of such therapy.[12] Flare-ups and worsening inflammation or severe nasal polyps are typically managed with a short course (1-3 weeks) of oral corticosteroids.[8, 9] While effective initially, improvements are typically not sustained for longer than 3 months.[13, 14] Additionally, oral corticosteroids can lead to systemic side effects including mood disturbance, gastrointestinal issues, diabetes, cataracts, glaucoma, and osteoporosis,[15, 16] which have limited their routine use. Approximately 50% of patients fail medical management[17] and become potential candidates for functional endoscopic sinus surgery (FESS). FESS removes inflamed tissues and bone to open the sinonasal passages to facilitate normal sinus drainage and aeration and provide greater access for delivery of topical steroids. Approximately 400,000 FESS procedures are performed each year,[17] and Lyra estimates approximately 40% of patients that present to an otolaryngologist with CRS have had a prior FESS. Given the essential role of the ethmoid bulla in sinus function, the ethmoid sinuses are opened in approximately 80% of FESS procedures.[18] Of the ethmoidectomies performed by an otolaryngologist, Lyra estimates approximately one-third are anterior or partial, and two-thirds are total. Although FESS can improve symptoms and quality of life, it does not correct the underlying cause of the inflammation nor obviate the need for continued medical management, primarily consisting of intranasal corticosteroids and nasal saline. Furthermore, approximately, 65% of patients have recurrent symptoms post FESS within the first year[19] and up to 20% elect a revision surgery.[20]

2.2 Product Rationale

Mometasone furoate (MF) is a potent, topically active, anti-inflammatory corticosteroid drug indicated for both therapeutic and prophylactic management of seasonal and perennial allergic rhinitis (AR), nasal polyps, a phenotype of CRS disease, (Nasonex®[21]), as well as asthma (Asmanex® Twisthaler®[22]). Propel®[23] and Sinuva™[24] are FDA-approved MF-eluting sinus implants placed in adults following ethmoid sinus surgery to maintain patency, and in the ethmoid sinus for up to 90 days for the treatment of recurrent nasal polyps in adults who have had ethmoid sinus surgery, respectively. CRS is characterized by inflammation of the mucosal membrane of the sinonasal cavities. Corticosteroids have a long history of use and have been shown to have a wide range of effects on multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. Results from pharmacokinetics (PK) studies in adults and children suggest that systemic exposure to MF after intranasal administration is negligible, underscoring MF as an ideal drug candidate for the development of an optimal topical drug formulation for CRS patients with and without polyps who have had a prior ethmoidectomy.

Drug-eluting implantable treatments have demonstrated the ability to provide therapy directly to the local site of disease in a sustained fashion while eliminating systemic effects of the drug.[25, 26] Propel® and Sinuva™ are topical MF-eluting nasal implants recently developed for patients immediately following ethmoid sinus surgery or for patients with recurrent polyposis post-ethmoid sinus surgery, that demonstrated clinical benefits over a no-drug implant control[27, 28] or a sham-procedure control[29, 30], respectively. The American Rhinologic Society (ARS) endorsed the utilization of steroid-eluting drug delivery implants into the paranasal sinuses for their demonstrated improvement of patient outcomes and limiting the need for oral steroids.[31] Recently, the FDA approved 2 monoclonal antibody therapies targeting aspects of Type 2 inflammation in CRSwNP patients: dupilumab[32] and omalizumab[33]. Despite their efficacy, these drugs are systemic in nature, their long-term safety profile is unknown, and they have annual costs exceeding $30,000 per patient in the US.

An ideal treatment for CRS patients with and without nasal polyps that have undergone an ethmoidectomy and have recurrent symptoms would provide local, sustained, anti-inflammatory drug delivery directly to the inflamed sinonasal mucosal tissues over a longer period of time and at a higher dose than what is currently available in a single administration. Such a therapy would be safe and tolerable throughout the entire treatment duration and not depend upon patient compliance. It would conform to the patient's operated ethmoid cavity and maintain prolonged mucosal contact with local drug absorption and minimal depletion. It would also allow for straightforward in-office placement and removal and resorb safely in case any remnants are left behind.

The LYR-220 drug matrix is comprised of 7500 µg of MF, embedded in a bioabsorbable polymer matrix allowing for controlled, sustained, and targeted release of MF for 24 weeks in a

single administration. The LYR-220 drug matrix is designed to fit within the ethmoid cavity in patients who have had a prior ethmoidectomy and maintain contact with the mucosa throughout the 24-week duration of drug delivery. LYR-220 is intended to be administered bilaterally into the previously operated ethmoid cavities by an otolaryngologist under endoscopic visualization using the provided single-use applicator. The administration of LYR-220 is office-based and performed with local anesthesia. LYR-220 can be removed at 24 weeks or earlier at the physician's discretion using standard instruments. LYR-220, if approved, is positioned for use in patients who despite previous sinus surgery continue to have recurrent CRS symptoms as a potential preferred alternative to revision surgery. LYR-220 is meaningfully differentiated from currently approved products for CRS patients that have undergone a FESS, because it would be the only product able to deliver up to six months of topical treatment in a single administration. Furthermore, unlike the monoclonal antibody therapies, LYR-220 would provide localized delivery which avoid systemic side effects.

The safety and efficacy of MF at the dose level of 2500 and 7500 µg MF delivered over 24 weeks in CRS patients have been evaluated previously by Lyra Therapeutics in Phase I (ClinicalTrials.gov ID: NCT02967731) and Phase II (ClinicalTrials.gov ID: NCT04041609) clinical studies in adult CRS patients who have failed previous medical management and have not undergone endoscopic sinus surgery. The LYR-210 clinical results indicated that LYR-210 is safe and well-tolerated in CRS patients with undisrupted middle meatuses. The LYR-210 (7500 µg) dose in the dose-ranging Phase 2 study clearly demonstrated clinically meaningful sinonasal symptoms improvement compared to a control group. Safety and efficacy summary of LYR-210 in humans can be found in the IB and in published literature[34]. These clinical experiences with LYR-210 in surgically naïve CRS subjects suggest encouraging clinical benefits of the 7500 µg MF-eluting drug matrix over the 24-week of drug delivery, while avoiding safety risks associated with prolonged oral steroid treatment.

2.3 Study Rationale

Lyra Therapeutics is conducting a multicenter study in a patient-blinded, two-part, randomized, parallel group manner in approximately 50 symptomatic adult CRS subjects who have had a prior bilateral ethmoidectomy. The study will consist of two parts. The safety, tolerability, pharmacokinetics, and efficacy of two designs, the LYR-220-32 (7500 µg) drug matrix and the LYR-220-16 (7500 µg) drug matrix, will be assessed through 28 weeks in Part 1 of the study. In addition to the safety and pharmacokinetics assessments of LYR-220, in part 1 of the study, the primary objective is to evaluate the feasibility of placement and optimize the LYR-220 insertion procedure before beginning part 2 of the study. [Note: Subject enrollment in part 2 can begin after subjects in part 1 have undergone the LYR-220 insertion procedure; subjects in part 1 do not need to complete a certain amount of follow-up prior to part 2 commencing.] The efficacy of the LYR-220-32 (7500 µg) drug matrix will also be evaluated through 28 weeks by comparing to a sham treatment control. A sham treatment control is included to reduce bias in subject reported efficacy outcomes. Subjects enrolled in part 2 will be blinded to the treatment assignment throughout the 28-week study duration.

3. STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are:

Study Objectives	Study Endpoints
Primary	
To evaluate unexpected serious adverse events related to LYR-220	- Product-related unexpected serious adverse events
Pharmacokinetics	
To evaluate the pharmacokinetics of LYR-220	- Plasma MF concentrations at 1 hour (±10 minutes) post study treatment administration and at Days 2 or 3, and Days 5 or 8, and Weeks 4, 12, 16 or 20, 24, and 25
Secondary - Safety	
To evaluate the safety and tolerability of LYR-220	- Treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) through Week 28 - Clinically significant abnormal laboratory values (hematology and chemistry) through Week 25 - Newly identified or worsened endoscopic findings (epistaxis and mucosal injury) in ethmoid cavity through Week 25 - Clinically significant increase of IOP through Week 25 *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 one or both eyes ≥10 mm Hg.* - Newly identified or worsened cataract in 1 or both eyes by slit-lamp examination through Week 25
Secondary - Efficacy	
To evaluate the efficacy of LYR-220 in improving total SNOT-22 and subdomain scores through Week 28	- Change from baseline (CFBL) in SNOT-22 total and subdomain scores at Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28 *The SNOT-22 questionnaire is a 22-item disease-specific quality of life instrument validated for use in CRS. Each symptom is scored as it has been over the past 2 weeks 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.
To evaluate the efficacy of LYR-220 in improving 3CS and individual cardinal symptom score through Week 28	- CFBL in the average composite score over the preceding 7 days of 3 cardinal symptoms (3CS) and individual cardinal symptom scores at Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28 *The 3 cardinal symptoms include nasal blockage/obstruction/congestion, facial pain/ pressure, and anterior/posterior nasal discharge. Each symptom is scored on a 0-3 scale as follows: 0 = none, 1 = mild, 2 = moderate, and 3 = severe.*
To evaluate the efficacy of LYR-220 in improving loss of smell symptom score through Week 28 for subjects with moderate-to-severe score at baseline	- CFBL in average loss of smell score over the preceding 7 days for all subjects and subjects with baseline score ≥2 at Weeks 2, 4, 6, 8, 12, 16, 20, 24, and 28
To evaluate the efficacy of LYR-220 in improving total Patient-Reported Outcome Measure for Chronic Rhinosinusitis (CRS-PRO) and subdomain scores through Week 28	- Change from baseline (CFBL) in Patient-Reported Outcome Measure for Chronic Rhinosinusitis (CRS-PRO) total and subdomain scores at Day 8 and Weeks 2, 3, 4, 6, 8, 12, 16, 20, 24, and 28 *The CRS-PRO questionnaire is a 12-item disease-specific health-related impairment for use in CRS. Each symptom is scored as it has been over the past 7 days on a 5-point scale as follows: 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much.*
To evaluate the time to first rescue treatment recommendation through Week 28	- Time to first rescue treatment recommendation through Week 28 *Rescue treatment is defined as, after subject enrollment, worsening or acute exacerbation of CRS in a subject resulting in the treating physician reporting an escalation of treatment, including systemic corticosteroids (SCS), and/or sinonasal surgery. Rescue treatment is not recommended if worsening of symptoms is for less than 3 days duration.*
To evaluate the percentage of subjects who have uncontrolled CRS symptoms requiring oral	- Oral steroid use or sinonasal surgery recommendation through Week 28

steroids or sinonasal surgery through Week 28	
To evaluate the effect of LYR-220 in reducing ethmoid cavity opacification as per CT	- CFBL in bilateral percent ethmoid cavity opacification by CT at Week 25
To evaluate the efficacy of LYR-220 in improving subject perception of symptom severity and improvement	- CFBL in the Patient Global Impression of Severity (PGIS) score at Weeks 8, 16, and 24 - Patient Global Impression of Change (PGIC) score at Week 24
To evaluate the effect of LYR-220 in converting a subject to not requiring revision surgery	- No longer a candidate for revision surgery *Subjects will be deemed as having converted if they do not undergo revision sinonasal surgery (planned or actual) during the study and if they meet the following criteria:* • *3CS score ≤4 at Week 24, or* • *No disease in ethmoid cavities on Week 25 CT*
To evaluate the effect of LYR-220 in reducing nasal inflammatory marker levels at Week 25	- CFBL in nasal inflammatory marker levels at Week 25

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design

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

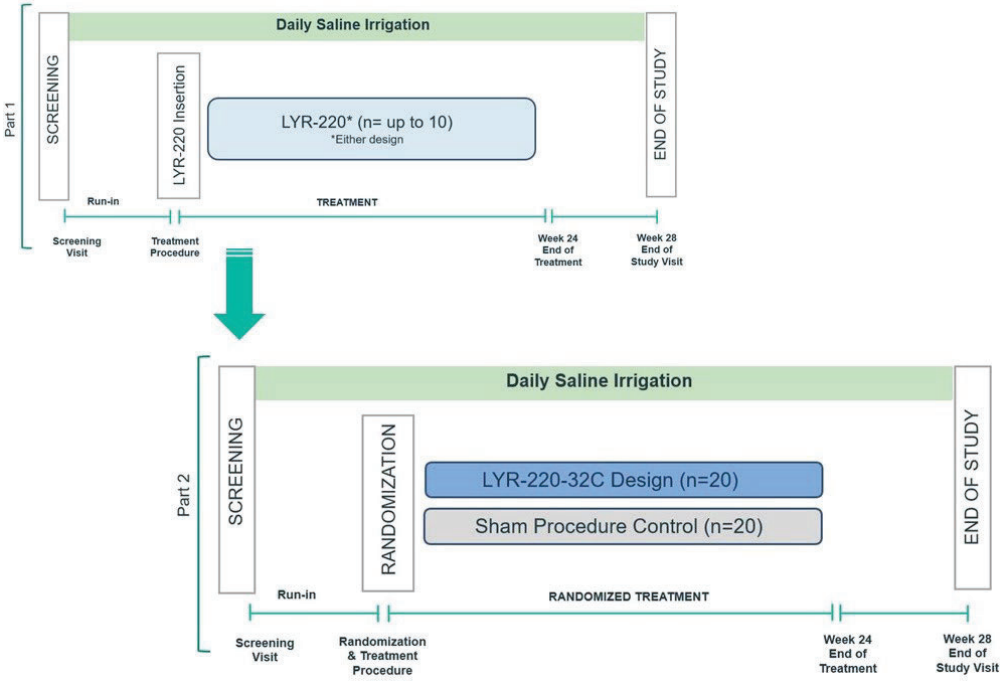
The study will consist of 2 parts. In part 1 of the study, up to 10 subjects will be treated with either design of LYR-220 bilaterally. The primary objective of the part 1 study, in addition to the safety and pharmacokinetics assessments of LYR-220, is to evaluate the feasibility of placement and optimize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

Each subject will undergo 3 stages during the study:

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

The overall study design flow diagram of subject enrollment and follow-up schedule is shown in **Figure 1**.

Figure 1: Study Design Schematic



4.1.1 Screening and Run-in Stage

After providing written informed consent, subjects who are qualified to participate in this study will have an initial Screening visit. Immediately following the initial Screening visit, subjects will undergo a 2–4-week run-in period. The run-in period is more than 5 elimination half-lives of MF (5.8 hours)[35] as recommended by FDA guidelines.[36] During this run-in period, except for a background therapy of daily saline irrigation, subjects will receive no other active treatment for CRS or any prohibited or rescue medications specified in the study protocol (Sections 6.4.2 and 6.4.4, respectively).

If a subject fails the initial screening, they are permitted to be rescreened under a new subject ID. If a patient is eligible for rescreening, the sinus CT and IOP/slit lamp assessments do not need to be repeated if the assessments were done within 4 months of rescreening and there were no significant changes in the subject's medical history according to the Investigator's judgement.

Subjects who fail screening due to administrative reasons (eg, visit window) or another screening assessment may be allowed to repeat certain screening assessment(s) and re-establish eligibility. Documentation of the decision will be filed in the subject's file.

Subjects will be provided with saline and instructions for daily intranasal saline irrigation starting from the Screening visit throughout the study. Subjects will be instructed to stop use of saline rinse approximately 24 hours prior to the scheduled sinus CT. Daily saline irrigation should then continue following the sinus CT. 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-220 insertion procedure on Treatment Day (Day 1), subjects will record daily cardinal symptoms (CS) of CRS on the electronic patient-reported outcomes (ePRO) questionnaire. At Screening, the SNOT-22 and CRS-PRO will also be collected.

4.1.2 Treatment Stage

The total duration of the Treatment Stage will be approximately 24 weeks.

In the part 1 of the study, on Day 1, subjects will be treated with any design of LYR-220 bilaterally. The LYR-220 insertion procedure will be assessed and optimized, if necessary, before the randomized part 2 phase. [Note: Subject enrollment in part 2 can begin after subjects in part 1 have undergone the LYR-220 insertion procedure; subjects in part 1 do not need to complete a certain amount of follow-up prior to part 2 commencing.] In the part 2 of the study, on Day 1, before any treatment, subjects will be randomized in a 1:1 ratio to 1 of the 2 study arms:

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

Subjects in part 2 of the study will be stratified for treatment assignment according to the following criteria:

- Nasal polyps (Yes vs No)

No more than 10 subjects with polyps will be enrolled in each treatment arm.

On Day 1, after completing any required pretreatment baseline assessments, subjects will receive local anesthetic and may receive decongestants in the ethmoid cavity for endoscopic assessment and in preparation for the insertion procedure.

All subjects will return to clinic for the scheduled follow-up assessments at Day 2 or 3, Day 5 or 8, Week 4, Week 12, Week 16 or 20, and Week 24 visits. Subjects will receive telephone follow-ups at Week 8 and Week 16 or 20 (ie, the week they are not scheduled to attend in-clinic visit for PK blood draw) to record AEs and concomitant medications/procedures that they have had since their last follow-up assessment.

At the Week 24 visit, all subjects will return to clinic for the **end-of-treatment (EOT)** visit assessments. Subjects who have received LYR-220 will have the bilateral matrices removed using standard surgical tools. Subjects in the sham treatment control arm will have a sham removal procedure.

If **spontaneous dislodgement of LYR-220** occurs before the scheduled Week 24/EOT visit, subjects are required to call the study clinic immediately to report the event. If a subject experiences dislodgement of 1 of the bilateral matrices, the subject will continue in the treatment phase unless an early treatment discontinuation is recommended by the treating physician or subject requests matrix removal from the remaining side of the nose. If matrices spontaneously dislodge from both sides of the nose, the subject will complete an unscheduled **early-termination (ET)** visit within 7 days of the second matrix dislodgement, and complete the assessments scheduled for the Week 24/EOT visit. Spontaneously dislodged LYR-220 should be retained, if available, and returned to the clinic at subject's next visit.

If medically warranted according to the treating physician's discretion (for example, needing sinonasal surgery as rescue treatment), early matrix removal may be performed at an unscheduled ET visit.

Any subject who undergoes an ET visit is required to complete the assessments scheduled for the Week 24/EOT visit and should stay in the study and complete the assessments scheduled for the Week 25 visit within 5-9 days after the ET visit.

4.1.3 Post-treatment Follow-Up Stage

All subjects will undergo a 1-week post-treatment follow-up visit (Week 25 visit). AEs, concomitant medications/procedures, endoscopy, nasal swabs, ophthalmologic assessments, CT, and other scheduled assessments will be performed at Week 25 visit. In addition, subjects will complete a 4-week post-treatment follow-up by telephone or in-clinic visit [Week 28/**end-of-study (EOS)**]. End of study assessments include AEs, concomitant medications/procedures, and final ePROs (4CS, SNOT-22, CRS-PRO, and End-of-Study Questionnaire).

4.1.4 End of the Trial

The end of the trial is defined as the date of the last EOS visit of the last subject of the study.

4.2 Rationale for Study Design

The primary objective of this study is to evaluate the safety, tolerability, and pharmacokinetics in subjects receiving LYR-220. The study design and endpoints are adequate for assessments of safety and pharmacokinetics of LYR-220 in adult subjects with CRS. The assessments of systemic and local nasal parameters in this study's CRS population and in the context of *in situ* drug delivery via drug matrix are appropriate for safety signal detection. The assessments of plasma MF concentration are sufficient to evaluate drug release profile of LYR-220. The secondary objective of this study is to determine the efficacy of LYR-220 in improving CRS symptoms. A sham treatment arm is added as a control for evaluating the LYR-220 treatment responses against control. The SNOT-22 and CRS-PRO questionnaires have been selected because they are disease specific to analyze quality of life. The 4CS questionnaire is used to evaluate daily cardinal symptoms of CRS subjects. Computed tomography (CT) scan is the gold standard diagnostic radiological tool for CRS and is adequate to evaluate the opacification of ethmoid cavity in the study subject population. The measurement of changes in nasal inflammatory marker levels is appropriate for development and further refinement of study objective endpoints in the clinical program. The safety rationale for the selection of drug dose and polymers in LYR-220 are summarized in the Investigator's Brochure (IB).

4.3 Discontinuation of Study Subjects

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

- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol, including early removal of LYR-220 (Section 6.5).
- Any serious AE (SAE, Section 8.3.11.2), clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the subject.
- Subject's decision to withdraw.
- Requiring sinonasal surgery as rescue treatment.
- If deviations to the use of prohibited medications occur during run-in and study treatment periods, the Investigator, in consultation with the Sponsor and Sponsor's medical monitor will decide on a case-by-case basis whether the subject may continue in the study based on the time the prohibited medication was administered and its pharmacology.
- Subject's failure to comply with protocol requirements or study related procedures.
- Termination of the study by the Sponsor or a regulatory authority that has provided approval to proceed.

Subjects who withdraw or are withdrawn from the study treatment will be requested to return to the clinic for the assessments and procedures scheduled for the EOT and EOS visits (Section 8.1).

The Investigator or study staff will document the reason(s) for subject discontinuation on the electronic Case Report Form (eCRF), notify the EC/IRB as required by their Institution's procedures, and notify the Sponsor of the reason for discontinuation.

4.4 Criteria for Study Termination

If the Sponsor, the Investigator, the medical monitor, EC/IRB, and/or appropriate regulatory officials discover conditions arising during the study that indicate the study should be halted or that the study center should be terminated, appropriate action may be taken after consultation among (at a minimum) the Sponsor, the EC/IRB, and the medical monitor. Refer to Section 10.13 for additional information.

5. SELECTION OF SUBJECTS

5.1 Subject Screening

All subjects evaluated for participation in this study will be screened for study eligibility. A delegated member of the Institution's research team will review the subject's medical history to screen for study eligibility. All subjects who meet initial eligibility requirements will be asked to participate in the study. Each subject will indicate his or her willingness to participate in the study by signing an EC/IRB-approved informed consent form (ICF).

Each subject will be assigned a unique subject identification number upon signing informed consent. Subjects who are assigned a subject ID but do not meet the eligibility criteria will be considered Screen Failures.

If the Investigator believes rescreening is warranted, a subject can be rescreened. Subject identification numbers assigned to subjects who fail screening should not be reused. Investigators must account for all subjects who sign an ICF. If the subject is found to be not eligible at this visit, the investigator/designee should still complete the applicable electronic case report forms (eCRFs).

Subjects who fail screening due to administrative reasons (eg, visit window) or another screening assessment may be allowed to repeat certain screening assessment(s) and re-establish eligibility. Documentation of the decision will be filed in the subject's file.

5.2 Subject Informed Consent

Prior to enrollment in the study, all subjects must review and complete an EC/IRB-approved ICF. All potential subjects must complete the consent process prior to undergoing procedures performed specifically for this study that are outside the standard of care for the institution. Failure to obtain a signed ICF renders the subject ineligible for the study. Sites will comply with ICH Guidelines for obtaining informed consent.

5.3 Inclusion Criteria

A subject must meet <u>all</u> of the following criteria to be eligible for this study:

1. Age ≥18 years.
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. Has had a prior bilateral ethmoidectomy involving both anterior and posterior ethmoids (>3 months ago). NOTE: The postsurgical ethmoid cavity should be large enough to accommodate the LYR-220 matrix.
4. Has ≥5% opacification in the ethmoid cavity on each side on CT.
5. SNOT-22 ≥20 at Screening visit.

6. Mean 3CS score over the preceding 7 days of ≥4.5 (on a 0-9 scale for the total 3CS symptoms score) determined within 7 days of Day 1 (the determination for eligibility can be made on any day from Day -7 through Day 1).
7. Not currently using INCS or decongestants at Screening or able to cease use of INCS and decongestants from Screening through the duration of the study.
8. Ability to tolerate local anesthesia.
9. 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.
10. Agrees to comply with all study requirements.

5.4 Exclusion Criteria

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

1. Ethmoidectomy that was unilateral.
2. Presence of nasal polyp grade 2 or higher (ie, polyps extending outside of the middle meatus) on either side.
3. Endoscopic exclusion criteria at Screening and Day 1 visit:
    a. Obstructing the nasal cavity for proper placement or retention of LYR-220.
    b. Dense and obstructing adhesion/synechiae of ethmoid cavity that is difficult to separate or complete adhesion of the middle turbinate to the lateral nasal wall.
    c. Severe scarring or residual ethmoid cells within ethmoid cavity preventing proper placement of LYR-220.
    d. Resected or degenerated middle turbinate that could interfere with retention of LYR-220.
    e. Evidence of mucosal erosion or ulceration within nasal cavity.
    f. Acute nasal/sinus infection or purulence.
    g. Evidence of nasal septal perforation.
4. Screening CT exclusion criteria:
    a. Anatomic variation which, in the opinion of the Investigator, would adversely impact placement or retention of LYR-220.
    b. Structural, noninflammatory related CRS (eg, large concha bullosa, tumor).
    c. Sinus disease extended into orbital or intracranial space.
    d. Evidence of mycetoma/fungal ball, allergic fungal rhinosinusitis.
    e. Sinus mucocele.
5. Seasonal allergic rhinitis (SAR) subjects with symptoms and/or, based on time of year, would anticipate onset of symptoms within 24 weeks of Day 1 procedure.
6. Perennial rhinitis subjects whose symptoms are well controlled by regular use of INCS.
7. With severe asthma or with 1 or more exacerbations of asthma requiring SCS use within the 3 months prior to the Screening visit. Subjects 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. History or clinical evidence or suspicion of invasive fungal sinusitis, allergic fungal rhinosinusitis, or atrophic rhinitis.
9. Known history of hypersensitivity or intolerance to corticosteroids.
10. Oral steroid or monoclonal antibody (Xolair, Nucala, Dupixent) dependent condition, including biologics use within 3 months of screening per protocol clarification letter.
11. SCS within 1 month prior to Screening visit.
12. Known history of hypothalamic pituitary adrenal axial dysfunction.
13. Previous pituitary or adrenal surgery.
14. 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.
15. Acute exacerbation of nasal allergy, CRS, upper respiratory tract infection (URTI), common cold, or clear worsening or acute change in symptoms within 4 weeks of the Screening visit. The infection/exacerbation must be resolved, and antibiotic or other medication use must be discontinued prior to screening per protocol clarification letter.
16. Dental procedure/implant on maxillary dentition within 4 weeks of the Screening visit.
17. Past or present acute or chronic intracranial or orbital complications of CRS (eg, brain abscess, related problems with eyes or central nervous system).
18. History or diagnosis (in either eye) of glaucoma or ocular hypertension (IOP >21 mm Hg).
19. Presence (in either eye) of posterior subcapsular cataract of grade 2 or higher, nuclear cataract 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.
20. Loss of functional vision in 1 or both eyes.
21. Diagnosed with ongoing rhinitis medicamentosa.
22. 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.
23. Past, present, or planned organ transplant or chemotherapy with immunosuppression.
24. History or diagnosis of ciliary dysfunction (eg, cystic fibrosis, primary ciliary dyskinesia [Kartagener syndrome]).
25. Past or present systemic vasculitis (eg, granulomatosis with polyangiitis).
26. Evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments.
27. 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 the time of treatment based on a urine pregnancy test. Both male and female subjects of reproductive potential must agree to use highly effective methods of birth control, throughout the study.

28. Previously received an experimental treatment in another clinical study within 5 half-lives or 30 days (whichever is longer) of Screening visit.
29. Currently participating in another drug or device study.
30. Currently positive for COVID-19 or residual sinonasal symptoms from a previous COVID-19 infection.
31. Determined by the Investigator as not suitable to be enrolled for reasons not already specified if the health of the subject or the validity of the study outcomes may be compromised.

6. TREATMENT OF SUBJECTS

6.1 Subject Allocation

6.1.1 Enrollment

Approximately 50 subjects who complete the study Screening assessments and the run-in period and meet all eligibility criteria will be enrolled and treated bilaterally with either the LYR-220-32 design or a sham treatment on Day 1 (as described in Section 4.1).

For any reason, if the Investigator is unable to successfully administer LYR-220 into both ethmoid cavities in a subject (as described in Section 6.2.4), this subject will be considered as an Enrollment Failure.

6.1.2 Randomization (Part 2 Study Only)

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

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

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

- Nasal polyps (Yes vs No)

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

6.2 Study Product Administration

6.2.1 Pre-procedure Medication

Prior to LYR-220 administration, all subjects will receive local anesthetic and decongestants in the ethmoid cavity for endoscopic assessment and in preparation for the insertion procedure according to the individual clinic/site standards.

6.2.2 Study Product Preparation

LYR-220 and sham products will be provided to the study site as described in Section 7.2.1. Preparation of LYR-220 and the sham product should be performed in accordance with the instructions for use (IFU) provided in a separate document and should not start until the subject has been prepared, anesthetized, and is ready for the insertion procedure.

6.2.3 Study Product Administration

LYR-220 is designed to be administered intranasally under endoscopic visualization. Subjects who are assigned to either design of LYR-220 will have LYR-220 administered bilaterally into the ethmoid cavity. Subjects who are assigned to the sham procedure arm, will undergo bilateral mock administration (ie, sham procedure), consisting of a bilateral insertion of an applicator (without LYR-220 matrix) into the ethmoid cavity until the applicator tip touches the posterior

wall of the ethmoid cavity for a minimum of 20 seconds, followed by withdrawal of the applicator. To maintain subject blinding to the treatment assignment in part 2 of the study, subjects will wear an eye mask (ie, blindfold) and ear/headphones at the time of the LYR-220 administration/sham procedure. A Sponsor representative/case manager may be present during Day 1 visit to provide guidance regarding product administration.

Following administration procedure, all enrolled subjects should be monitored to ensure there is no epistaxis or any other untoward conditions that requires medical attention. Subjects should remain in/around the clinic and complete any further assessments (such as the 1-hour post procedure PK blood draw) until they are cleared to leave by the study clinic personnel.

6.2.4 Enrollment Failure

The Investigator will be allowed up to 2 attempts at LYR-220 administration per side. If the Investigator is unable to administer LYR-220 bilaterally into both ethmoid cavities of a subject, the Investigator will remove any LYR-220 already administered and treat the subject with any appropriate therapy, if necessary. The subject will be considered as an **Enrollment Failure**. Follow-up with subjects will occur within 7 (± 2) days by telephone for AE and concomitant medication assessments.

6.2.5 End of Day 1 Visit

Prior to discharge at Day 1 visit, the study staff will remind enrolled subjects of the following:

- That they are currently enrolled in an investigational study for up to 6 months.
- To avoid nose blowing for the rest of the day post procedure.
- To wipe or gently blow their nose during the treatment stage.
- To sneeze with an open mouth to avoid over-pressurization to the nose.
- To call the study clinic if they have any unexpected epistaxis.
- To call the study clinic immediately should the subject experience severe discomfort or if LYR-220 falls out of the nose.

6.3 Blinding

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

6.3.1 Procedures for Breaking the Blind Prior to Study Completion

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

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

6.4 Prior and Concomitant Medications

Subjects participating 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 safety, pharmacokinetic, and efficacy assessments of LYR-220.

6.4.1 Prior Medications

Beginning at Screening, all medications and other treatments taken by subjects will be recorded on the concomitant medications CRF. In addition, all subjects will be required to refrain from use of prohibited medications (Section 6.4.2) beginning at Screening.

Subjects may be permitted to continue medications that do not meet exclusionary criteria (Section 6.4.3). If any additional concomitant medications are to be administered during the study, or a dose adjustment is required for any existing concomitant medication, the Investigator may contact the Sponsor's medical monitor for guidance prior to administration as needed, provided the safety of the subject would not be compromised.

6.4.2 Prohibited Concomitant Medications

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

- Any drug or product containing mometasone furoate (MF).
- Oral/ocular/intramuscular/intravenous/intranasal corticosteroids (except for oral corticosteroids permitted as rescue medication only).
- Anti-allergy medications, including: first generation antihistamines (eg, diphenhydramine, dimenhydrinate, chlorpheniramine), leukotriene receptor antagonists (except for a stable regimen for asthma), nasal cromolyn sodium or sodium cromoglycate, nedocromil sodium, atropine, ipratropium bromide, or guaifenesin.
- Oral/intranasal decongestants (except for short course of intranasal decongestants permitted for severe acute nasal blockage or during endoscopic procedures).
- Inhaled anticholinergic medications (except for a stable regimen for subjects with chronic obstructive pulmonary disease [COPD]).
- 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).
- Oral anti-fungal medication.

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

6.4.3 Permitted Concomitant Medications

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

- All subjects will be instructed to use daily intranasal saline irrigation as background treatment starting from Screening through the study duration.

- Subjects who have been on a stable regimen of inhaled corticosteroids (not containing MF) or leukotriene receptor antagonists for asthma 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.[1]
- 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 sprays for a maximum of 3 consecutive days and a total maximum of 10 days during the treatment period. [NOTE: Oxymetazoline cannot be used within 24 hours before CT assessments.]
- Nonsedating oral antihistamine such as loratadine (10 mg per day) or equivalent for acute allergic symptoms.
- Perennial allergic rhinitis subjects who have been on a stable regimen of a nonsedating oral antihistamine for a minimum of 3 months prior to the Screening visit should remain on the same dosage throughout the study.

6.4.4 Rescue Concomitant Medications and Treatment

The following rescue medication is recommended for a worsening or uncontrolled severe CRS symptoms that last for a minimum of 3 days and result in the subject contacting the Investigator who determines an initiation of rescue treatment is necessary at any time during the study:

- A course of oral 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 corticosteroid must be recorded.
- Sinonasal surgery as rescue treatment according to the Investigator's recommendation. The type and rationale for sinonasal surgery must be recorded.

6.5 Removal Procedure

Subjects will have the LYR-220 drug matrices removed bilaterally at the Week 24/EOT visit or earlier in an unscheduled early termination (ET) visit, if medically warranted according to the treating physician's discretion (eg, require sinonasal surgery as rescue treatment or use of any other MF medications). The removal procedure will be performed under endoscopic visualization after local anesthetic and decongestants applied to each nostril. Standard surgical tools are used to remove LYR-220. LYR-220 is made of polymers designed to gradually soften over time. Care should be taken to remove LYR-220 in 1 piece or in sections should any disintegration of LYR-220 occur.

To maintain blinding through the end of the study, subjects enrolled in the sham procedure group will undergo a sham removal procedure either at the scheduled Week 24 visit or earlier in an unscheduled early termination (ET) visit if the subject requests early study product removal.

6.6 Treatment Compliance

Administration and removal of LYR-220 and the sham procedure will be performed in a clinical setting by trained personnel who will be responsible for ensuring and recording compliance with all treatment procedures.

7. DRUG PRODUCT MATERIALS AND MANAGEMENT

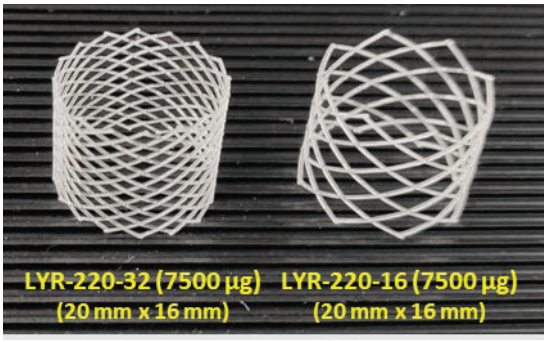
7.1 Investigational Product

7.1.1 Product Description

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

LYR-220 has a tubular braid configuration with a uniform diamond pattern throughout. It is designed to be self-retaining against the mucosal tissues to allow effective drug transfer for up to 24 weeks. The matrix is comprised of a base structure and a drug formulation layer. The base structure is composed of poly(L-lactide-co-glycolide) and poly(L-lactide-co-ε-caprolactone) elastomer to provide a 3-dimensional structure and elasticity. The drug formulation layer consists of the active ingredient, MF, embedded in the inactive ingredients containing poly(L-lactide-co-ε-caprolactone) and poly(L-lactide) to control the release rate of MF. Two designs of LYR-220, LYR-220-32 drug matrix and LYR-220-16 drug matrix, manufactured with 32 and 16 woven fibers, respectively, will be assessed in this study (**Figure 2**). Both designs have the same nominal dimensions of 20 mm in diameter and 16 mm in length in the unconstrained state.

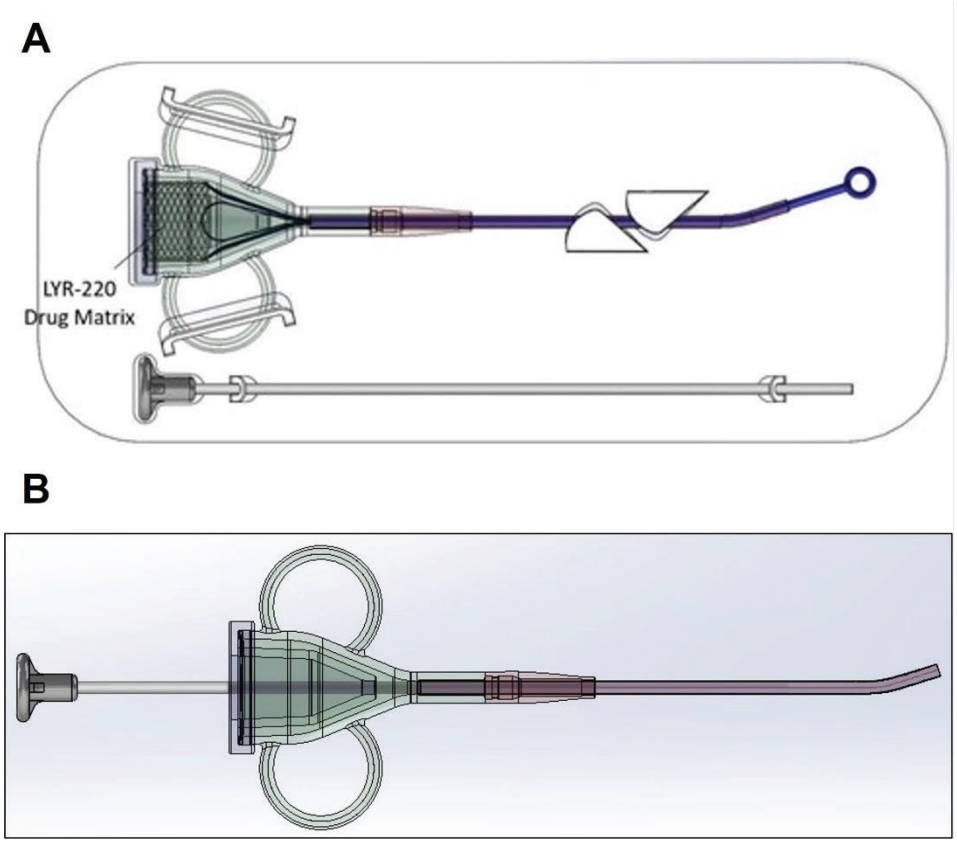
Figure 2: Images of the Two LYR-220 Drug Matrices



7.1.2 Dosage and Administration

Each LYR-220 drug matrix contains 7500 µg MF. LYR-220 is intended to be administered bilaterally into the ethmoid cavity, in which ethmoid sinuses have been removed previously by a bilateral ethmoidectomy, by an otolaryngologist under endoscopic visualization using the provided single-use applicator (**Figure 3**). Once administered, each LYR-220 is designed to gradually deliver sustained doses of MF to the inflamed mucosal tissue over a 24-week resident time. Bilateral placement of LYR-220 (7500 µg) is designed to deliver a total dose of 15,000 µg MF over the 24 weeks, or an average daily dose of 89 µg MF per person (or 45 µg MF per nostril).

Figure 3: LYR-220 Applicator Packaged with Drug Matrix (A) and Sham Applicator (B)



7.2 Drug Product Management

7.2.1 Packaging and Labeling

The investigational products (LYR-220 and sham) will be packaged and labeled, as required by regional legislation and industry guidelines. The LYR-220 System and sham products are individually packaged in a foil pouch, which is sterilized and placed within a shelf carton.

The Sponsor or designee will ship study products to the sites as needed. Specific instructions for ordering product will be provided to the sites.

7.2.2 Storage

It is recommended that the study product be stored at 15 °C to 25 °C (59 °F to 77 °F) and in the original packaging to protect from moisture and light. The labeled expiry dates are specified on the label. The location of drug product storage must be locked, and access must only be allowed to the study team or a designated person involved with the study team.

7.2.3 Product Traceability

Traceability of study products shall be achieved by assigning each product package a unique serial/kit number as described on the label.

7.2.4 Product Accountability

The Sponsor will supply sufficient quantities of LYR-220 and sham products to allow completion of the study. The Investigator or designee must maintain accurate records to document the disposition of all product received by the clinical site. Investigational sites will use a form to document product disposition which will be reviewed by the study monitor during routine monitoring visits. When enrollment in the Clinical Study is complete, any unused investigational product will be returned to Sponsor or discarded per Sponsor authorization along with a final Accountability Log. The Accountability Log must document the disposition of all investigational products including those that have been returned to the Sponsor.

7.2.5 Product Return

All products that are not administered into a subject 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. For all investigational products that are associated with a malfunction, the products and all ancillary components (eg, applicator) remaining from the index procedure should be retained in case they need to be returned to the Sponsor. 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.

8. STUDY ASSESSMENTS

8.1 Study Schedule of Assessment

The schedule of study assessments for subjects is summarized in **Table 1** below and detailed in Sections 8.2, 8.3, and 8.4. All subjects in Part 1 and Part 2 will undergo these study assessments per the schedule.

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events (AEs) or untoward findings. Any AEs observed by the Investigator or reported by the subjects, whether or not attributed to the investigational procedure or product, will be monitored and evaluated throughout the study. If AEs occur, the first concern will be the safety and welfare of the subject. Appropriate medical intervention will be undertaken per the treating physician's discretion.

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

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

Ophthalmologic assessments will include IOP and slit-lamp examination during Screening and at Week 25 visit. IOP assessment will also be performed at Week 4 and 12 visits.

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

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

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

(pretreatment) and at Weeks 8, 16, and 24/EOT. The PGIC will be assessed at Week 24/EOT. At Week 28/EOS visit, an end-of-study questionnaire will be administered.

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

Table 1: Schedule of Assessments for Subjects Enrolled

Evaluation	Screening & Run-In	Procedure Day	Treatment Stage													Post-Treatment Stage	
Visits #	1	2	3		4		T	T	5	T	T	6	7/T		8	9	10/T [p]
Study Day/Week	DAY -28 (Day -28 to Day 0)	DAY 1 (Day 1)	DAY 2 (Day 2)	DAY 3 (Day 3)	DAY 5 (Day 5)	DAY 8 (Day 8)	WK 2 (Day 15±1)	WK 3 (Day 22±2)	WK 4 (Day 29±3)	WK 6 (Day 43±3)	WK 8 (Day 57±3) [a]	WK 12 (Day 85±3)	WK 16 (Day 113±3) [a]	WK 20 (Day 141±3) [a]	WK 24/EOT/ET (Day 169±7)	WK 25 (5-9 days after EOT/ET)	WK 28 (EOS) (25-31 days after EOT)
Informed Consent	X [c]																
Demographics	X																
Medical History	X																
Vital Signs	X																
Limited Physical Exam [l]	X																
Pregnancy Test [f]	X [e]	X [d,e]							X [e]			X [e]			X [e]		
Hematology/Chemistry [f]	X															X	
Sinus CT	X															X [m, n]	
PK		X [d, o]	X [g]		X [g]				X			X	X [g]		X [d]	X	
Nasal Endoscopy	X	X [i]							X [i]			X [i]			X [d, i]	X [i]	
Ophthalmology (IOP and slit-lamp)	X								X [b]			X [b]				X [m]	
Eligibility Assessment	X	X [d]															
Nasal secretion & mucosal RNA (culture & cytology swabs)		X [d]														X	
Run-in	X [h]																
Randomization (Part 2 study only)		X [d]															
Insertion Procedure		X															
Removal Procedure															X		
Daily 4CS ePRO [j]	X																
SNOT-22 Questionnaire [j]	X [r]	X [d, r]					X [r]		X [r]	X [r]	X [r]	X [r]	X [r]	X [r]	X [d, r]		X [r]
CRS-PRO Questionnaire [j]	X [s]	X [d, s]				X [s]	X [s]	X [s]	X [s]	X [s]	X [s]	X [s]	X [s]	X [s]	X [d, s]		X [s]
PGIS		X [d,q]									X [q]		X [q]		X [q]		

Evaluation	Screening & Run-In	Procedure Day	Treatment Stage													Post-Treatment Stage	
Visits #	1	2	3		4		T	T	5	T	T	6	7/T		8	9	10/T [p]
Study Day/Week	DAY -28 (Day -28 to Day 0)	DAY 1 (Day 1)	DAY 2 (Day 2)	DAY 3 (Day 3)	DAY 5 (Day 5)	DAY 8 (Day 8)	WK 2 (Day 15±1)	WK 3 (Day 22±2)	WK 4 (Day 29±3)	WK 6 (Day 43±3)	WK 8 (Day 57±3) [a]	WK 12 (Day 85±3)	WK 16 (Day 113±3) [a]	WK 20 (Day 141±3) [a]	WK 24/EOT/ET (Day 169±7)	WK 25 (5-9 days after EOT/ET)	WK 28 (EOS) (25-31 days after EOT)
PGIC															X [q]		
End-of-Study Questionnaire																	X
Concomitant Medications/Procedures	X																
Adverse Events [k]	X																

Abbreviations: 4CS = 4 cardinal symptoms of CRS; ePRO = electronic patient-reported outcomes; T = Telephone follow-up; EOT = end of-treatment; ET = early termination; EOS = end-of-study; IOP = intraocular pressure; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic testing; RNA = ribonucleic acid; SNOT = 22-item Sino-Nasal Outcome Test; WK=week.

a: Phone follow-up to collect any potential AEs and use of concomitant medications/procedures.
b: IOP assessment only.
c: Informed consent to be obtained before any study-related assessments occur.
d: Occurs before the LYR-220/sham insertion on Day 1 or removal procedures at Week 24.
e: Complete a serum pregnancy test at initial Screening visit and a urine pregnancy test in clinic at all subsequent visits during the treatment stage for female subjects of childbearing potential.
f: Investigators must document their review of each laboratory report.
g: Subjects return to clinic for PK assessment at only 1 of 2 timepoints at Visits 3 and 4. Subjects return to clinic for Visit 7 PK assessment either at Week 16 or Week 20; a telephone follow-up will be performed the week the subject is not returning for a PK draw.
h: Subjects will start daily saline irrigation during run-in period.
i: Nasal safety assessments of ethmoid cavity including epistaxis, mucosal injury, and any other adverse findings will be performed on Day 1 (before LYR-220 insertion) and at Week 4, 12, 24/EOT, and 25 visits.
j: Daily (between 06:00:00AM and 11:59:59AM) cardinal CRS symptoms, to be recorded by the subject on ePRO questionnaire beginning at least 14 days preceding or on Day 1 visit (prior to randomization).
k: All adverse events shall be reported after subject signs informed consent.
l: A physical examination of the head, eyes, ears, nose, and throat (HEENT).
m: To be performed within 5-9 days after removal procedure.
n: If a subject is experiencing or recovering from a cold, acute exacerbation of nasal allergy, or upper respiratory tract infection at the Week 25/EOS visit, the CT assessment should be performed 4 weeks after resolution of the adverse event.
o: A blood sample for PK assessment should be collected 1 hour (±10 minutes) after bilateral LYR-220 insertion.
p: Week 28/EOS follow-up may be performed either as a telephone follow-up or an in-clinic visit (if subjects need to return a study supplied ePRO device).
q: It is recommended that the PGIS be completed after the 4CS questionnaire. The PGIS should be completed before the PGIC.
r: SNOT-22 to be recorded by the subject based on a recall period of 2 weeks (14 days) prior to visit.
s: CRS-PRO to be recorded by the subject based on a recall period of 7 days prior to the visit.

8.2 Assessment of Subject Characteristics

8.2.1 Demographics

Demographic information (age, sex, ethnicity, and race) will be obtained during Screening as specified in the Study Schedule of Assessments (Section 8.1).

8.2.2 Medical and Surgical History

Medical and surgical history information will be obtained during Screening as specified in the Study Schedule of Assessments (Section 8.1).

A general medical history will be collected. In addition, the medical history will document conditions, focusing specifically on the following body systems: head, eyes, ears, nose, throat (HEENT). The medical history will also include an assessment of the subject's lifetime history of the following:

- Chronic rhinosinusitis
- Asthma
- Chronic obstructive pulmonary disease (COPD)
- Perennial rhinitis
- Seasonal allergic rhinitis (SAR)
- Sensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs)
- Smoking

Subjects will also be assessed if they had the following history of surgery or injury in the past:

- Ethmoidectomy
- Polypectomy
- Nasal surgery involving nasal turbinates
- Functional endoscopic sinus surgery (FESS)
- Any known history of surgery or injury that may prevent placement or retention of LYR-220

8.3 Assessment of Safety

8.3.1 Physical Examination

A limited physical examination including a careful assessment of the head, eyes, ears, nose, and throat (HEENT), will be performed at Screening visit as specified in the Study Schedule of Assessment (Section 8.1). Height and weight will also be measured. Body mass index (BMI) will be calculated based on the measured height and weight.

8.3.2 Vital Signs

Vital signs will be measured at the screening visit as specified in the Schedule of Assessments (Section 8.1). Vital sign measurements will include blood pressure (systolic and diastolic, mm Hg), and pulse rate (beats per minute), aural/oral temperature (°C or °F), and respiration rate (breaths per minute). All measurements will be obtained after the subject has been seated for at least 5 minutes.

8.3.3 Laboratory Assessments

Laboratory testing will be performed at clinic visits as specified in the Schedule of Assessments (Section 8.1). Any unused duplicated samples collected for the purpose of this study will be destroyed after the completion of the study. Testing will be performed at a central laboratory.

8.3.3.1 Hematology

Samples for hematology assessments will be obtained during Screening and Week 25 visits as specified in the Schedule of Assessments (Section 8.1).

Hematology assessments will include white blood cell (WBC) count and WBC differential (neutrophils, eosinophils, lymphocytes, monocytes, and basophils), red blood cell (RBC) count, hematocrit, hemoglobin, and platelet count.

8.3.3.2 Blood Chemistry

Samples for blood chemistry assessments will be obtained during Screening and Week 25 visits as specified in the Schedule of Assessments (Section 8.1).

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.

8.3.4 Nasal Endoscopy Assessments

Ethmoid cavities will be assessed by endoscopy during Screening, on Day 1 prior to LYR-220 administration procedure, and at Week 4, 12, 24/EOT (before LYR-220 removal), and 25 visits as specified in the Schedule of Assessments (Section 8.1).

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

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

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

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

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

8.3.5 Ophthalmologic Assessments

The ophthalmologic assessment of IOP and slit-lamp examination to identify development or worsening of cataract will be conducted at Screening and Week 25 visits as specified in the Schedule of Assessments (Section 8.1). The cataract assessment will be conducted according to the Simplified Cataract Grading System authored by the World Health Organization Cataract Grading Group. Subject's eyes will be dilated with mydriatics following the WHO guidance for cataract assessment.[42] IOP may be measured using Goldmann applanation tonometer, noncontact tonometer, or tono-pen; however, it is recommended that the same method be used for consistency across serial assessments on a given subject. IOP assessment will also be performed at Week 4 and 12 visits. 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 that is blinded to the subject's treatment assignment.

8.3.6 SCS rescue

Oral steroids for rescue treatment of CRS or intravenous or oral steroids for another reason that are prescribed to the subject are to be recorded in the eCRF. All efforts should be made to complete the Week 25 assessments including nasal endoscopy and CT before starting treatment with SCS. However, the subject should continue with the study treatment and follow-up visits. The investigator (or designee) will record the dates and dosing information (dosage form, daily dose, duration, name of drug) on the appropriate page(s) of the eCRF. Indication for SCS use will also be captured. A course of SCS is considered continuous if treatment is separated by less than 7 days.

8.3.7 Sinonasal surgery (actual or planned) for CRS

For subjects who have a surgery or have a scheduled date for sinonasal surgery as rescue for CRS, the reason (worsening signs and/or symptoms during the study), the date the surgery was indicated, expected or actual surgery date, and the type and outcome of surgery will be recorded in the eCRF. Types of sinonasal surgery include, but are not limited to, repeat 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 Week 24/EOT visits will be completed prior to the surgery. Additionally, all efforts should be made to complete the Week 25 assessments including nasal endoscopy and CT prior to the surgery. The subject will be discontinued from the study.

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

8.3.8 Pharmacokinetic Analysis

Blood samples for assessment of plasma PK will be collected from all subjects on 9 occasions as specified in the Schedule of Assessments (Section 8.1):

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

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

8.3.9 Explanted LYR-220 Analysis

All removed or spontaneously dislodged LYR-220 will be collected and returned to Lyra Therapeutics (or designee) if allowed by the individual hospital standard operating procedures (SOPs). Instructions for the processing and return of removed or spontaneously dislodged LYR-220 will be provided.

The mass of remaining MF in LYR-220 and the molecular weights of the polymers in LYR-220 may be measured.

8.3.10 Pregnancy or Breast Feeding

Females of child-bearing potential must test negative for pregnancy at the time of Screening visit based on a serum pregnancy test and reverified before treatment at Day 1 visit based on a urine pregnancy test. Females who can confirm that they are surgically sterile or have been postmenopausal for at least 1 year prior to signing the ICF do not need to undergo a pregnancy test. Urine pregnancy test will be performed to successfully enrolled female subjects of child-bearing potential at Week 4, 12, and 24/EOT visits.

Female subjects who are of childbearing potential are required to practice a highly effective form of birth control to continue in the study and for 1 week after the removal procedure. Male subjects of reproductive potential who are having intercourse with female partners of childbearing potential must agree to use 2 forms of contraception, 1 of which must be a barrier method, during the study and for 1 week after the removal procedure. Acceptable barrier methods include a condom and diaphragm.

Definition of Childbearing Potential and Highly Effective Contraceptive Methods:

A woman is considered of childbearing potential (ie, fertile), following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

For women of childbearing potential, the following methods of contraception, when used consistently and correctly, are considered reliable for participation in the study:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable or implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner (provided that partner is the sole sexual partner and that vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (refraining from heterosexual intercourse during the entire study period; the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject).

If a female subject who has successfully received bilateral placement of LYR-220 becomes pregnant during the treatment stage, the Investigator must notify the Sponsor within 24 hours of becoming aware of the event on a Pregnancy Report Form. The Investigator must continue to follow the pregnancy until the completion of the pregnancy, including the outcome and the condition of the newborn at 8 weeks postpartum (if applicable). If not all information on the Pregnancy Report Form is available at the time of the initial report, follow-up reports should be provided to the Sponsor in a timely manner. Additional subsequent follow-up is not needed when a newborn baby is healthy.

8.3.11 Adverse Events and Serious Adverse Events

8.3.11.1 Adverse Event (AE)

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 subject. Appropriate medical intervention will be undertaken. Any AE observed by the Investigator or reported by the subjects, whether or not ascribed to the investigational procedure or product, will be recorded on the subject's AE CRF. All ongoing AEs that result in early termination from the

study or are deemed to be study product- or procedure-related by the Site Investigator will be followed up 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 subject upon indirect questioning.

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

A **Treatment Emergent AE (TEAE)** is an AE that occurs or worsens on or after initiation of the LYR-220 administration procedure.

8.3.11.2 Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that:

- Results in, leads to, or contributes to, a death;
- Is life-threatening ("Life-threatening" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe);
- Results in subject hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (ie, permanent impairment of a body function or permanent damage to a body structure);
- Results in fetal distress, fetal death or a congenital anomaly/birth defect;
- Is an important medical event which may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes.

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 subject (Section 8.3.11.4). Any treatment related SAE will be followed until resolution of the event, or until the subjects withdraw from the study.

8.3.11.3 Relationship to Study Drug Product and Procedure

The Investigator should initially classify the causality of an AE and determine the relationship between an AE and the study product or procedure.

8.3.11.3.1 Relationship to Study Drug Product

The relationship between an AE and the LYR-220 study drug product will be determined by the Investigator on the basis of his or her clinical judgment and the following definitions:

- **Definitely Related:** The AE follows a reasonable temporal sequence from administration of the investigational product; the AE follows a known or expected response pattern to the investigational product.

- **Possibly Related:** The AE follows a reasonable temporal sequence from administration of the investigational product; the AE follows a known or expected response pattern to the investigational product but could readily have been produced by a number of other factors.
- **Not Related:** An AE for which sufficient information exists to indicate that the etiology is unrelated to the investigational product. One or more of the following variables apply:
  - The AE does not follow a reasonable temporal sequence following administration of the investigational product;
  - The AE is readily explained by the subject's clinical state or other therapies.

For events that are determined to be definitely or possibly related, additional information on the timing of the event in relation to the LYR-220 study drug product administration will be captured.

8.3.11.3.2 Relationship to Study Procedure

The relationship between an AE and the LYR-220 administration or removal procedure (within 24 hours) will be determined by the Investigator on the basis of his or her clinical judgment and the following definitions:

- **Definitely Related:** The AE follows a reasonable temporal sequence from performance of the study procedure; the AE follows a known or expected response pattern to the study procedure.
- **Possibly Related:** The AE follows a reasonable temporal sequence from performance of the study procedure; the AE follows a known or expected response pattern to the study procedure but could readily have been produced by a number of other factors.
- **Not Related:** An AE for which sufficient information exists to indicate that the etiology is unrelated to the study procedure. One or more of the following variables apply:
  - The AE does not follow a reasonable temporal sequence following the study procedure;
  - The AE is readily explained by the subject's clinical state or other therapies.

For events that are determined to be definitely or possibly related to the study LYR-220 administration or removal procedure, additional information on the timing of the event in relation to the study procedure will be captured.

8.3.11.4 Severity of Adverse Events

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

- **Mild:** Event is noticeable to the subject but is easily tolerated and does not interfere with the subject's daily activities.

- **Moderate:** Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- **Severe:** Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

8.3.11.5 Expectedness of Serious Adverse Events

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

- **Unexpected:** An SAE that is not listed in the study protocol, 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.

8.3.11.6 Reporting

8.3.11.6.1 Adverse Event Reporting

Adverse events are to be collected from the time a subject signs the informed consent until the completion of all follow-up visits. At each office visit during the study, AEs that have occurred since the previous office visit must be recorded. All subjects 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 the course of 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 (eg, clinically significant) change from baseline for that individual subject. If this laboratory test result is determined to be a clinically significant abnormal change from baseline for that subject, the value will be considered to be an AE.

The description of the AE will include the date of onset, date of resolution (ongoing), severity, seriousness, relationship of the event to the investigational product and to the study procedure, and any procedure required. Specific procedures implemented in response to the AE will also be recorded. For all AEs, the Investigator is required to supply any additional data that may be deemed necessary by the Sponsor or designee.

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

8.3.11.6.2 Serious Adverse Event Reporting

The Investigator will be required to report all SAEs that occur throughout the course of the study. Information such as the Investigator name, study name/protocol number, subject identification number, the description of the SAE, the Investigator's assessment as to the relationship to the investigational product and the study procedure, and the reporting source should be included in the initial report. Any additional supporting documentation may be requested by the Sponsor or designee, as necessary. This also includes forwarding pertinent follow-up information (eg, clinic discharge summary) as it becomes available. A completed SAE form needs to be submitted with each follow-up. Reports relating to the subject's subsequent medical course must be submitted to the Sponsor until the event has resolved or, in case of permanent impairment, until the event stabilizes, and the overall clinical outcome has been ascertained.

Each SAE should be reported to the Sponsor or designee within 24 hours of knowledge of the event. The Sponsor will ensure that all SAEs are reported to the relevant authorities and Investigators, as required by local regulations.

8.3.11.6.3 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 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 subjects.

8.3.12 Safety Monitoring

Subject will be closely monitored throughout the trial with high priority for subject safety. The sponsor will establish 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.

Subject 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 may be undertaken. Reviews of aggregate data as well as individual subject data may be undertaken to identify outliers and trends that may impact safety of the subject and consistency of data.

8.4 Assessment of Efficacy

8.4.1 Subject Reported Outcomes

Subject symptoms, use of saline irrigation, and the overall experience of study will be captured using an ePRO system. Subjects will be instructed on the method for completing the ePRO. In instances where the ePRO may not be available for any reason, subjects will be instructed to complete the PRO questionnaires using paper forms. At all clinic visits, questionnaires will be completed prior to any intranasal procedure or clinic assessments.

8.4.1.1 Chronic Rhinosinusitis Cardinal Symptom Assessment

For assessment of the 4 CS of CRS, the ePRO will be completed by subjects on a daily basis as specified in the Schedule of Assessments (Section 8.1). Subjects will start recording their symptoms on the ePRO at least 14 days preceding the Day 1 visit. A minimum of 4 daily entries are required for composite score calculation over the preceding 7 days prior to Day 1 (not including Day 1) for assessing subject's eligibility for participating in the study.

The 4 CS of CRS, as defined in the European Position Paper on Rhinosinusitis and Nasal Polyps 2020[9], include nasal blockage/obstruction/congestion, facial pain/pressure, nasal discharge (anterior/posterior nasal drip), and reduction or loss of smell.

Subjects will complete the daily assessment of their CS severity each morning (between 06:00:00AM to 11:59:59AM) and rate the severity of each symptom at its worst over the past 24 hours on a 4-point scale (Section 13.1):

- 0 = absent symptoms (no sign/symptom evident)
- 1 = mild symptoms (sign/symptom present but minimal awareness; easily tolerated)
- 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

8.4.1.2 Saline Irrigation Use

The ePRO will also be used to collect the frequency of daily saline irrigation by the subjects. Subjects will be instructed to stop use of saline rinse approximately 24 hours prior to the scheduled sinus CT. Daily saline irrigation should then continue following the sinus CT.

8.4.1.3 22-Item Sino-Nasal Outcome Test (SNOT-22) Questionnaire

The ePRO will also be used to collect responses to the SNOT-22 questionnaire at the time points specified in the Schedule of Assessments (Section 8.1).

The SNOT-22 questionnaire is a 22-item disease-specific quality of life instrument validated for use in CRS (Section 13.2).[37] Subjects will score the severity of their symptoms and social/emotional consequences of CRS on a 6-point scale over the past 2 weeks:

- 0 = no problem
- 1 = very mild problem
- 2 = mild or slight problem
- 3 = moderate problem
- 4 = severe problem
- 5 = problem as bad as it can be

The scores are summed; higher scores on the SNOT-22 instrument total score or subdomain scores (as defined in Table 2) indicate higher severity of symptoms or social/emotional consequences of CRS.[38]

Table 2: Categorized Survey Items for Separate Domains of the SNOT-22 Instrument

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

SNOT-22 = 22-item Sino-nasal Outcome Test.

8.4.1.4 Patient-Reported Outcome Measure for Chronic Rhinosinusitis (CRS-PRO) Questionnaire

The ePRO will also be used to collect responses to the CRS-PRO questionnaire at the time points specified in the Schedule of Assessments (Section 8.1). The 12-item CRS-PRO is a new disease-specific measure of CRS (Section 13.3).[39] It is a validated measure of CRS symptoms and was developed by using extensive input from CRS patients. The questionnaire assesses CRS in 3 domains including physical symptoms, sensory impairment, and psychosocial effects. Subjects will score the severity of their CRS symptoms on a 5-point scale over the past 7 days, with higher score representing worse quality of life:

- 0 = not at all
- 1 = a little bit
- 2 = somewhat
- 3 = quite a bit
- 4 = very much

8.4.1.5 Patient Global Impression of Severity (PGIS)

The ePRO will also be used to collect responses to the PGIS questionnaire at the time points specified in the Schedule of Assessments (Section 8.1). Subjects will be asked a single question

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

8.4.1.6 Patient Global Impression of Change (PGIC)

The ePRO will also be used to collect responses to the PGIS questionnaire at Week 24, as specified in the Schedule of Assessments (Section 8.1). The PGIC is a self-assessment of the subject's overall change in CRS-related symptom severity compared to pretreatment. The PGIC 7-point balanced scale is as follows: very much better, much better, a little better, no change, a little worse, much worse, very much worse.

8.4.1.7 End-of-Study Questionnaire

At Week 28/EOS visit, subjects will complete an end-of-study questionnaire collected by the ePRO (Section 13.4). The questionnaire will query subjects about their general experience and satisfaction with their assigned study treatment. Subjects will describe their experiences by answering multiple-choice questions or providing narrative responses.

8.4.2 Ethmoid Cavity Opacification Imaging

Ethmoid cavity opacification will be assessed by CT at the time points specified in the Schedule of Assessments (Section 8.1), unless medically contraindicated. The Screening CT should be performed anytime between the Screening and Day 1 visits. Alternatively, a historical CT scan can be used if done within 3 months preceding the Screening visit. The follow-up CT will be conducted within 5-9 days after the LYR-220 removal procedure at Week 25 visit. If a subject is experiencing or recovering from a cold, acute exacerbation of nasal allergy, or upper respiratory tract infection at the Week 25 visit, the CT assessment should be performed 4 weeks after resolution of the adverse event. If a subject early terminates from the study or requires SCS or sinonasal surgery as rescue treatment during the study, every attempt should be made to perform the follow-up CT before subject receives the rescue treatment. The percent opacification of ethmoid cavity will be evaluated by an imaging core lab.

8.4.3 Nasal Inflammatory Marker Levels

Nasal inflammatory marker levels will be assessed by collecting nasal swabs at the visits specified in the Study Schedule of Assessments (Section 8.1). The baseline nasal swabs will be collected before LYR-220 administration at Day 1 visit. The follow-up nasal swabs will be collected at Week 25 visit. Nasal swabs will be collected from each side nasal passage to assess levels of T2 inflammatory markers. Two nasal swabs per side (1 for protein sample collection and 1 for RNA sample collection) will be collected. Nasal swabs will be collected according to the guidelines provided by the Sponsor.

9. STATISTICAL ANALYSIS

9.1 Sample Size

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

9.2 Analysis Populations

The following analysis sets are defined for analysis purposes:

- Safety analysis set: All subjects who received the study treatment. Subjects will be analyzed according to the treatment received. This is the primary analysis set for assessment of safety.
- Efficacy analysis set: All subjects who received the study treatment. This is the primary analysis set for assessment of efficacy. Subjects will be analyzed according to the treatment they actually received.

9.3 Disposition and Population Assignment

Subject disposition will be summarized for all consented subjects and will include the total number and percentage of subjects enrolled into the study, treated, and completed the study. The number and percentage of subjects prematurely discontinuing from the study will be presented for each treatment group. Subjects who discontinue from the treatment or the study are categorized by reason for discontinuation; the number and percentage of subjects in each category will also be summarized for each treatment group. Analysis set assignment will be summarized by treatment group.

9.4 Demographic and Other Baseline Characteristics

All demographic (age, sex, race, ethnicity, height, weight, and BMI) and baseline disease characteristics recorded at screening and prior to LYR-220 administration will be summarized by treatment group for the efficacy analysis set. 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 subjects in each category. Medical history and pregnancy test results will only be listed by subject.

9.5 Prior and Concomitant Medications

Prior medications are those medications that were stopped prior to investigational product administration. Concomitant medications are medications that are taken at least once after investigational product administration. Medications stopping on the same day as investigational product administration will be considered as concomitant medications.

All prior and concomitant medications will be listed. In addition, for each treatment group, the number and percentage of subjects taking at least 1 concomitant medication will be presented.

9.6 Safety Analyses

All safety analyses will be performed using the safety analysis set. There will be no formal statistical tests comparing treatments on safety endpoints and there will be no imputation of missing data.

Treatment-emergent adverse events (TEAEs) are defined as AEs that first occurred or worsened in severity after the initiation of study treatment administration.

Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). For each study treatment, incidence rates (number and percentage of subjects with at least 1 TEAE) will be tabulated by preferred term and system organ class.

TEAEs by maximum severity, TEAEs by highest relationship to study procedure and product, TESAEs, TESAEs leading to death, and TEAEs leading to discontinuation of study treatment will be tabulated as number and percentage of subjects with at least 1 such TEAE for each treatment group overall and by preferred term and system organ class. Note that subjects experiencing >1 event within the same system organ class will be tabulated only under the maximum severity and highest relationship experienced for that system organ class; similarly, subjects experiencing >1 event within the same preferred term will be tabulated only under the maximum severity and highest relationship experienced for that preferred term.

All laboratory test results will be summarized by treatment group using descriptive statistics for actual value and change from baseline. Treatment-emergent abnormal and clinically significantly abnormal laboratory test results, ophthalmology examination findings, and nasal endoscopy findings will be summarized by treatment group.

9.7 Pharmacokinetic Analyses

9.7.1 Pharmacokinetic Concentrations

PK concentration will be summarized for subjects in the Efficacy analysis set with available plasma MF concentration data by treatment group as follows:

- A listing by subject of all concentrations, nominal times post dose, and actual times. Deviations from the nominal times per protocol will be given in a separate listing. In listings, concentrations below the lower limit of quantification (LLOQ) will be reported as "<LLOQ", where LLOQ will be the actual value of LLOQ (to be determined).
- A descriptive statistics summary of concentrations by LYR-220 design and actual PK sampling time, including number (n), mean, SD, coefficient of variation (CV), median, minimum, maximum, and the number of concentrations ≥LLOQ. The "<LLOQ" values will be set to zero based on the Beal's method M7.[40]

9.7.2 Pharmacokinetic Parameters

If plasma MF levels are detectable, PK parameters of MF will be estimated using a standard noncompartmental PK approach based on individual plasma concentration-time data. Actual PK sampling times will be used in the derivation of PK parameters. Maximum concentration (C_{max}) and time to reach maximum concentration (T_{max}) will be taken directly from the observed data.

Total drug exposure up to the last measured concentration ($AUC_{0\text{-last}}$) and the 12-hour average drug exposure ($AUC_{0\text{-12h average}}$) will be calculated from the plasma concentrations versus time profiles. Descriptive statistics of these parameters will be presented by treatment group.

9.8 Efficacy Analyses

All efficacy analyses will be carried out after the last subject completes the Week 28/EOS visit or withdraws prematurely prior to Week 28/EOS. Each efficacy analysis will be performed based on the Efficacy analysis set.

9.8.1 Efficacy Endpoint Analysis

The efficacy endpoints are:

- CFBL in SNOT-22, CRS-PRO, or cardinal symptom scores
- Time to first rescue treatment recommendation
- Oral steroid use or sinonasal surgery
- CFBL in bilateral percent ethmoid cavity opacification by CT at Week 25
- CFBL in PGIS score at Weeks 8, 16, and 24
- PGIC score at Week 24
- Conversion to a candidate no longer requiring revision surgery
- CFBL in biomarker level at Week 25

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

9.8.1.1 CFBL in SNOT-22, CRS-PRO, PGIS, or Cardinal Symptom Scores

Descriptive statistics (number of observations[n], mean, SD, median, minimum, and maximum) of the observed score and the CFBL score at each timepoint will be presented for each treatment group for SNOT-22, CRS-PRO, PGIS, or CS scores.

A mixed model repeated measures (MMRM) approach will be used to compare changes from baseline (CFBL) between each LYR-220 group and the sham procedure group in SNOT-22, CRS-PRO, PGIS, and CS scores. *P* values ≤ 0.05 will be considered statistically significant. An analysis of covariance (ANCOVA) model will be used to analyze the CT score and biomarker levels.

9.8.1.1.1 Handling of Missing Data and Data Post-Rescue Treatment

Efficacy data collected after early termination will be included in the analysis. A last observation carried forward (LOCF) method will be used to impute post rescue treatment and missing data. Rescue treatments include SCS and/or sinonasal surgery for any reason. There will be no imputation for missing follow-up CT or biomarker assessments.

9.8.1.2 Time-to-First Recommendation of Rescue Treatment

This efficacy endpoint is to analyze the first time a subject uses rescue treatment for worsening of CRS symptoms. Rescue treatment is defined as, after subject enrollment, worsening or acute exacerbation of CRS in a subject resulting in the treating physician reporting an escalation of

treatment with either systemic corticosteroids (SCS) and/or sinonasal surgery. Time to first recommendation of rescue treatment will be analyzed using Kaplan-Meier (K-M) method. The K-M estimate of median time to first recommendation of rescue treatment (if estimable) will be presented for each treatment group. The K-M curve of time to first recommendation of rescue treatment will be compared between each LYR-220 group and the sham procedure group using the log-rank test.

9.8.1.3 Oral Steroids or Sinonasal Surgery Recommendation

The endpoint will be summarized using the percentage of subjects being recommend by treating physician for oral/systemic steroids (SCS) or sinonasal surgery in each treatment group. Comparison between each LYR-220 group and the sham procedure group will be performed using a Cochran-Mantel-Haenszel (CMH) test controlling for nasal polyp status.

9.8.1.4 CFBL in Bilateral Percent Ethmoid Cavity Opacification by CT at Week 25

Mean CFBL in bilateral percent ethmoid cavity opacification by CT at Week 28 will be compared between each LYR-220 group and the sham procedure group using an ANCOVA model with fixed-effect terms for treatment group and nasal polyp status with baseline score as a covariate.

9.8.1.5 Conversion to A Candidate No Longer Requiring Revisions Surgery

This responder endpoint will be summarized using the percentage of subjects that meet the criteria for no longer requiring revision surgery in each treatment group. Comparison between each LYR-220 group and the sham procedure group will be performed using the CMH test controlling for nasal polyp status.

9.8.1.6 CFBL in Nasal Inflammatory Marker Levels at Week 25

Mean CFBL in nasal inflammatory marker levels at Week 25 will be compared between each LYR-220 group and the sham procedure group using an ANCOVA model with fixed-effect terms for treatment group and nasal polyp status with baseline score as a covariate.

9.9 Interim Analysis/ Study Adaptation

An interim analysis may be performed to assist with better understanding of the study progress and optimal management of time and resources. Details of the interim analysis performed will be included in the statistical analysis plan.

Based on feedback from study Investigators in Part 1 regarding maneuverability and ease of use of the LYR-220-16 matrix, the Sponsor decided to drop this treatment arm in Part 2 of the study; patients will be randomized 1:1 to LYR-220-32 or sham procedure control.

10. REGULATORY OBLIGATIONS

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 Harmonization (ICH) Good Clinical Practices (GCP), United States Food and Drug Administration (USFDA) Guidelines and all applicable regulatory requirements. The Sponsor will not commence the clinical study until all required approval is obtained from the relevant ECs, IRBs 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, and at a minimum:

- A signed FDA Form 1572 or equivalent Investigator Statement
- A current (ie, updated no more than 24 months prior) curriculum vitae for the Principal Investigator and each subinvestigator listed on the FDA Form 1572 or Investigator Statement
- A copy of the current medical license for the investigator and each subinvestigator
- A letter from the IRB/EC stipulating approval of the protocol, the informed consent document, and any other material provided to potential trial subjects with information regarding the trial (eg, advertisements)
- The current IRB/EC membership list for the reviewing IRB/EC
- A signed Investigator Protocol Agreement
- A completed financial disclosure form for the investigator and all sub-investigators

10.2 Site Selection and Training

The Sponsor will select Investigators with appropriate training and experience to participate in this clinical investigation. 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 Sponsor's Trial Master File.

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 and Investigators' brochure, CRF completion, GCP, and clinical study personnel responsibilities. All training will be documented prior to engaging in study-related activities.

10.3 Ethics Committee (EC) or Institutional Review Board (IRB) Approval

The clinical protocol and informed consent form (ICF) must have the approval of a properly constituted EC/IRB responsible for approving clinical studies prior to commencing the study at that site. Any additional approval requirement(s) of the EC/ IRB will be followed. Any

advertisements used to recruit subjects or any subject facing documents will also be reviewed and approved by the EC/IRB prior to use.

No investigative procedures other than those defined in this clinical protocol will be undertaken on the enrolled subjects without the written agreement of the EC/IRB and Sponsor. Each site Principal Investigator will advise their EC/IRB of the progress of this clinical investigation on a regular basis, according to EC/IRB 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 its designee will submit reports as required by EC/IRB and local and national regulations. These reports may include SAEs, withdrawal of EC/IRB or regulatory authority's approval, annual progress reports, recall information, and final reports.

10.4 Informed Consent

The Investigators have both an ethical and legal responsibility to ensure that each subject 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 subject. The subject will be informed that, should an unexpected adverse product- or study procedure related AE occur, which presents an unreasonable risk to participating subjects, he/she will be notified. The subject will be informed that his/her medical records are available for review by representatives of the Sponsor or designee, the EC/IRB, and the appropriate regulatory authority, as necessary.

The subject will be informed that the information obtained during the study will be used to evaluate the safety and performance of the investigational product. However, his/her confidentiality will be maintained at all times. The subject 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.

The subject must be made aware and agree that personal information may be reviewed during an audit by regulatory authority and properly authorized persons. However, personal information will be treated as strictly confidential and will not be publicly available. As part of the informed consent process, the Investigator will obtain subjects' permission for the Sponsor personnel or designees, EC/IRB, and regulatory authority to review, in confidence, any pertinent records relating to the subjects in this clinical investigation.

A sample subject ICF template with standard wording suggested for this study will be provided to each investigator. A copy of the informed consent form 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 EC/IRB.

The EC/IRB-approved written consent form is to be reviewed with the subject by the Investigator or designee and will be signed by each subject prior to enrolling in the study. The

investigator or designee is responsible for maintaining each subject's ICF in the study file and providing each subject with a copy of the ICF.

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

10.5 Protocol Amendments

The clinical protocol, eCRFs, ICF and other subject information, or other clinical investigation documents shall be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of a document. Proposed amendments to the protocol shall be agreed upon between the Sponsor and principal investigator. The amendments to the protocol and the subject's ICF (if required) shall be provided to and approved by the local regulatory authorities and EC/IRB, 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 subjects, or not related to the clinical investigation objectives or endpoints, a simple notification to the EC/IRB and, where appropriate, local regulatory authority can be sufficient. The version number and date of amendments shall be documented.

10.6 Protocol Deviations

The investigator agrees to conduct the study according to the clinical protocol and agrees that all persons delegated to perform study procedures will do so as well. An investigator is not permitted to deviate from the protocol without the prior written approval of the Sponsor unless there are concerns of subject's safety. Under emergency circumstances, deviations from the protocol to protect the rights, safety, and well-being of human subjects may proceed without prior approval of the Sponsor and the EC/IRB. Such deviations shall be documented and reported to the Sponsor and the EC/IRB (as required) as soon as possible.

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 subject who does not meet all of the inclusion/exclusion criteria specified in the protocol, visits performed outside of the protocol specified visit window, and missed study visits. Each site investigator shall conduct this clinical study in accordance with this clinical study protocol, local regulatory authority regulations, GCP, and any conditions of approval imposed by their EC/IRB.

The investigator agrees to inform the EC/IRB of all protocol deviations according to institutional requirements. The occurrence of protocol deviations will be monitored by the Sponsor personnel or designee on an ongoing basis. Deviations from the protocol include, but are not limited to, the use of prohibited medications or therapies and out of window visits. All protocol deviations should be documented and explained. Major protocol violations are defined as those that could impact the performance evaluation such as a subject is ineligible, missing key data, received an

unauthorized treatment. All subjects with protocol deviations will continue to be followed for safety and performance assessments.

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

10.7 Study Monitoring

An appropriate representative of the Sponsor or designee (Study Monitor) will verify subject data and ensure compliance with GCP, clinical protocol and other study requirements, according to the guidelines set forth in the monitoring 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.

Completed CRFs will be verified by the 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, subject CRFs, subject medical records and other related study documents as required.

All CRFs will be reviewed for completeness and clarity. Missing or unclear data will be investigated by the 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 adverse events are observed and reported.

10.8 Data Quality Assurance

The investigator/designees will maintain accurate source documentation as part of subject case histories. Electronic data capture (EDC) will be utilized for collecting subject data in the clinical database. Each site is required to have a computer and internet connection available for site entry of clinical data. 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 CRO 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.

10.9 Record Retention

Each investigator will maintain all records pertaining to this clinical study as required by local regulations, the relevant EC/IRB and the Institution. The investigator will maintain all study related documentation including all correspondence, records of financial interest, individual subject 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 Clinical Trial Research Agreement (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.

10.10 Auditing

The investigator will make all pertinent records available including source documentation for inspection by their EC/IRB or a regulatory authority and for auditing by the Sponsor or designee. This information will be considered confidential. The Sponsor's or designee's audit will be independent of and separate from routine internal monitoring or quality control function and will serve to evaluate the study conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

In the event that an Investigator is contacted by a regulatory authority or EC/IRB in relation to this clinical study, the investigator will notify the Sponsor immediately and must provide the Sponsor with copies of any associated correspondence (eg, EC audit reports, warning letters). The Sponsor will provide any necessary support in responding to regulatory authority and EC/IRB audit requests.

10.11 Use and Publication of Study Results

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 EC/IRB 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 investigation. An investigator may only publish data generated by this clinical study in accordance with the terms of the CTRA.

10.12 Confidentiality

The investigator has a responsibility to ensure that subject anonymity is protected and maintained. He or she must also ensure that their 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.

Subjects 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 subject's privacy is guaranteed. Subject's participation in the study will be treated as confidential and subject's will not be referred to by name in any report of the study. Subject 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 subject identification code will be used that allows identification of all data reported for each subject. The identity of the subjects will not be disclosed in any study records and subjects' data will be described using the unique subject identifier. Subject data will be processed electronically to determine the outcome of this study, and to provide to health authorities. Subjects will be advised that all data may be transferred to other countries.

10.13 Early Study Discontinuation

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 following reasons:

- The discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study
- A decision by the Sponsor to suspend or discontinue testing, evaluation, or development of the investigational product
- Failure of the Investigator to enroll subjects into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of IRB/EC or appropriate regulatory authorities
- 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 United States Code of Federal Regulations (CFR) 21 CFR 312, Australian Clinical Trial Handbook, 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, Australian Clinical Trial Handbook, and other relevant national regulations, as appropriate, which require a 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 subjects 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 EC/IRB 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. CLINICAL RISK AND BENEFIT ANALYSIS

The most common first-line therapy for CRS symptoms management is topical corticosteroids with adjunctive use of daily nasal saline irrigation.[10] However, inefficient drug delivery to the inflamed mucosal tissues[11] and poor patient compliance limit the effectiveness of such therapy.[12] Flare-ups and worsening inflammation or severe nasal polyps are typically managed with a short course (1-3 weeks) of oral corticosteroids.[8, 9] While effective initially, improvements are typically not sustained for longer than 3 months.[13, 14] Additionally, oral corticosteroids can lead to systemic side effects including mood disturbance, gastrointestinal issues, diabetes, cataracts, glaucoma, and osteoporosis,[15, 16] which have limited their routine use. Approximately 50% of patients fail medical management[17] and become potential candidates for functional endoscopic sinus surgery (FESS). FESS removes inflamed tissues and bone to open the sinonasal passages to facilitate normal sinus drainage and aeration and provide greater access for delivery of topical steroids. Although FESS can improve symptoms and quality of life, it does not correct the underlying cause of the inflammation nor obviate the need for continued medical management, primarily consisting of intranasal corticosteroids and nasal saline. Furthermore, approximately 65% of patients have recurrent symptoms post FESS within the first year[19] and up to 20% elect a revision surgery.[20]

Subjects enrolled in this Phase II study will include patients who have had a prior bilateral ethmoidectomy, but their symptoms are recurring and not adequately controlled on medical management and are seeking further treatment. This may include patients who are considering an alternative therapy to a revision sinus surgery. The anticipated benefits over existing medical therapies, for subjects in this trial are local delivery of a known effective anti-inflammatory corticosteroid drug (mometasone furoate) to a targeted area for an extended duration of time without the need for daily use compliance. Subjects are expected to experience decreased sinonasal symptoms, which will be assessed and recorded by daily CRS cardinal symptoms, 2 disease-specific questionnaires, SNOT-22 and CRS-PRO, and a general symptom severity questionnaire, the PGIS (Section 8.4.1 Subject Reported Outcomes).

Although there is no prior human experience with LYR-220 drug matrices for treating adult CRS patients who have had a prior bilateral ethmoidectomy, Lyra Therapeutics has previously developed LYR-210 (2500 µg and 7500 µg) drug matrices for treating adult CRS patients who have failed previous medical management but have not undergone FESS. The LYR-210 drug matrix is designed for bilateral placement and retention of the drug matrices in undisrupted middle meatuses for 24 weeks, compared to LYR-220 drug matrices that are placed bilaterally in the ethmoid cavities. The LYR-220 (7500 µg) drug matrices are formulated with identical bioresorbable polymers, drug dose, and similar *in vitro* drug release kinetics to LYR-210 (7500 µg) drug matrix. The completed Phase I study was to evaluate the safety of LYR-210 in adult CRS patients receiving LYR-210 (2500 µg) drug matrices bilaterally. No local nasal AEs, including epistaxis, nasal burning, nasal dryness, nasal irritation, and nasal septal perforation, were reported. Mean changes from baseline over time in intraocular pressure (IOP) were

minimal and not statistically significant. No subject had intraocular hypertension (IOP >21 mm Hg) and no AEs indicative of high IOP were reported. Mean changes from baseline over time in morning serum cortisol levels were minimal and not statistically significant. No AEs indicative of adrenal insufficiency were reported. There were no adverse events associated with systemic levels of MF. The completed Phase II study is to evaluate the safety and efficacy of LYR-210 in adult CRS patients receiving LYR-210 (2500 µg) drug matrices, LYR-210 (7500 µg) drug matrices, or control in a 1:1:1 ratio. The most frequent local nasal AE reported in the 3 study groups was epistaxis; 4, 3, and 2 patients reported epistaxis in the LYR-210 (2500 µg), LYR-210 (7500 µg), and control groups, respectively. Eight of the 9 epistaxis events were reported as mild; only 1 epistaxis event was reported as moderate in severity. None of the subjects in this study had a clinically significant increase of IOP. Only 1 subject in the control group reported a higher grade of nuclear cataract at Week 24 that was deemed abnormal not affecting vision and reported as an adverse event by the investigator. There was no significant decrease of morning serum cortisol levels at Week 4, 12, and 24. No AEs indicative of adrenal insufficiency were reported (Refer to the LYR-220 IB).

The safety of the active ingredient in LYR-220, mometasone furoate, has been demonstrated across a range of commercially approved nasal and oral medication dosage forms including Nasonex®[21], Asmanex® Twisthaler®[22], Sinuva™[24] and Propel™[23] for the treatment of allergic rhinitis and nasal polyps, asthma, nasal polyps in patients who have had ethmoid sinus surgery, or maintaining patency following sinus surgery, respectively. The systemic safety of the 7500-µg dose MF in CRS patients has been demonstrated in the LYR-210 clinical studies. The MF systemic exposure in surgically naïve CRS patients that received LYR-210 (7500 µg) bilaterally is generally within the steady state exposure range observed in patients with asthma that received 400 µg BID Asmanex® Twisthaler® (Refer to the LYR-220 IB).

In terms of the bioabsorbable polymers, polyester families 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[41].

Risks Analysis

Potential risks to the trial subjects are similar to those associated with current therapies using local or systemic delivery of MF and endoscopic procedures. More detailed information regarding clinical safety data can be found in the IB.

In the Phase I clinical study of LYR-210 (2500 µg) drug matrix, the most common (ie, occurred in more than 1 subject) treatment-emergent adverse events (TEAEs) that are related to study treatment were facial pain, nasopharyngitis, sinusitis, upper respiratory tract infection, nasal discomfort, and nasal odor. All these events were considered to be nonserious, mild or moderate in severity, and anticipated risks related to study treatment. In the Phase II clinical study of LYR-210, the most common TEAEs that are related to study treatment reported in the LYR-210 (2500

µg) group were epistaxis and rhinorrhoea; in the LYR-210 (7500 µg) group was rhinitis; and in the control group was headache. All these events were considered to be nonserious and anticipated risks related to study treatment (Refer to the LYR-220 IB).

The possible risks and the highest incidence rates reported in clinical studies of similar products and/or LYR-210 clinical studies that are related to endoscopic procedures were procedural headache, epistaxis, facial pain, nasal congestion, nasal discomfort, parosmia, post procedural discomfort, and presyncope (Refer to the LYR-220 IB).

Subjects will be closely monitored as part of the trial according to the MMP, which defines in detail objectives, scope and roles and responsibilities of each team member involved (Section 8.3.12 Safety Monitoring). Safety monitoring will be followed strictly in accordance with the study MMP.

Extensive inclusion and exclusion criteria will also apply (Sections 5.3 Inclusion Criterion and 5.4 Exclusion Criterion) for which both the risks with MF and endoscopic procedures have been fully considered. These include those contraindications detailed in the product literature for approved MF Nasal Sprays, such as excluding those subjects with localized infection, those who have experienced recent nasal surgery and those who are immunosuppressed (Nasonex® product literature).

Following the use of intranasal corticosteroids, instances of increased intraocular pressure have been reported (Nasonex®). Subjects who have had past or present acute or chronic intracranial or orbital complications of CS (eg, brain abscess, related problems with eyes or central nervous system) or a history/diagnosis (in either eye) of glaucoma or ocular hypertension (IOP >21 mm Hg) will be excluded from this trial. Nasonex is also not recommended in cases of nasal septum perforation; again, subjects with evidence of mucosal erosion and ulceration or nasal septal perforation will be excluded from this trial. In addition, subject who have had more than 1 episode of epistaxis 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, will be excluded (epistaxis is mentioned in Section 5 Warnings and Precautions of the prescribing information of Nasonex®).

Subjects with obstruction, moderate-to-severe adhesion/synechiae, severe scarring or residual ethmoid cells within ethmoid cavity or resected and degenerated middle turbinate preventing proper placement or retention of LYR-220 will also be excluded.

Strict subject withdrawal/discontinuation criteria will also apply (Section 4.3 Discontinuation of Study Subjects) including any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the subject. Subjects will be withdrawn from the study if they require surgical intervention to manage their CRS symptoms.

Prior and concomitant medications criteria are specified (Sections 6.4.2 Prohibited Concomitant Medications and 6.4.3 Permitted Concomitant Medications) to avoid confounding the safety,

pharmacokinetics, and efficacy assessments of LYR-220. Specific rescue medications are recommended for worsening of CRS symptoms that last for a minimum of 3 days and resulted in the subject contacting the Investigator (Section 6.4.4 Rescue Concomitant Medications).

In the Phase I and Phase II clinical studies of LYR-210, no AEs were associated with drug matrix dislodgements. In this study, if spontaneous dislodgement of LYR-220 occurs before the scheduled removal visit at Week 24, subjects are required to call the study clinic immediately. Subject will remain in the study unless an early treatment discontinuation is recommended by the treating physician, or subject requests matrix removal from the remaining side of the nose, or matrices spontaneously dislodged from both sides of the nose (Section 4.1.2 Treatment Stage).

Only Investigators with substantial experience in endoscopic interventions will be allowed to participate in the Study. Once selected, Investigators will undergo product-specific training prior to enrolling subjects.

Through a systematic analysis of relevant commercially approved MF drugs and based on the Phase I and Phase II clinical results of LYR-210 and the safety assessments and measures implemented in this clinical trial, the potential benefits of LYR-220 outweigh the potential associated risks and support conducting the proposed Phase II clinical trial.

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13. APPENDICES

13.1 CRS Cardinal Symptoms (CS) Questionnaire (Daily ePRO) [SAMPLE]

13.2 22-Item Sino-Nasal Outcome Test (SNOT-22) [SAMPLE]

13.3 Patient-Reported Outcome Measure for Chronic Rhinosinusitis (CRS-PRO) Questionnaire [SAMPLE]

13.4 Patient Global Impression of Severity (PGIS) Scale [SAMPLE]

13.5 Patient Global Impression of Change (PGIC) Scale [SAMPLE]

13.6 LYR-220 End-of-Study Questionnaire [SAMPLE]

13.7 Summary of Protocol Changes