COVER PAGE

CLINICAL STUDY PROTOCOL

Protocol Number: LYR-210-2018-002

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

EUDRACT Number: 2018-004621-89

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

Current Version 8.0: 30 June 2020

Confidentiality Statement

SPONSOR SIGNATURE PAGE

Protocol Number: LYR-210-2018-002

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

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

Current Version 8.0: 30 June 2020

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

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

Investigational Site:

Name: _____ Address: _____

Phone Number: _____ _____

Investigator:

Name (*Print*): _____ Date of Signature: _____
(*DD-MMM-YYYY*)

Signature: _____

TABLE OF CONTENTS

[redacted]

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation / Term	Definition
AE	adverse event
AECS	acute exacerbation of chronic sinusitis
CS7DA4S	composite score of 7-day average scores of 4 CS cardinal symptoms
CFBL	change from baseline
CFR	code of federal regulations
COPD	chronic obstructive pulmonary disorder
CP_{min}	the minimum of the conditional power of the promising zone
CRF	case report form
CSsNP	chronic sinusitis without nasal polyps
CSwNP	chronic sinusitis with nasal polyps
CS	chronic sinusitis
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CYP3A4	cytochrome P-450 3A4
DMC	data monitoring committee
EC	ethics committee
EOS	end-of-study
EOT	end-of-treatment
ePRO	electronic subject reported outcome
ESS	endoscopic sinus surgery
ET	early termination
FAS	full analysis set
FDA	food and drug administration
GCP	good clinical practice
GEE	generalized estimating equation
HEENT	head, ears, eyes, nose and throat
HRS	Hours
IB	investigator brochure
ICF	informed consent form
ICH	international council for harmonization
IFU	instructions for use
IgA	immunoglobulin-a
IgG	immunoglobulin-g
INCS	intranasal corticosteroid spray
IOP	intraocular pressure
IRB	institutional review board
IRT	interactive response technology

Abbreviation / Term	Definition
ITT	intention to treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
kg	Kilogram
LOCF	last observation carried forward
mcg	Microgram
MedDRA	medical dictionary for regulatory activities
MF	mometasone furoate
mg	Milligram
mL	Milliliter
mmHg	millimeters of mercury
mo	Month
NCI	national cancer institute
PAR	perennial allergic rhinitis
PAS	per-protocol analysis set
pg	Picogram
PK	Pharmacokinetics
PP	per protocol
SAE	serious adverse event
SAP	statistical analysis plan
SAR	seasonal allergic rhinitis
SD	standard deviation
SF-36v2	36-item short form health survey version 2
SNOT	sino-nasal outcome test
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
UADE	unexpected adverse device effect
UPSIT	University of Pennsylvania smell identification test
URTI	upper respiratory tract infection
US	United States
USP	united states pharmacopeia
WHO ATC	world health organization anatomical therapeutic classification

1. SYNOPSIS

Sponsor	Lyra Therapeutics, Inc. 480 Arsenal Way Watertown, MA 02472, USA
Protocol Title	A Randomized, Blinded, Sham Procedure-Controlled, Parallel-Group, Phase II Trial to Evaluate the Efficacy, Safety and Tolerability of LYR-210 in Adult Subjects with Chronic Sinusitis (CS) (LANTERN Study)
Protocol Number	LYR-210-2018-002
Phase of Development	Phase II
Trial Location	Worldwide
Number of sites	Up to 25 sites
Study Population	Adult CS subjects who have failed previous medical management and have not undergone endoscopic sinus surgery (ESS)
Estimated Number of Subjects	Approximately 70 subjects
Investigational Product	LYR-210 System, 2500 µg and 7500 µg
Active Ingredient	Mometasone Furoate (MF)
Study Objectives	**Endpoints**
Primary	
To evaluate the efficacy of LYR-210 in improving the composite score of 7-day average scores of 4 CS cardinal symptoms (CS7DA4S) at Week 4	- Change from baseline (CFBL) in CS7DA4S score at Week 4 *The 4 CS cardinal symptoms include nasal blockage/obstruction/congestion, facial pain/pressure, reduction/loss of sense of smell, 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.*
Key Secondary	
To evaluate the efficacy of LYR-210 in improving CS7DA4S score at end of treatment	- CFBL in CS7DA4S score at Week 24

To evaluate the effect of LYR-210 in reducing sinus inflammation as per magnetic resonance imaging (MRI)	- Percentage of subjects with at least 1-point decrease in the bilateral Zinreich score in at least 1 pair of the anterior ethmoid, maxillary, posterior ethmoid, frontal, or sphenoid sinuses at Week 24 *Each sinus is scored on a 0-5 scale per the Zinreich modified Lund-Mackay scoring system and based on the percentage of opacification as follows: 0 = 0%, 1 = 1% to 25%, 2 = 26% to 50%, 3 = 51% to 75%, 4 = 76 % to 99%, and 5 = 100% or completely occluded.*
To evaluate the time to treatment failure	- Time to treatment failure *A treatment failure is defined as, after subject enrollment, subject being recommended by treating physician for oral corticosteroid or ESS due to worsening of CS symptoms, or the subject complaint of persistent CS symptoms with an average CS7DA4S score over the preceding 30 days greater than or equal to the Baseline CS7DA4S score.*
Other Secondary	
To evaluate the safety and tolerability of LYR-210	- Severity and percentage of subjects reporting treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) through Weeks 2, 4, 12, and 24 - Severity and percentage of subjects reporting Day 1 administration procedure and Week 24 removal procedure related AEs and SAEs - Severity and percentage of subjects reporting product related AEs and SAEs on Day 1 and through Weeks 2, 4, 12, and 24 - Percentage of subjects with abnormal and clinically significant abnormal laboratory values (hematology and chemistry, vital signs) on Day 1 and at Weeks 4, 12, and 24 - Morning serum cortisol levels on Day 1 and at Weeks 4, 12, and 24 - Severity and percentage of subjects with adverse nasal endoscopic findings and adverse nasal endoscopic

	findings requiring medical treatment in one or both nostrils on Day 1 and at Weeks 2, 4, 12, and 24 - Percentage of subjects with elevated intraocular pressure (IOP) in one or both eyes at Weeks 4, 12, and 24 - Percentage of subjects with a clinically significant increase of IOP at Weeks 4, 12, and 24 *A clinically significant increase of IOP is defined as IOP in one or both eyes > 28 mmHg or an increase of IOP from Baseline in one or both eyes >= 10 mmHg.* - Percentage of subjects with newly identified or worsened cataract in one or both eyes by slit-lamp examination at Week 24
To evaluate the time to onset of action of LYR-210	- Time to onset of action *Time to onset of action is defined as, within the first 30 days, the time when all subsequent mean CFBL in the CS7DA4S score of the LYR-210 is statistically significantly greater than that for the sham procedure.*
To evaluate the efficacy of LYR-210 in improving CS7DA4S score and the 7-day average score of each of the 4 cardinal CS symptoms	- CFBL in the CS7DA4S score at Weeks 8, 12, 16, and 20 - CFBL in 7-day average score of nasal blockage/obstruction/congestion, reduction/loss of sense of smell, facial pain/pressure, and anterior/posterior nasal discharge at Weeks 1, 2, 3, 4, 8, 12, 16, 20, and 24
To evaluate the effect of LYR-210 in improving CS disease-specific quality of life as per 22-item sino-nasal outcome test (SNOT-22) questionnaire	- CFBL in total SNOT-22 score and SNOT-22 rhinologic, extra-nasal rhinologic, ear-facial, sleep dysfunction, and psychological subdomain scores at Weeks 2, 4, 8, 12, 16, 20, and 24
To evaluate the effect of LYR-210 in reducing sinus inflammation as per magnetic resonance imaging (MRI)	- CFBL in bilateral Zinreich scores of posterior ethmoid, frontal, sphenoid, maxillary, anterior ethmoid sinus and OMC pairs at Week 24 - CFBL in total Zinreich score at Week 24
To evaluate the effect of LYR-210 in reducing subjects' needs	- Percentage of subjects with use of oral antibiotics for CS through Weeks 4, 8, 12, 16, 20, and 24

for medical or surgical treatment for CS	- Percentage of subjects with use of oral corticosteroid for CS through Weeks 4, 8, 12, 16, 20, and 24 - Percentage of subjects with use of intranasal corticosteroid sprays for CS through Weeks 4, 8, 12, 16, 20, and 24 - Percentage of subjects being recommended by treating physician for ESS through Weeks 4, 8, 12, 16, 20, and 24
To evaluate the pharmacokinetics of LYR-210	- Plasma MF concentrations at Days 3, 7, 14, 21 and Weeks 4, 12, 24 *Plasma PK samples at Days 3, 7, 14, 21 will only be measured in approximately 15 randomized and successfully enrolled subjects at US sites.*
To evaluate the effect of LYR-210 in improving subjects' general quality of life as per 36-item short form health survey version 2 (SF-36v2) questionnaire	- CFBL in SF-36v2 physical health, mental health, and domain scores at Week 24
To evaluate LYR-210 in improving smell function assessed by the University of Pennsylvania Smell Identification Test (UPSIT™)	- CFBL in UPSIT score at Week 24
Exploratory	
To evaluate the percentage of subjects experiencing acute exacerbations of CS (AECS)	- Percentage of subjects experiencing AECS through Weeks 4, 8, 12, 16, 20, and 24 *AECS is defined as a sudden worsening of symptoms in a subject resulting in the treating physician reporting an escalation of treatment.*
To assess effect of LYR-210 in reducing polyp severity within middle meatus in subgroup of CS subjects with nasal polyps (CSwNP)	- Percentage of subjects with improvement from Baseline in nasal polyp severity within middle meatus in CSwNP subjects at Week 24

To assess efficacy of LYR-210 in improving CS7DA4S score, the 7-day average score of each of 4 CS cardinal symptoms, the SNOT-22 total and subdomain scores, and the SF-36v2 physical health, mental health, and domain scores in the subgroups of CS subjects without nasal polyps (CSsNP) and CSwNP subjects	- CFBL in the CS7DA4S score at Weeks 1, 2, 3, 4, 8, 12, 16, 20, and 24 - CFBL in 7-day average score of nasal blockage/obstruction/congestion, reduction/loss of sense of smell, facial pain/pressure, anterior/posterior nasal discharge in CSsNP and CSwNP subjects at Weeks 1, 2, 3, 4, 8, 12, 16, 20, and 24 - CFBL in total SNOT-22 score and SNOT-22 rhinologic, extra-nasal rhinologic, ear-facial, sleep dysfunction, and psychological subdomain scores in CSsNP and CSwNP subjects at Weeks 2, 4, 8, 12, 16, 20, and 24 - CFBL in SF-36v2 physical health, mental health, and each of the health domain scores in CSsNP and CSwNP subjects at Week 24
To assess efficacy of LYR-210 in reducing sinus inflammation in CSsNP and CSwNP subjects	- Percentage of subjects with at least 1-point decrease in the bilateral Zinreich score in at least 1 pair of the anterior ethmoid, maxillary, posterior ethmoid, frontal, or sphenoid sinuses in CSsNP and CSwNP subjects at Week 24 - CFBL in bilateral Zinreich scores of posterior ethmoid, frontal, sphenoid, maxillary, anterior ethmoid sinus, and OMC pairs in CSsNP and CSwNP subjects at Week 24 - CFBL in total Zinreich score at in CSsNP and CSwNP subjects at Week 24
To assess effect of LYR-210 in improving smell function in CSsNP and CSwNP subjects	- CFBL in UPSIT score in CSsNP and CSwNP subjects at Week 24
To assess the safety of subjects post LYR-210 treatment	- Severity and percentage of subjects reporting AEs and SAEs through Week 28 and Week 48 - Percentage of subjects with abnormal and clinically significant abnormal laboratory values (hematology and chemistry, vital signs) at Week 28 - Morning serum cortisol levels at Week 28 - Plasma MF concentrations at Week 28

	- Severity and percentage of subjects with adverse nasal endoscopic findings and adverse nasal endoscopic findings requiring medical treatment in one or both nostrils at Week 28 - Percentage of subjects with elevated IOP in one or both eyes at Week 48 - Percentage of subjects with a clinically significant increase of IOP at Week 48 - Percentage of subjects with newly identified or worsened cataract in one or both eyes by slit-lamp examination at Week 48
To assess the durability of efficacy post LYR-210 treatment	- Percentage of subjects with improvement from Baseline in nasal polyp severity within middle meatus in CSwNP subjects at Week 28 - CFBL in the CS7DA4S score at Weeks 28, 32, 36, 40, 44, and 48 - CFBL in 7-day average score of nasal blockage/obstruction/congestion, reduction/loss of sense of smell, facial pain/pressure, anterior/posterior nasal discharge in CSsNP and CSwNP subjects at Weeks 28, 32, 36, 40, 44, and 48 - CFBL in total SNOT-22 score and SNOT-22 rhinologic, extra-nasal rhinologic, ear-facial, sleep dysfunction, and psychological subdomain scores at Weeks 28, 32, 36, 40, 44, and 48 - CFBL in SF-36v2 physical health, mental health, and each of the health domain scores at Week 48
Study Design This global, multicenter study will be conducted in a randomized, sham procedure-controlled, parallel-group, subject-blinded fashion in approximately 70 adult CS subjects who have failed previous medical management and have not undergone ESS. Subjects enrolled in the study will include patients who have not had ESS but their symptoms are not adequately controlled on medical management and are seeking further treatment. This may include subjects who are considering sinus surgery or those who have decided against it. The efficacy and safety of LYR-210 (2500 μg) and LYR-210 (7500 μg) versus a sham procedure only control will be	

assessed. Additionally, LYR-210 (2500 µg) and LYR-210 (7500 µg) will be compared to evaluate dose related responses.

The study will consist of three stages:

- Screening and Washout Stage: 2 -4 weeks
- Treatment Stage: 24 weeks
- Post-Treatment Follow-Up Stage: 24 weeks

Screening and Washout 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 minimum of 2-week but a maximum of 4-week washout period. During this washout period, except for recommended twice daily saline irrigation, subjects will receive no active treatment for CS or any prohibited or rescue medications specified in the study protocol. Beginning at least 7 days prior to LYR-210 administration/sham procedure on Day 1, subjects will record cardinal symptoms of CS on the electronic subject reported outcomes (ePRO) questionnaire.

Treatment Stage

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

On Day 1, before any treatment, subjects will be randomized in a 1:1:1 ratio to one of the following study arms:

- Arm 1: bilateral administration of LYR-210 (2500 µg)
- Arm 2: bilateral administration of LYR-210 (7500 µg)
- Control Arm: bilateral sham procedure

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

- Nasal Allergy (Yes vs No)
- Nasal polyps (Yes vs No)

Subjects who are assigned to the active treatment arms will have the LYR-210 administered bilaterally into the middle meatus on Day 1. Subjects who are assigned to the sham procedure arm, will undergo bilateral mock administration (i.e., sham procedure) on Day 1 consisting of bilateral insertion of an applicator (without LYR-210 loaded) into the middle meatus until the applicator tip touches the ethmoid bulla for a minimum of 20 seconds, followed by withdrawal of the applicator.

Prior to LYR-210 administration/sham procedure, all subjects will receive topical anesthetic and decongestant sprays for endoscopic assessment. Subjects will also receive anesthetic and

decongestant soaked cottonoid or pledget in each nostril to prepare middle meatuses for the insertion procedure. To maintain the subject blind to treatment assignment, each subject will wear an eye mask (i.e., blindfold) at the time of the LYR-210 administration/sham procedure. The study clinic staff, including the Investigator and study coordinator, will be unblinded to LYR-210 treatment vs the sham procedure but will remain blinded as to the dose administered to subjects who receive LYR-210.

All subjects will return to clinic for the scheduled follow up assessments at Week 2, 4, 12 and 24 visits and will remain blinded at these visits. Subjects will receive telephone follow-ups at Weeks 8, 16, and 20 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 receive LYR-210 will have bilateral depot removed using standard surgical tools. Sham control subjects will undergo a sham removal procedure to remain blinded.

If **spontaneous dislodgement of LYR-210** occurs before the scheduled Week 24/EOT visit in subjects who receive either dose of LYR-210, subjects are required to call the study clinic immediately to report the event. If a subject experiences dislodgement of one of the two LYR-210 depots, the subject will continue the study treatment unless an early treatment discontinuation is recommended by the treating physician or subject requests depot removal from the remaining side of the nose. If depots spontaneously dislodge from both sides of the nose, the subject will complete Week 24/EOT assessments and subsequently, the post-treatment follow-up stage.

If medically warranted per the treating physician's discretion (for example, needing an ESS as rescue treatment), early depot removal may be performed at an Unscheduled **early-termination (ET)** visit (an Unscheduled EOT visit). Any subject who undergoes an ET visit is required to complete the assessments scheduled for the Week 24/EOT visit, and all safety follow up visits post treatment.

Post-treatment Follow-Up Stage

All subjects will undergo a Post-treatment Follow-up Stage that will be approximately 24 weeks. Subjects will have 2 additional safety follow up visits during this stage, the Week 28 and a final Week 48/**end-of-study (EOS)** safety visits. Subjects will receive telephone follow-ups at Weeks 32, 36, 40, and 44 to record AEs and concomitant medications/procedures that they have had since their last follow-up assessment. Except for the cases of spontaneous depot dislodgement, subjects should remain blinded until the study database is locked.

Blinding

Except for the cases of spontaneous depot dislodgement, subjects should remain blinded to their treatment assignment (LYR-210 or sham) until the final study database is locked. The Sponsor

will be blinded to subjects' study treatment assignments until database lock for the primary data analysis after all enrolled subjects have completed Week 28 visit or withdrawn from study, whichever comes first.

Assessments

Enrolled subjects will be asked to complete a daily ePRO questionnaire to assess the instantaneous morning scores of 4 CS cardinal symptoms including nasal blockage/obstruction/congestion, reduction/loss of sense of smell, facial pain/pressure, and anterior/posterior nasal discharge. In addition, the ePRO will capture use of daily saline irrigation by the subjects. Subjects will also complete a validated CS-specific quality of life questionnaire, the SNOT-22, on Day 1 before treatment, at Week 2 and every 4 weeks after the Day 1 visit. Subjects will complete a general quality of life questionnaire, the SF-36v2, on Day 1 before the LYR-210 administration/sham procedure, and at Week 24/EOT and Week 48/EOS visits. At EOT visit, an end-of-treatment questionnaire will be administered.

Subjects will be asked to complete the UPSIT™ test for smell dysfunction at the Day 1 visit before the LYR-210 administration/sham procedure, and at Week 24/EOT and Week 28 visits.

Sinus inflammation will be assessed by MRI without contrast prior to the Day 1 visit and within 7 days after the LYR-210 removal/sham removal at the Week 24/EOT visit, unless medically contraindicated. If a subject is experiencing or recovering from a cold, acute exacerbation of nasal allergy, or upper respiratory tract infection at the Week 24/EOT visit, the MRI assessment should be performed 4 weeks after resolution of the adverse event. If a subject requires oral corticosteroid as rescue during the 24-week treatment period, the follow-up MRI should be performed before receiving the rescue treatment instead of at Week 24/EOT visit.

Nasal cavities will be assessed by endoscopy on Day 1 before the LYR-210 administration/sham procedure, and at Weeks 2, 4 and 12, Week 24/EOT, and Week 28 visits. Subjects are required to wear a blindfold if any endoscopy examination is performed at these visits to remain blinded to treatment assignment. Local nasal safety evaluation will be performed at these visits to document presence of epistaxis, mucosal erosion or ulceration, perforation, infection, and any other local nasal adverse effects. For CSwNP subjects, real-time, qualitative endoscopic evaluation of change of polyp severity in the middle meatus will be performed by site Investigators at Week 24/EOT visit after LYR-210 removal/sham removal procedure and at Week 28 visit by comparing to that of the Day 1 visit.

Ophthalmologic assessments will include IOP and slit-lamp examination during Screening, and within 7 days of Week 24/EOT and Week 48/EOS visits. IOP assessment will also be performed at Weeks 4 and 12 visits.

Plasma samples for PK will be collected from all subjects on Day 1 before the LYR-210 administration/sham procedure, and at Week 4, 12, 24/EOT, and 28 visits. Additional plasma PK samples will be collected at Days 3, 7, 14±1 (Week 2), 21±1 from approximately 15

randomized and successfully enrolled subjects at participating US sites for a minimum of 6 subjects for each LYR-210 dose. The concentration of MF in plasma will be measured by a central laboratory.

Routine safety assessments will be performed during the study including vital signs and physical exams. Samples for hematology, chemistry, and serum cortisol will be collected at Screening, Weeks 4, 12, 24/EOT, and 28 visits. An additional hematology, chemistry, and cortisol sample will be collected within 72 hours prior to LYR-210 administration/sham procedure for Baseline value. All post Screening serum cortisol samples will be evaluated by a central laboratory.

For female subjects of childbearing potential, a serum pregnancy test will be performed at Screening visit and a urine pregnancy test will be performed on Day 1 prior to randomization to confirm eligibility for participating in the study. A urine pregnancy test will be performed at every 4 weeks in clinic during the treatment stage in these female subjects.

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.

Data Monitoring Committee (DMC)

An independent DMC will be formed by charter to assist in examining safety data periodically during the study.

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 washout and treatment stages to avoid confounding the efficacy or safety assessments of LYR-210.

Prohibited Concomitant Medications:

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

- Oral/ocular/intramuscular/intravenous/intranasal corticosteroids (except for oral or intranasal corticosteroids permitted as rescue medication only);
- Anti-allergy medications, including: first generation antihistamines; leukotriene receptor antagonists, nasal cromolyn sodium or sodium cromoglycate, nedocromil sodium, atropine, ipratropium bromide, or guaifenesin;

- Oral decongestants;
- Inhaled anti-cholinergic medications (except for a stable regimen for chronic obstructive pulmonary disease (COPD) subjects);
- Any potent cytochrome P-450 3A4 (CYP3A4) inhibitors (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.

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 provided with saline and instructions for daily intranasal saline irrigation twice a day starting from washout till Week 24/EOT.
- If sinus infection is suspected at any time during the study, treatment with antibiotics will be allowed after a clinic visit and per Investigator's judgment.
- Subjects who have been on a stable regimen of inhaled corticosteroids 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 2018 Global Initiative for Asthma Management and Prevention [1].
- Perennial allergic rhinitis (PAR) subjects who have been on a stable regimen of a non-sedating 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 an acute exacerbation of the following conditions that result in the subject contacting the Investigator who determines an initiation of rescue therapy:

- Any time during the 24-week treatment stage:
  - After a clinic visit and per Investigator's judgment, antibiotics for sinus infection.
  - After a clinical visit and evaluation for worsening or uncontrolled severe CS symptoms, the Investigator using his/her best judgement may give 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 not responding to an INCS, or a flare-up of asthma. The rationale for the use of oral corticosteroid must be recorded.

- After the Week 4 visit only:
  - For acute allergic symptoms: Non-sedating oral antihistamine such as loratadine (10 mg per day) or equivalent.
  - For severe acute nasal blockage (score of 2 or more over the past 3 days): a course of oxymetazoline spray for a maximum of 3 consecutive days and a total maximum of 10 days during the treatment period. Oxymetazoline cannot be used within 24 hours before MRI assessments.
  - For worsening CS symptoms: intranasal MF sprays with dose and duration per Investigator's recommendation.
  - For worsening or uncontrolled severe CS symptoms: ESS as rescue treatment per Investigator's recommendation.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

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

1. Age ≥18.
2. A CS subject who
   a. has twelve weeks or longer of two 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

      and one or more of the following findings:
      • evidence of inflammation within paranasal sinuses or ostiomeatal complex on MRI
      • evidence of purulence coming from paranasal sinuses or ostiomeatal complex
      • nasal polyps
   b. has a composite score of 7-day average scores of 4 CS cardinal symptoms [2, 3] (CS7DA4S) ≥ 7 (0-3 scale for each of the symptoms) at Day 1 visit, and

c. has had at least two trials of medical treatments in the past, one of which must include intranasal corticosteroid sprays (INCS) for a minimum of 4 weeks.

3. Must be able to cease treatment with intranasal corticosteroid and decongestant sprays at Screening.
4. Ability to tolerate topical anesthesia.
5. 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.
6. Agrees to comply with all study requirements.

Exclusion Criteria:

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

1. With previous balloon sinuplasty or any endo-nasal surgery (including sinus surgery), except for septoplasty or surgical manipulation to nasal turbinates more than 6 months prior to the Screening visit.
2. Seasonal allergic rhinitis (SAR) subjects with symptoms and/or, based on time of year, would anticipate onset of symptoms within 4 weeks of randomization.
3. Perennial allergic rhinitis (PAR) subjects whose symptoms are well controlled by regular use of intranasal corticosteroids.
4. With severe asthma or with one or more exacerbations of asthma requiring systemic corticosteroid use within the 6 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.
5. Endoscopic exclusion criteria:
    a. Complete/near complete middle meatal obstruction preventing proper placement and/or visualization of LYR-210.
    b. Evidence of mucosal erosion or ulceration.
    c. Ongoing nasal infection.
    d. Evidence of nasal septal perforation.
6. MRI exclusion criteria:
    a. A bilateral Zinreich score < 4 in all 3 pairs of the posterior ethmoid, frontal, or sphenoid sinuses (0-5 scale for each of sinuses) on Screening MRI.

b. Anatomic variation which, in the opinion of the Investigator, would adversely impact placement of LYR-210.

c. Structural, non-inflammatory related CS (e.g., large concha bullosa, tumor).

d. Sinus disease extended into orbital or intracranial space.

e. Evidence of mycetoma/fungal ball, allergic fungal rhinosinusitis.

f. Sinus mucocele.

7. History or clinical evidence or suspicion of invasive fungal sinusitis, allergic fungal rhinosinusitis, or atrophic rhinitis.
8. Known history of hypersensitivity or intolerance to corticosteroids.
9. Oral-steroid or monoclonal antibody (Xolair, Nucala) dependent condition.
10. Having had systemic corticosteroids within 1 month prior to Screening visit.
11. Known history of hypothalamic pituitary adrenal axial dysfunction or having a clinically significant out of normal range morning serum cortisol level at screening.
12. Previous pituitary or adrenal surgery.
13. Has had 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.
14. Has had acute exacerbation of nasal allergy or chronic sinusitis, upper respiratory tract infection (URTI), or common cold within 4 weeks of the Screening visit.
15. Had dental procedure/implant on maxillary dentition within 4 weeks of the Screening visit.
16. Has past or present acute or chronic intracranial or orbital complications of CS (e.g., brain abscess, related problems with eyes or central nervous system).
17. History or diagnosis (in either eye) of glaucoma or ocular hypertension (IOP > 21 mmHg).
18. With prior cataract surgery or presence (in either eye) of posterior subcapsular cataract of grade 2 or higher, nuclear sclerosis of grade 3 or higher, or cortical cataract of grade 2 or higher or involving a minimum of center optic zone of 3 mm diameter.
19. Past or present functional vision in only one eye.
20. Diagnosed with ongoing rhinitis medicamentosa.

21. Known history of immune dysfunction including immune deficiency (IgG subclass deficiency or IgA deficiency) or autoimmune disease (e.g., Wegener's granulomatosis, sarcoidosis).
22. Past, present, or planned organ transplant or chemotherapy with immunosuppression.
23. History or diagnosis of ciliary dysfunction (e.g., cystic fibrosis, primary ciliary dyskinesia [Kartagener syndrome]).
24. Past or present systemic vasculitis (e.g., granulomatosis with polyangiitis).
25. Evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments.
26. Pregnant or breast feeding. Females of child-bearing potential must test negative for pregnancy at the time of screening based on a serum pregnancy test and reverified at the time of enrollment based on a urine pregnancy test. Both male and female subjects of reproductive potential must agree to use highly effective methods of birth control, throughout the study.
27. Previously participated in LYR-210 Phase I clinical study or received an experimental treatment in another clinical study within 5 half-lives of Screening visit.
28. Currently participating in an investigational drug or device study.
29. 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-210 System is a combination product comprised of a single-use applicator, pre-loaded with the LYR-210 drug depot, an anti-inflammatory drug depot. The LYR-210 drug depot 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 CS disease, as well as asthma. The LYR-210 drug depot is designed to gradually soften over time and made of bioabsorbable polymers that have been used as components of approved pharmaceutical drugs and/or medical devices.

Each LYR-210 drug depot contains a total MF dose of 2500 µg or 7500 µg [referred to as LYR-210 (2500 µg) or LYR-210 (7500 µg), or LYR-210 for either dose in this document]. LYR-210 is intended to be administered bilaterally into the ESS-naïve middle meatus by an otolaryngologist under endoscopic visualization via the provided single use applicator. Once administered, each LYR-210 is designed to gradually deliver sustained doses of MF to the inflamed mucosal tissue over a 24-week resident time. Bilateral placement of LYR-210 (2500 µg) is designed to deliver a total dose of 5,000 µg MF over the 24 weeks, or an average daily

dose of 30 µg MF per human subject (or 15 µg MF per nostril). In the case of LYR-210 (7500 µg), a total dose of 15,000 µg MF will be delivered over the 24 weeks with an average daily dose of 89 µg MF per human subject (or 45 µg MF per nostril). LYR-210 can be removed at 24-weeks or earlier at the physician's discretion using standard instruments.

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

Duration of Study:

The total duration of the study, including the enrollment period, is approximately 22 months. Each enrolled subject is planned to participate in the study for a total duration of approximately 12 months, which includes the Screening/Washout, Treatment, and Post-treatment 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:

Analysis Sets:

- Safety (SAF) analysis set: All randomized subjects who received the study treatment (Sham procedure or a dose of LYR-210) or treatment attempt on Day 1. Subjects will be analyzed according to the treatment received or attempted. This is the primary analysis set for assessment of safety.
- Intention-to-treat (ITT) analysis set: All randomized subjects who received the study treatment (Sham procedure or a dose of LYR-210) or treatment attempt on Day 1 and have post-Day 1 assessments available. This is the primary analysis set for assessment of efficacy. Subjects will be analyzed according to the treatment they were assigned to at randomization.
- Per-Protocol (PP) analysis set: All randomized subjects who received the study treatment, have specific post-Day 1 assessments, and are without major protocol deviations at the time of the primary analysis.
- Pharmacokinetic (PK) analysis set: All SAF patients with at least one evaluable drug concentration post-Day 1.

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, 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:

Analysis set assignment will be summarized for all enrolled subjects by randomized treatment. Subject disposition will be summarized for the ITT set. Demographics and other baseline characteristics and study drug exposure will be summarized for the SAF and ITT sets.

Safety Analyses:

Safety will be assessed through AEs and changes in laboratory tests, vital signs, morning serum cortisol levels, nasal endoscopy assessment, IOP and slit-lamp examination using the SAF 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 and 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.

All efficacy endpoints will be assessed using the ITT (primary analysis population) and PP analysis sets with available data for the endpoint.

For the primary efficacy endpoint (CFBL in the CS7DA4S score at Week 4) analysis, descriptive statistics will be presented for each treatment group. The null and alternative hypotheses to be tested are:

$H_0: \mu L_{2500} = \mu_C$ $H_0: \mu L_{7500} = \mu_C$

vs. vs.

$H_1: \mu L_{2500} < \mu_C$ $H_1: \mu L_{7500} < \mu_C$

where μL_{2500}, μL_{7500} and μ_C are true mean value of, the CFBL in the CS7DA4S score at Week 4 for the LYR-210 (2500 µg), LYR-210 (7500 µg) and sham procedure (control) groups, respectively. An analysis of covariance (ANCOVA) model for CFBL in CS7DA4S score at Week 4 will be used to determine which of the two null hypotheses stated above can be rejected. This ANCOVA model will include terms for baseline CSD7A4S score as a covariate and the fixed effects of treatment group (LYR-210 7500 µg, LYR-210 2500 µg, sham procedure) and

the randomization stratification variables, presence of nasal allergy and presence of nasal polyps.

Secondary analyses of efficacy endpoints will also be performed in subjects in the PP analysis set with available data.

To assess consistency of treatment difference across study region, descriptive statistics of the primary endpoint will be presented by treatment group within each region. All subgroups to be assessed for treatment effect consistency on the primary endpoint will be detailed in the formal SAP.

The key secondary endpoints and other non-key secondary and exploratory efficacy endpoints that are continuous variables will be compared in the same manner as the primary endpoint. For dichotomous efficacy endpoints treatments will be compared at each time point measured using logistic regression adjusting for relevant baseline value and the randomization strata variables and other baseline covariates to be specified in the formal SAP. Each secondary endpoint will be compared between each LYR-210 dose and sham at a one-sided 0.05 level of significance. There will be no adjustment of the significance level adjusting for multiple comparisons.

As further exploratory analyses comparing treatments on all endpoints measured over time, generalized estimating equation (GEE) linear regression (for continuous outcomes) and GEE logistic regression (for dichotomous outcomes) will be used to compare treatments over time.

Sample Size:

Per the null and alternative hypotheses described above, and under the assumptions that μ_C = -1.30 and μL_{2500} and/or μL_{7500} = -3.00 (approximately 130% larger decrease than the assumed control mean of -1.3) and that the true SD within each treatment group is at most 2.4, then an evaluable sample size of 63 patients (21 per treatment group) yields 73% power to reject at least one null hypothesis in favor of the alternative at a one-sided 0.05 level of significance. An additional 6-9 patients will be enrolled to account for potential subject dropout.

Handling of Missing Data:

The primary analysis on the efficacy endpoints will be performed based on subjects in the ITT analysis set with available data. Additional secondary analysis will be performed using the above ANCOVA model for all subjects in the ITT analysis set. Two imputation approaches will be carried out: (a) Last observation carried forward (LOCF) single imputation method; and (b) multiple imputation. This will be carried out on the primary endpoint and the key secondary endpoint of CFBL in CS7DA4S score at Week 24.

For remaining secondary efficacy endpoints, sensitivity analyses of continuous variable will be conducted on all ITT subjects where missing data are first imputed by LOCF prior to carrying out the treatment comparisons.

2. INTRODUCTION

2.1 Chronic Sinusitis

Chronic sinusitis (CS), commonly referred as chronic rhinosinusitis (CRS) by the medical community, is a common condition defined by symptomatic inflammation of the paranasal sinuses lasting longer than 12 weeks. The cardinal symptoms of CS include nasal blockage/obstruction/congestion, facial pain/pressure, anterior/posterior nasal discharge, and reduction/loss of sense of smell [2, 3]. The underlying cause of CS-related symptoms is inflammation of mucosal tissue leading to impairment of mucociliary clearance.

CS affects 10.9% European population [4] and 12.5% of the US population [5], and is the 5th most common condition in people under age 65 in the US [6]. CS results in 18 million annual office visits [6], and the economic implications are at more than $9 billion each year in US alone [7]. The socioeconomic cost data outside of the US is limited, however, a 2002 randomized and controlled study by a university hospital in Netherland reported that, over a 24-week treatment period, the total direct and indirect treatment costs of a regular CS subject was €3661, and this number was as high as €8908 for a complicated CS subject [8].

Despite the high prevalence of the disease, no approved drug therapy for the treatment of CS is available. 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 intranasal corticosteroids (INCS) with adjunctive use of daily saline irrigation [9]. However, inefficient drug delivery to the inflamed mucosal tissues [10] and/or poor subject compliance limit the effectiveness of such therapy [11]. Second line medical therapy generally used for management of flare-ups and worsening inflammation or severe nasal polyps includes a short course (1-3 weeks) of oral corticosteroids [2, 3]. While effective initially, improvements are not sustained for more than 3 months [12, 13]. Additionally, oral corticosteroids can lead to systemic side effects including mood disturbance, gastrointestinal issues, diabetes, cataracts, glaucoma, osteoporosis and rarely avascular necrosis of the hip and shoulder [14, 15]. Approximately half (40-60%) of CS subjects do not benefit from this recommended medical regimen, and so become potential candidates for endoscopic sinus surgery (ESS) [16]. However, many surgical candidates opt out of surgical treatment [17].

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 parenteral allergic rhinitis [18], nasal polyps [18], a phenotype of CS disease , as well as asthma [17]. Both rhinitis and sinusitis are characterized by an inflammation of the mucosal membrane of the sino-nasal cavities. Despite the effectiveness of MF topical therapy in management of rhinitis and nasal polyposis, results from pharmacokinetic studies in adults and children suggest that systemic exposure to MF after intranasal administration is negligible, underscoring MF as an ideal choice

of safe drug for developing a new drug formulation for this group of underserved subject population [19].

Drug-eluting drug delivery systems have demonstrated the ability to provide therapy directly at the local site of disease in a sustained fashion while eliminating systemic effects of the drug in many therapeutic areas[20, 21]. More recently, local drug delivery systems were approved by the FDA for CS subjects immediately following sinus surgery [22, 23] or subjects with recurrent polyposis post ESS procedure(s) [24, 25]. The American Rhinologic Society (ARS) endorsed the utilization of steroid-eluting drug delivery systems into the paranasal sinuses for their demonstrated improvement of subjects outcomes and limiting the need for oral steroids [26].

An ideal treatment for CS would provide local, sustained, anti-inflammatory drug delivery in subjects as an option, prior to sinus surgery. Such a therapy would be safe yet provide sustained drug delivery via a single administration. It would conform to irregularly shaped sino-nasal cavities and maintain prolonged mucosal contact time with local drug absorption and minimal depletion. It would also allow easy removal at the end of treatment.

The LYR-210 System is a combination product comprised of a single-use applicator, pre-loaded with the LYR-210 drug depot, containing a total dose of 2500 µg or 7500 µg mometasone furoate [referred to as LYR-210 (2500 µg) or LYR-210 (7500 µg) or LYR-210 for either dose in this document]. LYR-210 is a miniaturized local drug delivery implant designed to fit within, and conform to, the confined space of a subject's ESS-naïve middle meatus. LYR-210 consists of an active ingredient MF embedded in the inactive ingredients composed of bioabsorbable polymers with a wide range of medical applications that aid in the controlled and sustained delivery of MF to the sino-nasal mucosal tissue from a single drug administration.

LYR-210 is intended to be administered bilaterally into the non-operated middle meatus by an otolaryngologist under endoscopic visualization via a provided single use applicator. The administration of LYR-210 is office-based and performed with topical anesthesia. Once administered, LYR-210 was designed to gradually release 2500 µg or 7500 µg of MF to the inflamed mucosal tissue over 24 weeks, from a single administration. Bilateral placement of LYR-210 (2500) µg is designed to deliver a total dose of 5000 µg MF over the 24 weeks, or an average daily dose of 30 µg MF per human subject (or 15 µg MF per nostril). In the case of LYR-210 (7500 µg), a total dose of 15000 µg MF will be delivered over the 24 weeks with an average daily dose of 89 µg MF per human subject (or 45 µg MF per nostril). LYR-210 can be removed at 24-weeks or earlier at the physician's discretion using standard instruments.

2.3 Study Rationale

LYR-210 has undergone non-clinical safety assessments to demonstrate suitability for human study. A summary of non-clinical studies of LYR-210 is provided in Investigator Brochure (IB, Section 4.2). LYR-210 (2500 µg) was assessed in a multi-centered, prospective, open-label, single-arm study (clinicaltrials.gov ID: NCT02967731) in 20 adult CS subjects who had failed

previous medical management and have not undergone ESS. A summary of this Phase I study is provided in IB (Section 5).

The Phase I study concluded that LYR-210 (2500 µg) is safe and well-tolerated in ESS-naïve CS subjects and leads to sustained symptom improvement, measured by a CS disease specific 22-item sino-nasal outcome test (SNOT-22) questionnaire [27], in subjects. These initial clinical experiences with LYR-210 (2500 µg) in CS subjects suggest encouraging clinical benefits without the need for surgery, while avoiding safety risks associated with prolonged oral steroid treatment. The main limitations in the Phase I study, however, include the small sample size and lack of a concurrent control group. Therefore, the potential contribution of a placebo effect is unknown. A larger clinical study which is randomized and blinded to a control will reduce the potential for treatment and assessment bias and will improve the veracity of detected safety and efficacy, particularly in the use of self-reported ePRO instruments for assessment of CS symptoms.

Additionally, CS subject symptom severity can be stratified with being “normal” defined on the SNOT-22 score as <8, “Mild” as 8-20 inclusive, “moderate” as >20-50 and “severe” as >50 [28]. After 24 weeks of treatment with LYR-210 (2500 µg), although 20% subject had achieved optimal “normal” symptom scores, some remained symptomatic (data on file with Lyra Therapeutics). These results indicate room for further symptom reduction in more subjects, possibly with more optimal drug dosing.

Lyra Therapeutics is conducting a global, multicenter study in a randomized, sham procedure-controlled, parallel-group, subject-blinded fashion in approximately 70 adults CS subjects who have failed previous medical management and have not undergone ESS. Subjects enrolled in the study will include patients who have not had ESS but their symptoms are not adequately controlled on medical management and are seeking further treatment. This may include patients who are considering sinus surgery or those who have decided against it. The efficacy and safety of LYR-210 (2500 µg) and LYR-210 (7500 µg) versus a sham procedure control will be assessed. Additionally, LYR-210 (2500 µg) and LYR-210 (7500 µg) will be compared to evaluate dose related responses.

3. STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are:

Study Objectives	Endpoints
Primary	
To evaluate the efficacy of LYR-210 in improving the composite score of 7-day average scores of 4 CS cardinal symptoms (CS7DA4S) at Week 4	- Change from baseline (CFBL) in CS7DA4S score at Week 4 *The 4 CS cardinal symptoms include nasal blockage/obstruction/congestion, facial pain/pressure, reduction/loss of sense of smell, 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.*
Key Secondary	
To evaluate the efficacy of LYR-210 in improving CS7DA4S score at end of treatment	- CFBL in CS7DA4S score at Week 24
To evaluate the effect of LYR-210 in reducing sinus inflammation as per magnetic resonance imaging (MRI)	- Percentage of subjects with at least 1-point decrease in the bilateral Zinreich score in at least 1 pair of the anterior ethmoid, maxillary, posterior ethmoid, frontal, or sphenoid sinuses at Week 24 *Each sinus is scored on a 0-5 scale per the Zinreich modified Lund-Mackay scoring system and based on the percentage of opacification as follows: 0 = 0%, 1 = 1% to 25%, 2 = 26% to 50%, 3 = 51% to 75%, 4 = 76 % to 99%, and 5 = 100% or completely occluded.*
To evaluate the time to treatment failure	- Time to treatment failure *A treatment failure is defined as, after subject enrollment, subject being recommended by treating physician for oral corticosteroid or ESS due to worsening of CS symptoms, or the subject complaint of persistent CS symptoms with an average CS7DA4S score over the preceding 30 days greater than or equal to the Baseline CS7DA4S score.*
Other Secondary	

To evaluate the safety and tolerability of LYR-210	- Severity and percentage of subjects reporting treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) through Weeks 2, 4, 12, and 24 - Severity and percentage of subjects reporting Day 1 administration procedure and Week 24 removal procedure related AEs and SAEs - Severity and percentage of subjects reporting product related AEs and SAEs on Day 1 and through Weeks 2, 4, 12, and 24 - Percentage of subjects with clinically significant abnormal and clinically significant abnormal laboratory values (hematology and chemistry, vital signs) on Day 1 and at Weeks 4, 12, and 24 - Morning serum cortisol levels on Day 1 and at Weeks 4, 12, and 24 - Severity and percentage of subjects with adverse nasal endoscopic findings and adverse nasal endoscopic findings requiring medical treatment in one or both nostrils on Day 1 and at Weeks 2, 4, 12, and 24 - Percentage of subjects with elevated intraocular pressure (IOP) in one or both eyes at Weeks 4, 12, and 24 - Percentage of subjects with a clinically significant increase of IOP at Weeks 4, 12, and 24 *A clinically significant increase of IOP is defined as IOP in one or both eyes > 28 mmHg or an increase of IOP from Baseline in one or both eyes >= 10 mmHg.* - Percentage of subjects with newly identified or worsened cataract in one or both eyes by slit-lamp examination at Week 24
To evaluate the time to onset of action of LYR-210	- Time to onset of action *Time to onset of action is defined as, within the first 30 days, the time when all subsequent mean CFBL in the CS7DA4S score of the LYR-210 is statistically significantly greater than that for the sham procedure.*

To evaluate the efficacy of LYR-210 in improving CS7DA4S score and the 7-day average score of each of the 4 cardinal CS symptoms	- CFBL in the CS7DA4S score at Weeks 8, 12, 16, and 20 - CFBL in 7-day average score of nasal blockage/obstruction/congestion, reduction/loss of sense of smell, facial pain/pressure, and anterior/posterior nasal discharge at Weeks 1, 2, 3, 4, 8, 12, 16, 20, and 24
To evaluate the effect of LYR-210 in improving CS disease-specific quality of life as per 22-item sino-nasal outcome test (SNOT-22) questionnaire	- CFBL in total SNOT-22 score and SNOT-22 rhinologic, extra-nasal rhinologic, ear-facial, sleep dysfunction, and psychological subdomain scores at Weeks 2, 4, 8, 12, 16, 20, and 24
To evaluate the effect of LYR-210 in reducing sinus inflammation as per magnetic resonance imaging (MRI)	- CFBL in bilateral Zinreich scores of posterior ethmoid, frontal, sphenoid, maxillary, anterior ethmoid sinus and OMC pairs at Week 24 - CFBL in total Zinreich score at Week 24
To evaluate the effect of LYR-210 in reducing subjects' needs for medical or surgical treatment for CS	- Percentage of subjects with use of oral antibiotics for CS through Weeks 4, 8, 12, 16, 20, and 24 - Percentage of subjects with use of oral corticosteroid for CS through Weeks 4, 8, 12, 16, 20, and 24 - Percentage of subjects with use of intranasal corticosteroid sprays for CS through Weeks 4, 8, 12, 16, 20, and 24 - Percentage of subjects being recommended by treating physician for ESS through Weeks 4, 8, 12, 16, 20, and 24
To evaluate the pharmacokinetics of LYR-210	- Plasma MF concentrations at [redacted] 4, 12, 24 [redacted]
To evaluate the effect of LYR-210 in improving subjects' general quality of life as per 36-item short form health survey version 2 (SF-36v2) questionnaire	- CFBL in SF-36v2 physical health, mental health, and domain scores at Week 24

To evaluate LYR-210 in improving smell function assessed by the University of Pennsylvania Smell Identification Test (UPSIT™)	- CFBL in UPSIT score at Week 24
Exploratory	
To evaluate the percentage of subjects experiencing acute exacerbations of CS (AECS)	- Percentage of subjects experiencing AECS through Weeks 4, 8, 12, 16, 20, and 24 *AECS is defined as a sudden worsening of symptoms in a subject resulting in the treating physician reporting an escalation of treatment.*
To assess effect of LYR-210 in reducing polyp severity within middle meatus in subgroup of CS subjects with nasal polyps (CSwNP)	- Percentage of subjects with improvement from Baseline in nasal polyp severity within middle meatus in CSwNP subjects at Week 24
To assess efficacy of LYR-210 in improving CS7DA4S score, the 7-day average score of each of 4 CS cardinal symptoms, the SNOT-22 total and subdomain scores, and the SF-36v2 physical health, mental health, and domain scores in the subgroups of CS subjects without nasal polyps (CSsNP) and CSwNP subjects	- CFBL in the CS7DA4S score at Weeks 1, 2, 3, 4, 8, 12, 16, 20, and 24 - CFBL in 7-day average score of nasal blockage/obstruction/congestion, reduction/loss of sense of smell, facial pain/pressure, anterior/posterior nasal discharge in CSsNP and CSwNP subjects at Weeks 1, 2, 3, 4, 8, 12, 16, 20, and 24 - CFBL in total SNOT-22 score and SNOT-22 rhinologic, extra-nasal rhinologic, ear-facial, sleep dysfunction, and psychological subdomain scores in CSsNP and CSwNP subjects at Weeks 2, 4, 8, 12, 16, 20, and 24 - CFBL in SF-36v2 physical health, mental health, and each of the health domain scores in CSsNP and CSwNP subjects at Week 24
To assess efficacy of LYR-210 in reducing sinus inflammation in CSsNP and CSwNP subjects	- Percentage of subjects with at least 1 point of decrease in the bilateral Zinreich score in at least 1 pair of the posterior ethmoid, frontal, or sphenoid sinuses in CSsNP and CSwNP subjects at Week 24

	- CFBL in bilateral Zinreich scores of posterior ethmoid, frontal, sphenoid, maxillary, anterior ethmoid sinus, and OMC pairs in CSsNP and CSwNP subjects at Week 24 - CFBL in total Zinreich score at in CSsNP and CSwNP subjects Week 24
To assess effect of LYR-210 in improving smell function in CSsNP and CSwNP subjects	- CFBL in UPSIT score in CSsNP and CSwNP subjects at Week 24
To assess the safety of subjects post LYR-210 treatment	- Severity and percentage of subjects reporting AEs and SAEs through Week 28 and Week 48 - Percentage of subjects with abnormal and clinically significant abnormal laboratory values (hematology and chemistry, vital signs) at Week 28 - Morning serum cortisol levels at Week 28 - Plasma MF concentration at Week 28 - Severity and percentage of subjects with adverse nasal endoscopic findings and adverse nasal endoscopic findings requiring medical treatment in one or both nostrils at Week 28 - Percentage of subjects with elevated IOP in one or both eyes at Week 48 - Percentage of subjects with a clinically significant increase of IOP at Week 48 - Percentage of subjects with newly identified or worsened cataract in one or both eyes by slit-lamp examination at Week 48
To assess the durability of efficacy post LYR-210 treatment	- Percentage of subjects with improvement from Baseline in nasal polyp severity within middle meatus in CSwNP subjects at Week 28 - CFBL in the CS7DA4S score at Weeks 28, 32, 36, 40, 44, and 48 - CFBL in 7-day average score of nasal blockage/obstruction/congestion, reduction/loss of sense of smell, facial pain/pressure, anterior/posterior nasal

	discharge in CSsNP and CSwNP subjects at Weeks 28, 32, 36, 40, 44, and 48 - CFBL in total SNOT-22 score and SNOT-22 rhinologic, extra-nasal rhinologic, ear-facial, sleep dysfunction, and psychological subdomain scores at Weeks 28, 32, 36, 40, 44, and 48 - CFBL in SF-36v2 physical health, mental health, and each of the health domain scores at Week 48

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design

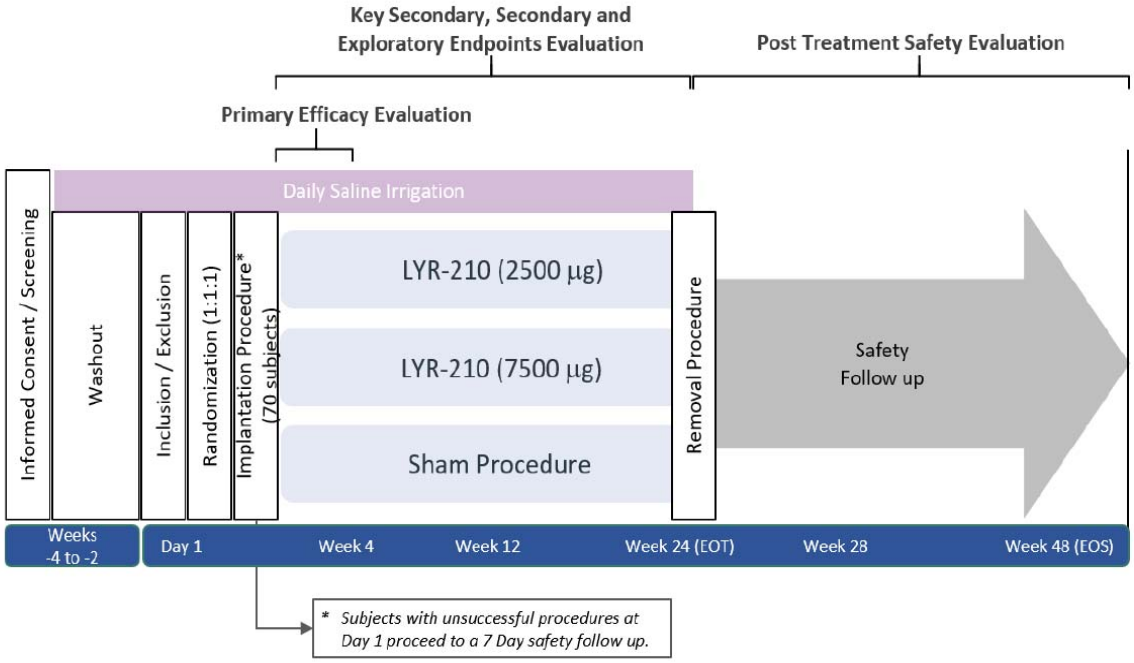
This global, multicenter study will be conducted in a randomized, sham procedure-controlled, parallel-group, subject-blinded fashion in approximately 70 adults CS subjects who have failed previous medical management and have not undergone ESS. Subjects enrolled in the study will include patients who have not had ESS but their symptoms are not adequately controlled on medical management and are seeking further treatment. This may include patients who are considering sinus surgery or those who have decided against it. The efficacy and safety of LYR 210 (2500 µg) and LYR-210 (7500 µg) versus a sham procedure only control will be assessed. Additionally, the study results of LYR-210 (2500 µg) and LYR-210 (7500 µg) will be compared to evaluate dose related responses.

The study will consist of three stages:

- Screening and Washout Stage: 2 - 4 weeks
- Randomized and Blinded Treatment Stage: 24 weeks
- Blinded Post-Treatment Follow-Up Stage: 24 weeks

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

Figure 1: Study Design Schematic



4.1.1 Screening 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 minimum of 2-week but a maximum of 4-week washout period. During this washout period, subjects will receive no active treatment for CS but are recommended to start daily saline irrigation twice a day. Subjects will be provided with saline and instructions for daily intranasal saline irrigations while participating in the study.

Medications that are prohibited during the washout period (and during the study) are listed in Section 6.4.2. Beginning at least 7 days prior to Day 1 visit, subjects will record the severity of the 4 cardinal symptoms of CS and the use of saline irrigation each day in the morning on the electronic subject reported outcomes (ePRO) questionnaire.

4.1.2 Treatment Stage

The total duration of the Treatment Stage will be 24 weeks. Subjects who complete the study Screening assessments and the washout period and meet all eligibility criteria on Day 1 will be stratified according to the presence or absence of nasal allergy and nasal polyps and, then, randomized in a 1:1:1 ratio to receive LYR-210 (2500 µg), LYR-210 (7500 µg), or sham procedure. Subjects who are assigned to the experimental arms will have the LYR-210 administered bilaterally into the middle meatus (Section 6.2) and, then, removed at Week 24 (Section 6.5). Subjects who are assigned to the sham procedure arm, will undergo bilateral mock administration (i.e., sham procedure) on Day 1. Enrolled subjects will undergo scheduled study visits at Weeks 2, 4, 12, and 24 during the treatment duration. Subjects will receive phone follow-ups at Weeks 8, 16, and 20 to record AEs and concomitant medications/procedures that they have had since last follow-up assessment. [NOTE: Female subjects of childbearing potential will be asked to return to the clinic for urine pregnancy test at Weeks 8, 16, and 20.] All subjects will remain blinded and undergo the assessments and procedures scheduled for these visits (Section 8.1).

At the Week 24 visit, all subjects will return to clinic for the **end-of-treatment (EOT)** visit assessments. Subjects who receive LYR-210 will have bilateral depot removed using standard surgical tools. Sham control subjects will undergo a sham removal procedure to remain blinded.

If medically warranted per the treating physician's discretion (for example, needing an ESS as rescue treatment), early depot removal before the schedule EOT visit at Week 24 may be performed at an unscheduled **early-termination (ET)** visit (an unscheduled EOT visit). Any subject who undergoes an ET visit is required to complete the assessments scheduled for the Week 24/EOT visit, and all safety follow up visits post treatment.

If spontaneous dislodgement of LYR-210 occurs before Week 24 in subjects who receive either dose of LYR-210, subjects are required to call the study clinic immediately to report the event. If

a subject experiences a dislodgement of one of the two LYR-210 depots, the subject will continue the study treatment unless an early treatment discontinuation is recommended by the treating physician or subject requests depot removal from the remaining side of the nose. If depots spontaneously dislodge from both sides of the nose, subject will complete Week 24/EOT assessments and subsequently, the post-treatment follow-up stage.

4.1.3 Post-Treatment Follow-Up Stage

After the Week 24/EOT visit, all enrolled subjects will undergo a blinded Post-treatment Follow-up Stage that will be approximately 24 weeks. Subjects will have 2 additional scheduled safety follow up visits, the Week 28 and a final Week 48/EOS visit. Subjects will receive phone follow-ups at Weeks 32, 36, 40, and 44 to record AE and concomitant medications/procedures that they have had since last follow-up assessment. Except for the cases of depot dislodgement, subjects should remain blinded until the study database is locked.

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 goal of treatment is to reduce the symptoms of adult CS with a well-tolerated product. The study design and endpoints are adequate for assessment of safety and efficacy of LYR-210 in the context of a Phase II study of subjects with CS. Blinding and randomization will reduce the potential for treatment and assessment bias and will improve the veracity of detected safety and efficacy, particularly in the use of self-reported ePRO instruments for assessment of CS symptoms. The parallel arm study design and 1:1:1 randomization scheme of LYR-210 (2500 µg): LYR-210 (7500 µg): sham procedure permits adequate statistical comparison of groups for efficacy assessment and safety signal detection. The ePRO of daily morning cardinal symptoms and the SNOT-22 subject reporting instruments have been selected because they are specific to the subject population to be enrolled in this study. Other efficacy endpoints involving objective changes in the sino-nasal cavities (i.e., inflammation and polyps), smell dysfunction improvement, and general quality of life improvement are appropriate for development and further refinement of study endpoints in the clinical program. Although MF is well-characterized as a treatment in other indications, chronic assessments of local nasal and ophthalmologic parameters in this study's CS population and in the context of in situ delivery via drug-depot are appropriate for associating safety results with local MF levels. Summarized in Section 9.1 is the safety rationale for the selection of drug doses and polymers in LYR-210 in this Phase II study.

4.3 Discontinuation of Study Subjects

Subjects will be encouraged to complete the study through the treatment and post-treatment follow up periods. 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-210 (Section 6.5).
- Any serious AE (SAE, Section 8.4.9.2), 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 ESS as rescue treatment.
- If deviations to the use of prohibited medications occur after randomization and study treatment, 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 visit and the safety follow up visits post EOT (Section 8.1).

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

4.4 Criteria for Study Termination

If the Sponsor, the Investigator, the medical monitor, the data monitoring committee (DMC), Institutional Review Board (IRB)/Ethics Committee (EC), 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 IRB/EC, and the medical monitor. Refer to Section 11.13 for additional information.

4.5 Data Monitoring Committee (DMC)

An independent DMC will be formed by charter to assist in examining safety data periodically during the study and will include independent physicians with appropriate experience of clinical trials but who are not participating in this study. The DMC will:

- Review the safety and tolerability data at predefined time points. The first study level safety review will occur after the 30th subject has completed 4 weeks of treatment or early terminated from the study, whichever occurs first. A second safety review will occur after all enrolled subjects have completed the Week 4 follow-up. The timing and details of subsequent data review will be detailed in the DMC charter.

- Review the safety data at *ad hoc* time points if significant safety concerns are identified during the study.
- Review events that may impact subject continuation and make recommendations regarding study progression.
- Review any other data, as appropriate.

The membership, responsibilities and operating procedures of the DMC will be described in a DMC Charter.

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 IRB/EC-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 upon consultation with the study Medical Monitor or study Sponsor. Subject 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 (eCRF).

5.2 Subject Informed Consent

Prior to enrollment in the study, all subjects must review and complete an IRB/EC-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 all of the following criteria to be eligible for this study:

1. Age ≥ 18.
2. A CS subject who
   a. has twelve weeks or longer of two 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

      and one or more of the following findings:

      • evidence of inflammation within paranasal sinuses or ostiomeatal complex on MRI

• evidence of purulence coming from paranasal sinuses or ostiomeatal complex

• nasal polyps

b. has a composite score of 7-day average scores of 4 CS cardinal symptoms [2, 3] (CS7DA4S) ≥ 7 (0-3 scale for each of the symptoms) at Day 1 visit, and

c. has had at least two trials of medical treatments in the past, one of which must include intranasal corticosteroid sprays (INCS) for a minimum of 4 weeks.

3. Must be able to cease treatment with intranasal corticosteroid and decongestant sprays at Screening.
4. Ability to tolerate topical anesthesia.
5. Has been informed of the nature of the study and has provided written informed consent as approved by the IRB/ EC of the respective clinical site or regulatory authority if applicable by national law.
6. 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. With previous balloon sinuplasty or any endo-nasal surgery (including sinus surgery), except for septoplasty or surgical manipulation to nasal turbinates more than 6 months prior to the Screening visit.
2. Seasonal allergic rhinitis (SAR) subjects with symptoms and/or, based on time of year, would anticipate onset of symptoms within 4 weeks of randomization.
3. Perennial allergic rhinitis (PAR) subjects whose symptoms are well controlled by regular use of intranasal corticosteroids.
4. With severe asthma or with one or more exacerbations of asthma requiring systemic corticosteroid use within the 6 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.
5. Endoscopic exclusion criteria:
   a. Complete/near complete middle meatal obstruction preventing proper placement and/or visualization of LYR-210.
   b. Evidence of mucosal erosion or ulceration.
   c. Ongoing nasal infection.
   d. Evidence of nasal septal perforation.
6. MRI exclusion criteria:
   a. A bilateral Zinreich score < 4 in all 3 pairs of the posterior ethmoid, frontal, or sphenoid sinuses (0-5 scale for each of the sinuses) on Screening MRI.

b. Anatomic variation which, in the opinion of the Investigator, would adversely impact placement of LYR-210.
c. Structural, non-inflammatory related CS (e.g., large concha bullosa, tumor).
d. Sinus disease extended into orbital or intracranial space.
e. Evidence of mycetoma/fungal ball, allergic fungal rhinosinusitis.
f. Sinus mucocele.

7. History or clinical evidence or suspicion of invasive fungal sinusitis, allergic fungal rhinosinusitis, or atrophic rhinitis.
8. Known history of hypersensitivity or intolerance to corticosteroids.
9. Oral-steroid or monoclonal antibody (Xolair, Nucala) dependent condition.
10. Having had systemic corticosteroids within 1 month prior to Screening visit.
11. Known history of hypothalamic pituitary adrenal axial dysfunction or having a clinically significant out of normal range morning serum cortisol level at screening.
12. Previous pituitary or adrenal surgery.
13. Has had 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.
14. Has had acute exacerbation of nasal allergy or chronic sinusitis, upper respiratory tract infection (URTI), or common cold within 4 weeks of the Screening visit.
15. Had dental procedure/implant on maxillary dentition within 4 weeks of the Screening visit.
16. Has past or present acute or chronic intracranial or orbital complications of CS (e.g., brain abscess, related problems with eyes or central nervous system).
17. History or diagnosis (in either eye) of glaucoma or ocular hypertension (IOP > 21 mmHg).
18. With prior cataract surgery or presence (in either eye) of posterior subcapsular cataract of grade 2 or higher, nuclear sclerosis of grade 3 or higher, or cortical cataract of grade 2 or higher or involving a minimum of center optic zone of 3 mm diameter.
19. Past or present functional vision in only one eye.
20. Diagnosed with ongoing rhinitis medicamentosa.
21. Known history of immune dysfunction including immune deficiency (IgG subclass deficiency or IgA deficiency) or autoimmune disease (e.g., Wegener's granulomatosis, sarcoidosis).
22. Past, present, or planned organ transplant or chemotherapy with immunosuppression.
23. History or diagnosis of ciliary dysfunction (e.g., cystic fibrosis, primary ciliary dyskinesia [Kartagener syndrome]).
24. Past or present systemic vasculitis (e.g., granulomatosis with polyangiitis).

25. Evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments.
26. Pregnant or breast feeding. Females of child-bearing potential must test negative for pregnancy at the time of screening based on a serum pregnancy test and reverified at the time of enrollment based on a urine pregnancy test. Both male and female subjects of reproductive potential must agree to use highly effective methods of birth control, throughout the study.
27. Previously participated in LYR-210 Phase I clinical study or received an experimental treatment in another clinical study within 5 half-lives of Screening visit.
28. Currently participating in an investigational drug or device study.
29. 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 Randomization

Subjects who complete the study Screening assessments and the washout period, and meet all eligibility criteria on Day 1 will be, before any treatment, randomized in a 1:1:1 ratio to one of the following study arms:

- Arm 1: bilateral administration of LYR-210 (2500 µg)
- Arm 2: bilateral administration of LYR-210 (7500 µg)
- Control Arm: bilateral sham procedure

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

- Nasal allergy (Yes vs No)
- Nasal polyps (Yes vs No)

For any reason, if the Investigator is unable to successfully administer LYR-210 or perform sham procedure into both middle meatuses in a subject (as described in Section 6.2), this subject will be considered as an Enrollment Failure.

Randomization will be conducted using Interactive Response Technology (IRT) and treatment will be assigned according to a randomization scheme generated by the Sponsor's unblinded biostatistician. The person generating the randomization scheme will not be involved in the collection, review, and/or analysis of study data before database lock and unblinding.

6.2 Study Product Administration

6.2.1 Pre-procedure Medication

Prior to LYR-210 administration or the sham procedure, all subjects will receive topical anesthetic and decongestant sprays for endoscopic assessment. Subjects will further receive anesthetic and decongestant soaked cottonoids or pledgets in each nostril to prepare the middle meatus for the study product insertion procedure.

6.2.2 Study Product Preparation

LYR-210 and the sham procedure article will be provided to the study site as described in Section 7.2.1. Preparation of LYR-210 or the sham procedure article should be performed in accordance with the instructions of use (IFU) provided in a separate document and should not start until the subject has been prepared and is ready for the administration procedure.

6.2.3 Study Product Administration

LYR-210 is designed to be administered intranasally under endoscopy visualization. Subjects who are assigned to either dose of LYR-210 will have LYR-210 administered bilaterally into the middle meatus. Subjects who are assigned to the sham procedure arm, will undergo bilateral mock administration (i.e., sham procedure), consisting of a bilateral insertion of an applicator

(without LYR-210 loaded) into the middle meatus until the applicator tip touches the ethmoid bulla for a minimum of 20 seconds, followed by withdrawal of the applicator. To maintain subject blinding to the treatment assignment, each subject will wear an eye mask (i.e., blindfold) at the time of the LYR-210 administration/sham procedure. An independent, unblinded case manager may be present during day 1 visit to assist product administration.

Following administration procedure, all enrolled subjects will rest for at least 1 hour and be monitored to ensure there is no epistaxis that requires medical attention.

6.2.4 Enrollment Failure

The Investigator will be allowed up to two attempts at LYR-210 administration or at the sham procedure per side. A treatment attempt is defined as that an applicator of a LYR-210 or sham article is inserted to a subject's left or right nostril for an attempt of investigational product administration. If the Investigator is unable to administer LYR-210 bilaterally or perform sham procedure successfully into both middle meatuses of a subject, the Investigator will remove any LYR-210 already administered and treat the subject with any appropriate therapy, if necessary. The subject will be considered as an **Enrollment Failure** as described in Section 6.1. Subjects will be followed within 7 (± 2) days via telephone for AE and concomitant medication assessment.

6.2.5 End of Day 1 Visit

Prior to discharge at Day 1 visit, all enrolled subjects will be provided with clear instructions and the following reminders:

- That they are currently enrolled in an investigational study for up to 12 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 mouth open 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-210 falls out of the nose. If this occurs - instruct subject to retain the depot (place in a plastic bag/vial and store in a freezer if possible) and return to the clinic at the next clinic visit.

6.3 Blinding

Except for the cases of spontaneous depot dislodgement, subjects should remain blinded to their treatment assignment (LYR-210 or sham) until the final study database is locked. To maintain subject blinded (LYR-210 or sham), each subject will wear an eye mask (i.e., blindfold) at the time of the LYR-210 administration/sham procedure and at all post Day 1 visits (scheduled or unscheduled) if an endoscopy assessment is performed.

The investigational site staff will be blinded regarding the impending treatment assignment until after a study subject has completed all baseline assessments required on Day 1 visit (Section 8.1) prior to randomization assignment. After randomization assignment, the investigational site staff, including the Investigator and study coordinator, will be unblinded as to whether the subjects receive LYR-210 administration or sham procedure. The study clinic staff, including the Investigator and study coordinator, will be blinded as to the dose administered to subjects receiving LYR-210.

The Sponsor will be blinded to subjects' study treatment assignments until database lock for the primary data analysis after all enrolled subjects have completed Week 28 visit or withdrawn from study, whichever comes first.

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-210, 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. The unblinding should be noted in the subject's eCRF.

6.3.2 Revealing Randomization

In the absence of a medical emergency or inadvertent unblinding due to depot dislodgement, the blinded randomization for this study will not be revealed until all data are entered in the database, edit checks are performed, queries are closed, CRFs are signed by the Investigator at each site, and the database is officially locked per study unblinding plan.

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 washout and treatment stages to avoid confounding the efficacy or safety assessments of LYR-210.

All medications taken by subjects during the course of the study will be recorded.

6.4.1 Prior Medications

Beginning at Screening, all medications and other treatments taken by subjects will be recorded on the 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 (see also 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

should contact the Sponsor's medical monitor for approval prior to administration, provided the safety of the subject would not be compromised.

6.4.2 Prohibited Concomitant Medications

The following medication that could potentially affect symptoms of CS or the safety assessment of LYR-210 will not be allowed during the Screening and washout period or during the treatment stage:

- Oral/ocular/intramuscular/intravenous/intranasal corticosteroids (except for oral or intranasal corticosteroids permitted as rescue medication only);
- Anti-allergy medications, including: first generation antihistamines; leukotriene receptor antagonists, nasal cromolyn sodium or sodium cromoglycate, nedocromil sodium, atropine, ipratropium bromide, or guaifenesin;
- Oral decongestants;
- Inhaled anti-cholinergic medications (except for a stable regimen for chronic obstructive pulmonary disease (COPD) subjects);
- Any monoclonal antibody;
- Any potent cytochrome P-450 3A4 (CYP3A4) inhibitors (ketoconazole and ritonavir);
- Any allergen immunotherapy (except for a stable dose and regimen);
- Oral anti-fungal medication.

Subjects who received prohibited medications will be considered a protocol deviation and may require withdrawal from the study as detailed in Section 4.3.

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 provided with saline and instructions for daily intranasal saline irrigation twice a day starting from washout till Week 24/EOT.
- If a sinus infection is suspected at any time during the study, treatment with antibiotics will be allowed after a clinic visit and per Investigator's judgment.
- Subjects who have been on a stable regimen of inhaled corticosteroids 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 2018 Global Initiative for Asthma Management and Prevention [1].
- Perennial allergic rhinitis (PAR) subjects who have been on a stable regimen of a non-sedating 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 medications are recommended in the event of an acute exacerbation of the following conditions that result in the subject contacting the Investigator who determines an initiation of rescue therapy:

- Any time during the 24-week treatment stage:
  - After a clinic visit and per Investigator's judgment, antibiotics for sinus infection.
  - After a clinical visit and evaluation for worsening or uncontrolled severe CS symptoms, the Investigator using his/her best judgement may give 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 not responding to an INCS, or a flare-up of asthma. The rationale for the use of oral corticosteroid must be recorded.
- After the Week 4 visit only:
  - For acute allergic symptoms: non-sedating oral antihistamine such as loratadine (10 mg per day) or equivalent.
  - For severe acute nasal blockage (score of 2 or more over the past 3 days): a course of oxymetazoline spray for a maximum of 3 consecutive days and a total maximum of 10 days during the treatment period. Oxymetazoline cannot be used within 24 hours before MRI assessments.
  - For worsening CS symptoms: intranasal MF sprays with dose and duration per Investigator's recommendation.
  - For worsening or uncontrolled severe CS symptoms: ESS as rescue treatment per Investigator's recommendation.

6.5 Removal Procedure

Subjects who receive LYR-210 will have the bilateral drug depots removed at the Week 24/EOT visit or earlier in an Unscheduled early termination (ET) visit if medically warranted per the treating physician's discretion (for example, requiring an ESS as rescue treatment). The removal procedure will be performed under endoscopic visualization after topical anesthetic and decongestant sprays applied to each nostril. Standard surgical tools are used to remove LYR-210. LYR-210 is made of polymers designed to gradually soften over time. Care should be taken to remove LYR-210 in one piece or in sections should any disintegration of LYR-210 occur.

To keep the subjects enrolled in the sham procedure group fully blinded in the post-treatment safety follow up stage, all sham control subjects will undergo a sham removal procedure either at the scheduled Week 24 visit or earlier in an unscheduled early termination (ET) visit if the subjects request early depot removal.

6.6 Treatment Compliance

Administration and removal of LYR-210 and the sham procedure article will be performed in a clinical setting by trained personnel who will be responsible for ensuring and recording compliance with all treatment procedures.

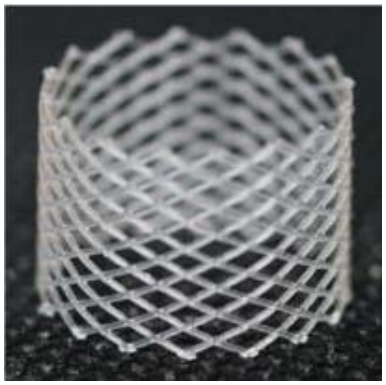
7. DRUG PRODUCT MATERIALS AND MANAGEMENT

7.1 Investigational Product

7.1.1 Product Description

The LYR-210 System is a combination product comprised of a single-use applicator, pre-loaded with the LYR-210 drug depot, containing 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 CS disease, as well as asthma. The LYR-210 drug depot is made of bioabsorbable polymers designed to gradually soften over time. It has a tubular braid configuration with a uniform diamond pattern throughout and dimensions of 13 mm in diameter and 10 mm in length in the unconstrained state (Figure 2). It is designed to be self-retaining against the mucosal tissue to allow effective drug transfer for up to 24 weeks.

Figure 2: LYR-210 Images



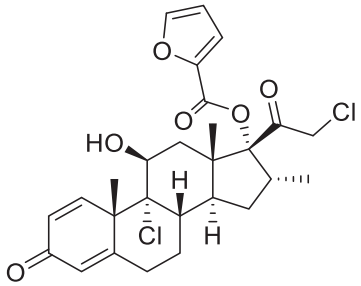
7.1.2 Dosage and Administration

Each LYR-210 drug depot contains either 2500 µg or 7500 µg MF. LYR-210 is intended to be administered bilaterally into the ESS-naive middle meatus by an otolaryngologist under endoscopic visualization via a provided single use applicator. Once administered, each LYR-210 is designed to gradually deliver MF to the inflamed mucosal tissue over 24 weeks with a single drug administration. Bilateral placement of LYR-210 (2500 µg) is designed to deliver a total dose of 5,000 µg MF over the 24 weeks, or an average daily dose of 30 µg MF per human subject (or 15 µg MF per nostril). In the case of LYR-210 (7500 µg), a total dose of 15,000 µg MF will be delivered over the 24 weeks with an average daily dose of 89 µg MF per human subject (or 45 µg MF per nostril).

7.1.3 Active Ingredient: Mometasone Furoate

Mometasone furoate, USP, is the active pharmaceutical ingredient. It is a potent, topically active, anti-inflammatory corticosteroid, having the chemical name of 9α,21-dichloro-11β,17α-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2-furoate), with an empirical formula of $C_{27}H_{30}Cl_2O_6$ and a molecular weight of 521.43 g/mol. It has the chemical structure shown in Figure 3.

Figure 3: Chemical Structure of Mometasone Furoate



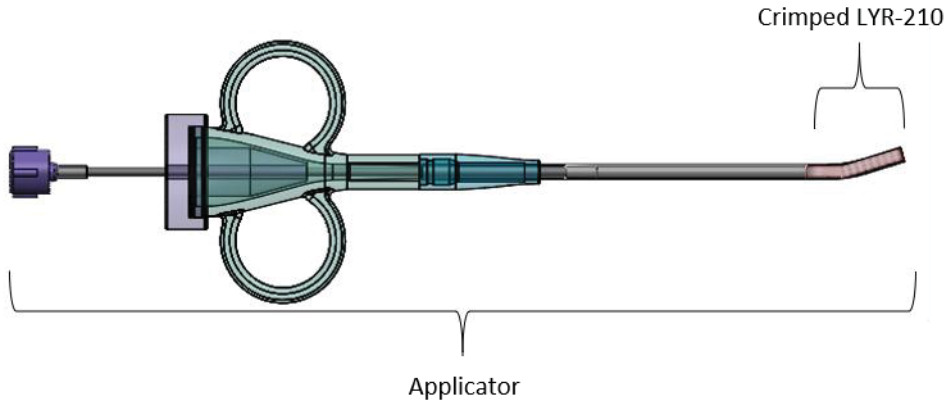
7.1.4 Inactive Ingredients

[redacted]

7.1.5 Applicator

LYR-210 is designed to be administered intranasally under endoscopy visualization via a single use applicator that contains the drug depot (Figure 5). The applicator compresses LYR-210 just prior to use, accesses the treatment site, and administers the drug depot. The applicator is constructed from materials commonly used in medical devices with well-established biocompatibility: polycarbonate, polytetra-fluoroethylene, Pebax® (comprised of polyamide and polyether), polyethylene, nylon, and stainless steel.

Figure 5: Applicator, Ready for LYR-210 Administration



7.2 Drug Product Management

7.2.1 Packaging and Labeling

LYR-210 will be packaged and labeled appropriately for the blinded clinical study, as required by regional legislation and industry guidelines.

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 LYR-210 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 of LYR-210 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 LYR-210 or the sham procedure articles shall be achieved by assigning each depot and applicator a unique serial number, designated next to the "SN" symbol on the label.

7.2.4 Product Accountability

The Sponsor will supply sufficient quantities of LYR-210 and the sham procedure articles 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. Required information includes the date received, date used, lot number, product description, expiry date, and a subject identifier for product that has been administered. Investigational sites will use a form to document product disposition which will be reviewed by the study monitor during routine monitoring visits. When 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 product 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 product that are associated with a malfunction, the product and all ancillary components (e.g., applicator) remaining from the index procedure should 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.

Enrolled subjects will be asked to complete an ePRO questionnaire daily in the morning to assess the 4 cardinal symptoms of CS including nasal blockage/obstruction/congestion, reduction/loss of sense of smell, facial pain/pressure, and anterior/posterior nasal discharge. In addition, the ePRO will capture the recommended daily use of nasal saline irrigation by the subject. Subjects will also complete a validated CS-specific quality of life questionnaire, the SNOT-22, throughout the study; and a general quality of life questionnaire, the SF-36v2, on Day 1 and at Week 24/EOT and Week 48/EOS visits. At the Week 24/EOT visit, an end-of-treatment questionnaire will be administered.

Subjects will be asked to complete the UPSIT™ for smell dysfunction on Day 1 before the LYR-210 administration/sham procedure, and at Week 24/EOT and Week 28 visits.

Sinus inflammation will be assessed by MRI without contrast before the LYR-210 administration/sham procedure during Screening and at the Week 24/EOT visit, unless medically contraindicated. If a subject is experiencing or recovering from a cold, acute exacerbation of nasal allergy, or upper respiratory tract infection at this visit, perform assessment 4 weeks after resolution of the adverse event. If a subject requires oral corticosteroid as rescue during the 24-week treatment period, the follow-up MRI should be performed before receiving the rescue treatment instead of at Week 24/EOT visit.

Nasal cavities will be assessed by endoscopy before the LYR-210 administration/sham procedure on Day 1, at Weeks 2, 4 and 12, Week 24/EOT, and Week 28 visits. Subjects are required to wear a blindfold if endoscopy examination is performed at these visits to remain blinded to treatment assignment. Local nasal safety evaluation will be performed at these visits to document presence of epistaxis, mucosal erosion or ulceration, perforation, infection, and any other local nasal adverse effects. For CSwNP subjects, real-time, qualitative endoscopic evaluation of change of polyp severity within middle meatus will be performed by site Investigators at the Week 24/EOT visit after LYR-210 removal/sham removal procedure and at Week 28 visit by comparing to that of the Day 1 visit.

Ophthalmologic assessments will include IOP and slit-lamp examination for cataract development at Screening, Week 24/EOT and Week 48/EOS visits. IOP assessment will be also performed at Week 4 and Week 12 visits.

Plasma samples for PK will be collected from all subjects on Day 1 before the LYR-210 administration/sham procedure, and at Weeks 4 and 12, Week 24/EOT, and Week 28 visits.

Additional plasma PK samples will be collected at Days 3, 7, 14 (Week 2), 21 from approximately 15 randomized and successfully enrolled subjects at participating US sites. The concentration of MF in plasma will be measured by a central laboratory.

Routine safety assessments will be performed during the study including vital signs and physical exams at all clinic visits. Samples for hematology, blood chemistry, and cortisol will be collected during Screening, at Weeks 4 and 12, Week 24/EOT, and Week 28 visits. An additional hematology, chemistry, and serum cortisol sample will be collected within 72 hours prior to LYR-210 administration/sham procedure for Baseline value. All post-Screening serum cortisol samples will be evaluated by a central laboratory.

For female subjects of childbearing potential, a serum pregnancy test will be performed at Screening visit and a urine pregnancy test will be performed on Day 1 prior to randomization to confirm eligibility for participating in the study. A urine pregnancy test will be performed every 4 weeks in clinic during the treatment stage in these female subjects.

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 at the treating physician's discretion.

Additional visits may occur as clinically warranted. At these **Unscheduled Visits**, any of these assessments may be performed per the treating physician's discretion.

Table 1: Schedule of Assessments for Subjects Randomized and Enrolled

Evaluation	Screening	Procedure Day [a]	Treatment Stage [a] (24 weeks)							Post-Treatment Stage [a] (24 weeks)					
Visits #	1	2 [b]	3 [b]	4 [b]		5 [b]			6 [b]	7 [b]					8
Study Day/Week	DAY -28 to -14	DAY 1	WK 2 (±1 day)	WK 4 (±3 days)	WK 8 (±3 days) [r]	WK 12 (±3 days)	WK 16 (±3 days) [r]	WK 20 (±3 days) [r]	WK 24 / EOT (±3 days)	WK 28 (±7 days)	WK 32 (±7 days) [r]	WK 36 (±7 days) [r]	WK 40 (±7 days) [r]	WK 44 (±7 days) [r]	WK 48 / EOS (±7 days)
Informed Consent	X [c]														
Demographics	X														
Medical History	X														
Vital Signs	X	X [d]	X	X		X			X [d]	X					X
Physical Exam	X	X [d]		X		X			X [d]	X					X
Pregnancy Test [f]	X [e]	X [d,e,t]		X [e]	X [e]	X [e]	X [e]	X [e]	X [e]						
Hematology/Chemistry [f]	X	X [d,t]		X		X			X [d]	X					
Morning Serum Cortisol [f,g]	X	X [d,t]		X		X			X [d]	X					
Magnetic Resonance Imaging	X [h]								X [p,q]						
Ophthalmology Assessment [i]	X [h]			X [j]		X [j]			X [p]						X
UPSIT ™		X [d]							X [d]	X					
Endoscopy	X	X [k, m]	X	X		X			X [k,m]	X [k]					
Eligibility Assessment	X	X [d]													
Washout Period	X [l]														
Randomization		X [d]													
Baseline LYR-210/Sham Procedure		X													
Plasma Pharmacokinetics [s]		X [d]		X		X			X [d]	X					
LYR-210/Sham Removal Procedure									X						
Daily ePRO	X [n]														
SNOT-22 Questionnaire	X	X [d]	X	X	X	X	X	X	X [d]	X	X	X	X	X	X
SF-36v2 Questionnaire		X [d]							X [d]						X
End-of-Treatment Questionnaire									X						
Concomitant Medications/Procedures	X														
Adverse Events [o]	X														

Abbreviations: UPSIT = university of pennsylvania smell identification test; CS = chronic sinusitis; ePRO = electronic patient reported outcomes; EOT = end of-treatment; EOS = end-of-study; SF-36v2 = short form health survey version 2; SNOT = sino-nasal outcome test; WK=week

a: Subjects remain blinded starting from the time of randomization
b: Subjects will wear a blindfold during any endoscopy procedure or endoscopy imaging.
c: To be obtained before any study related assessments occur.
d: Occurs before the LYR-210 or sham administration and removal procedures.
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: Blood samples will be collected during the morning hours before 10:00 AM (i.e., before 1000 HRS). Screening cortisol samples will be performed locally at the study site. Cortisol samples collected at all post-Screening visits will be sent to a central laboratory for testing.
h: Performed anytime between Screening and Day 1 visits.
i: Performed by a blinded ophthalmologist/optometrist.
j: IOP assessment only.
k: For CSwNP subjects, endoscopic evaluation of severity of polyps within middle meatus will be performed by the site Investigator at the time of imaging recording. Polyp severity evaluation should occur after topical anesthetic and decongestant sprays are administered, but before anesthetic and decongestant soaked pledgets or cottonoids are applied.
l: For a minimum of 2 weeks on all prohibited medications before the Day 1 visit. Subjects will start daily saline irrigation twice a day during washout.
m: Local nasal safety and polyp assessments to be performed before LYR-210/sham insertion on Day 1 or after LYR-210/sham removal at EOT visit.
n: Daily instantaneous morning (between 06:00:00AM and 11:59:59AM) CS symptoms to be recorded by the subject on ePRO questionnaire beginning at least in the preceding 7 days prior to Day 1 visit.
o: All adverse events shall be reported after subject signs informed consent.
p: To be performed within 7 days after removal procedure.
q: If a subject is experiencing or recovering from a cold, acute exacerbation of nasal allergy, or upper respiratory tract infection at EOT visit, perform assessment 4 weeks after resolution of the adverse event. If a subject requires oral corticosteroid as a rescue treatment, perform follow-up MRI before receiving the rescue treatment instead of at EOT visit.
r: Phone follow up to collect any potential AEs and use of concomitant medications/procedures.
s: [redacted]
t: Samples can be collected within 72 hours prior to LYR-210 administration/sham procedure.

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 sinusitis
- Asthma
- Chronic obstructive pulmonary disease (COPD)
- Perennial allergic rhinitis (PAR)
- Seasonal allergic rhinitis (SAR)
- Sensitivity to Non-steroidal anti-inflammatory drugs (NSAIDs)
- Smoking

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

- Endoscopic sinus surgery (ESS)
- Septoplasty
- Sinuplasty
- Polypectomy
- Nasal surgery involving nasal turbinates
- Facial trauma

8.3 Assessment of Efficacy

8.3.1 Subject Reported Outcomes

Subject symptom improvement, 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. At all clinic visits, the ePRO will be completed prior to any intranasal procedure or clinic assessments.

8.3.1.1 Chronic Sinusitis Cardinal Symptom Assessment

For assessment of the 4 cardinal symptoms of CS, the ePRO will be completed by subjects on a daily basis as specified in the Schedule of Events (Section 8.1). Subjects will start recording their symptoms on the ePRO at least 7 days preceding the Day 1 visit. A minimum of 5 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 cardinal symptoms of CS, as defined in the 2012 European position paper on rhinosinusitis and nasal polyps (EPOS-2012) [2] and the 2016 international consensus statement on allergy and rhinology: rhinosinusitis (ICAR:RS-2016) guidelines [3], include nasal blockage/obstruction/congestion, reduction/loss of sense of smell, facial pain/pressure, and nasal discharge (anterior/posterior nasal drip).

Subjects will score the severity of their morning (between 06:00:00AM to 11:59:59AM) instantaneous symptoms of CS on a 4-point scale (Section14.1):

- 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)

8.3.1.2 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 Events (Section 8.1).

The SNOT-22 questionnaire is a 22-item disease-specific quality of life instrument validated for use in CS [27] (Section 14.2). Subjects score the severity of their symptoms and social/emotional consequences of CS on a 6-point scale:

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

The scores are summed; higher scores on the SNOT-22 instrument total score or subdomain scores as defined in Table 2 [29] indicate higher severity of symptoms or social/emotional consequences of CS.

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

8.3.1.3 Saline Irrigation Use

The ePRO will also be used to collect the frequency of daily saline irrigation by the subjects.

8.3.1.4 36-item Short Form Health Survey version 2 (SF-36v2®) Questionnaire

At Day-1, Week 24/EOT, and Week 48/EOS visits, subjects will complete the SF-36v2® questionnaire by ePRO. SF-36v2® is a generic health survey that asks 36 questions to measure functional health and well-being of a subject (Section 14.4). It is a valid measure of physical and mental health and the most frequently used PRO instrument in clinical trials today [30]. Additionally, the SF-36v2® provides scores for each of the eight health domains and psychometrically based physical component summary (PCS) and mental component summary (MCS) scores (Table 3) [31]. The items of the SF-36v2 are transformed and summed to a norm-based scores (Mean = 50, SD = 10) scale for each PCS and MCS domain in which higher scores indicate a better health-related QoL.

Table 3. SF-36v2® Health Survey Measurement Model

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

8.3.1.5 End-of-Treatment Questionnaire

At Week 24/EOT visit, subjects will complete an end-of-treatment questionnaire by ePRO (Section 14.3). The questionnaire will query subjects about their general experience and satisfaction with their assigned study treatment. Subjects will describe their experiences by answering multi-choice questions or providing narrative responses.

8.3.2 Sinus Inflammation Imaging

Sinus inflammation will be assessed by MRI without contrast at the time points specified in the Schedule of Events (Section 8.1), unless medically contraindicated. The Screening MRI should be performed anytime between the Screening and Day 1 visits. The follow up MRI will be conducted within 7 days after the LYR-210 removal/sham procedure at Week 24/EOT visit. If a subject is experiencing or recovering from a cold, acute exacerbation of nasal allergy, or upper respiratory tract infection at the EOT visit, the MRI will be performed 4 weeks after resolution of the adverse event. If a subject requires oral corticosteroid as rescue during the 24-week treatment period, the follow-up MRI should be performed before receiving the rescue treatment instead of at Week 24/EOT visit.

The sinus inflammation will be assessed using the Zinreich modified Lund-Mackay scoring system (referred herein as the Zinreich scores)[32] where each sinus is assigned a score based on the percentage of opacification as follows:

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

The ostiomeatal complex (OMC) is given a score of 0 to 2 as follows:

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

Each sinus pair has a bilateral Zinreich score in the range of 0 to 10, and the OMC pair in the range of 0 to 4, and the total sum of all sinuses and OMCs in the range of 0-54.

8.3.3 Nasal Polyp Assessment

Visualization and assessment of nasal polyps will be conducted using endoscopy at the time points specified in the Schedule of Events (Section 8.1). At the Day 1 visit, prior to the LYR-210 administration/sham procedure, an endoscopic assessment of nasal passageway for eligibility will be conducted after topical anesthetic and decongestant sprays are administered, but before any

anesthetic and decongestant soaked pledget or cottonoid is applied for the LYR-210 administration/sham procedure. The follow up endoscopic assessment of the nasal passageway will be conducted at Weeks 2, 4 and 12, Week 24/EOT, and Week 28 visits.

Investigators will evaluate the severity of nasal polyps in the middle meatus at the Week 24/EOT and Week 28 visits by grading polyp severity as "better," "worse," or "the same" in comparison to the Baseline severity evaluated at Day 1 visit before the insertion procedure.

8.3.4 The University of Pennsylvania Smell Identification Test (UPSIT™)

The UPSIT will be conducted at 3 time points during the study as specified in the Schedule of Events (Section 8.1). At Day 1 and Week 24/EOT visits, the UPSIT™ will be conducted prior to the LYR-210 administration/sham procedure and prior to the LYR-210 removal/sham procedure endoscopy assessment.

The UPSIT™ is composed of 40 odorants embedded on scent strips that are released when scratched with a sharply tipped object [33]. The UPSIT is comprised of 4 booklets, each containing 10 microencapsulated (scratch & sniff) odors. The UPSIT is a forced-choice test, and subjects will be instructed to identify each odorant with alternatives accompany each test item. The total olfaction score using the UPSIT is defined as the number of odorants correctly identified out of the 40 odors tested, with higher scores designating better olfactory performance.

8.4 Assessment of Safety

8.4.1 Physical Examination

A physical examination including a careful assessment of all body systems, including the skin, eyes, ears, nose and throat, respiratory will be performed at all clinic visits as specified in the Schedule of Events (Section 8.1). Height (cm) will only be measured at Screening visit. Weight (kg) and body mass index (BMI) will be measured at all visits.

8.4.2 Vital Signs

Vital signs will be measured at all clinic visits as specified in the Schedule of Events (Section 8.1). Vital sign measurements will include blood pressure (systolic and diastolic, mmHg), and pulse rate (beats per minute), aural/oral temperature (°C), and respiration rate (breaths per minute). All measurements will be obtained after the subject has been resting supine for at least 5 minutes.

8.4.3 Laboratory Assessments

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

8.4.3.1 Hematology

Samples for hematology assessments will be obtained during Screening, within 72 hours prior to LYR-210 administration/sham procedure, and at Weeks 4 and 12, Week 24/EOT, and Week 28 visits as specified in the Schedule of Events (Section 8.1).

Hematology assessments will include a leukocyte count with differential (neutrophils, eosinophils, lymphocytes, monocytes, and basophils), erythrocytes, hematocrit, hemoglobin, and platelet count.

Testing will be performed according to the standard of care at the investigational site.

8.4.3.2 Blood Chemistry

Samples for blood chemistry assessments will be obtained during Screening, within 72 hours prior to LYR-210 administration/sham procedure, and at Weeks 4 and 12, Week 24/EOT, and Week 28 visits as specified in the Schedule of Events (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.

Testing will be performed according to the standard of care at the investigational site unless otherwise noted in the Lab Manual.

8.4.3.3 Morning Serum Cortisol

Samples for serum cortisol will be collected during the morning hours before 10:00 (i.e., before 1000 HRS) during Screening, within 72 hours prior to LYR-210 administration/sham procedure, and at Weeks 4 and 12, Week 24/EOT, and Week 28 visits as specified in the Schedule of Events (Section 8.1).

All serum cortisol samples, except for Screening, will be sent to a central laboratory for testing.

8.4.4 Nasal Endoscopy Assessments

Nasal cavities will be assessed by endoscopy on Day 1 before the LYR-210 administration/sham procedure, and at Weeks 2, 4 and 12, Week 24/EOT, and Week 28 visits as specified in the Schedule of Events (Section 8.1). Local nasal safety evaluation will be performed at these visits to document presence of epistaxis, mucosal erosion or ulceration, perforation, infection, and any other adverse local nasal observations.

8.4.5 Ophthalmologic Assessments

The ophthalmologic assessment of IOP and slit-lamp examination to identify cataract development will be conducted at Screening, Week 24/EOT, and Week 48/EOS visits as specified in the Schedule of Events (Section 8.1). IOP assessment will also be performed at Weeks 4 and 12 visits.

Assessments will be conducted by a blinded ophthalmologist/optometrist.

8.4.6 Pharmacokinetic Analysis

Blood samples for assessment of plasma PK will be at Day 1, Weeks 4 and 12, Week 24/EOT, and Week 28 visits as specified in the Schedule of Events (Section 8.1). [redacted]

At the Day 1 visit, the blood sample for plasma PK analysis will be collected prior to the LYR-210 administration/sham procedure. Subsequent blood samples may be collected at any time of the day during the scheduled study visits.

The concentration of MF in plasma will be measured at a central core lab.

[redacted]

8.4.8 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 re-verified prior to randomization 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 every 4 weeks during the treatment stage.

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 4 weeks 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 4 weeks 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 (i.e., fertile), following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal 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 either dose of the LYR-210 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 post-partum (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.

8.4.9 Adverse Events and Serious Adverse Events

8.4.9.1 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 Case Report Form. A new AE Case Report Form will be used for each AE. All on-going 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 drug, 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, 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-210 administration/sham procedure.

8.4.9.2 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 (i.e., 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 8.4.9.4). Any treatment related SAE (Section 8.4.9.5) will be followed until resolution of the event, or until the subjects withdraw from the study.

8.4.9.3 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.

8.4.9.3.1 Relationship to Study Drug Product

The relationship between an AE and the LYR-210 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-210 study drug product administration will be captured.

8.4.9.3.2 Relationship to Study Procedure

The Relationship between an AE and the LYR-210 administration/sham 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-210 administration/sham procedure, additional information on the timing of the event in relation to the study procedure will be captured.

8.4.9.4 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 procedure or product 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.

8.4.9.5 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, Investigator's brochure, 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 Investigator's Brochure (IB) or prescribing information for the registered formulation of MF or is listed at the specificity and severity that has been observed.

8.4.9.6 Reporting

8.4.9.6.1 Adverse Event Reporting

Adverse events are to be collected from the time a subject signs 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 (e.g., clinically significant) change from Baseline for that individual subject. If this laboratory test result is determined to be an 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 (Version 21.1 will be used at the start of the study).

8.4.9.6.2 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 (e.g., 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.

8.4.9.6.3 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.

8.4.10 Safety Monitoring

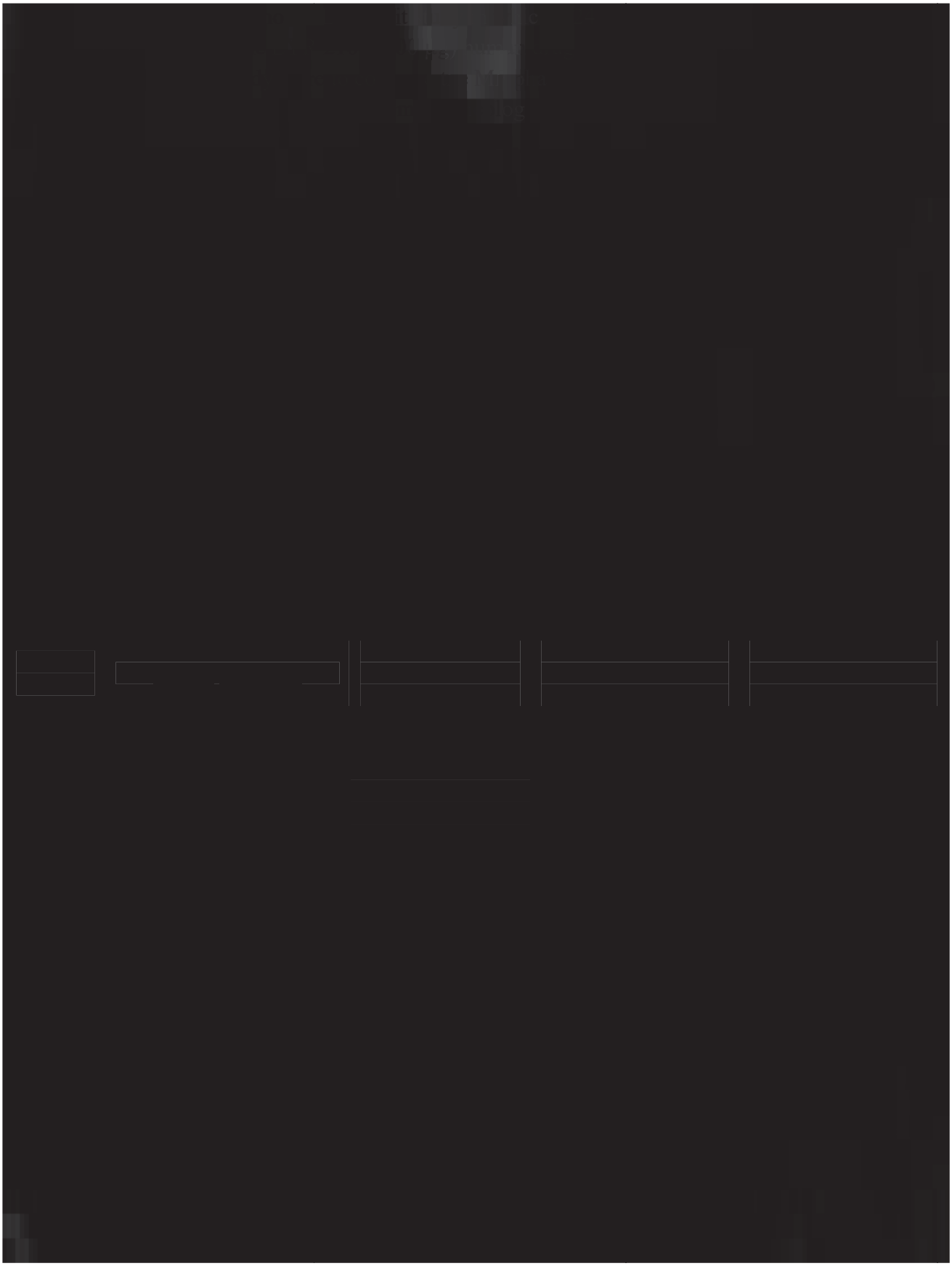
Subject will be closely monitored throughout the trial with high priority for subject safety. The sponsor will establish Safety/Medical Monitoring team early in the study. The team will be responsible for developing a Safety/Medical Monitoring Plan (MMP) which will define in detail the objectives, scope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

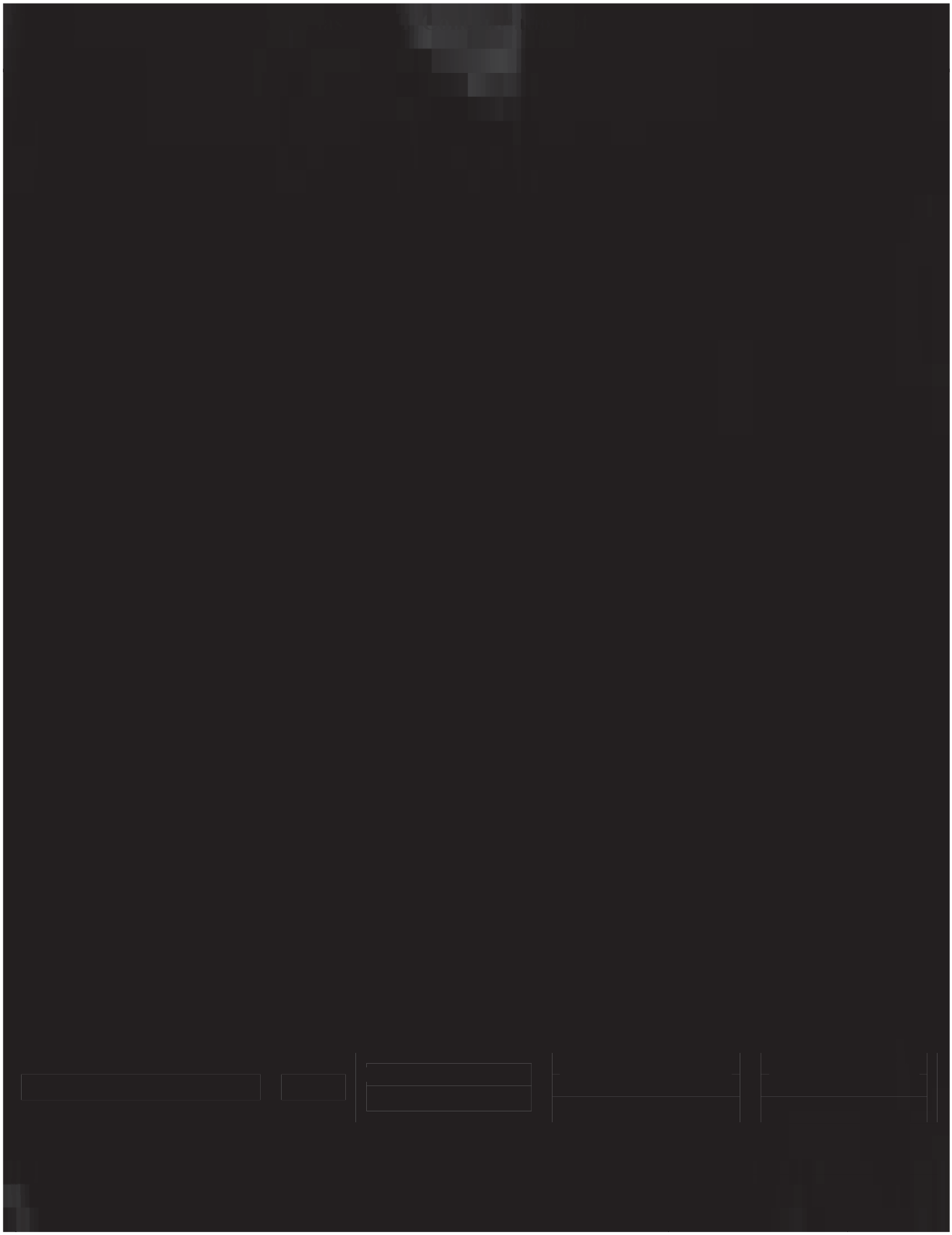
Subject safety monitoring encompasses, but is not limited to, providing advice to sites and the project team for protocol-related issues, providing input into decisions requiring medical advice and routine safety monitoring of the study, review of serious and non-serious AEs, various data listings, lab results, vital signs, and other clinical data may be undertaken. Reviews of blinded 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.

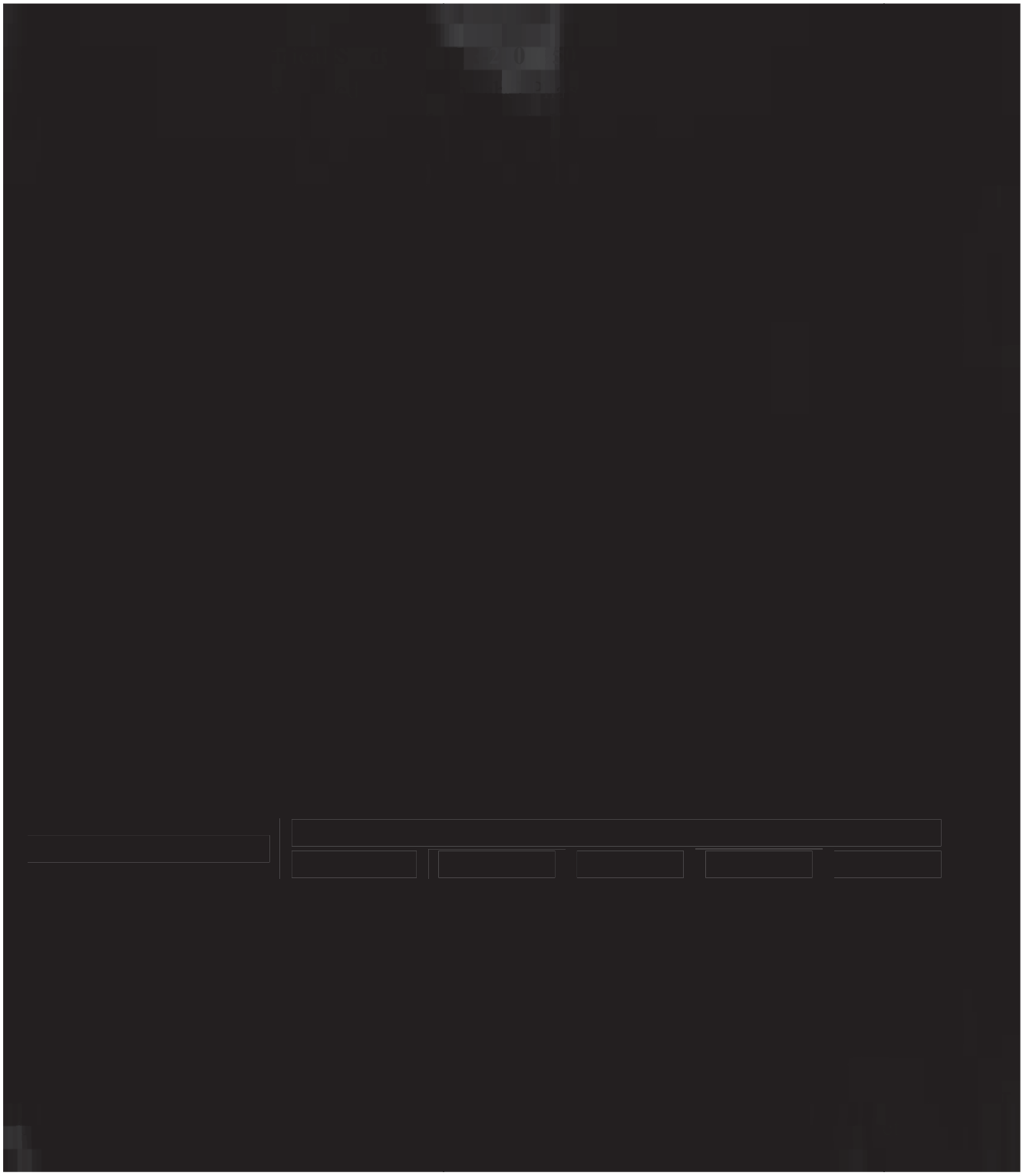
9. SAFETY INFORMATION OF STUDY DRUG PRODUCT

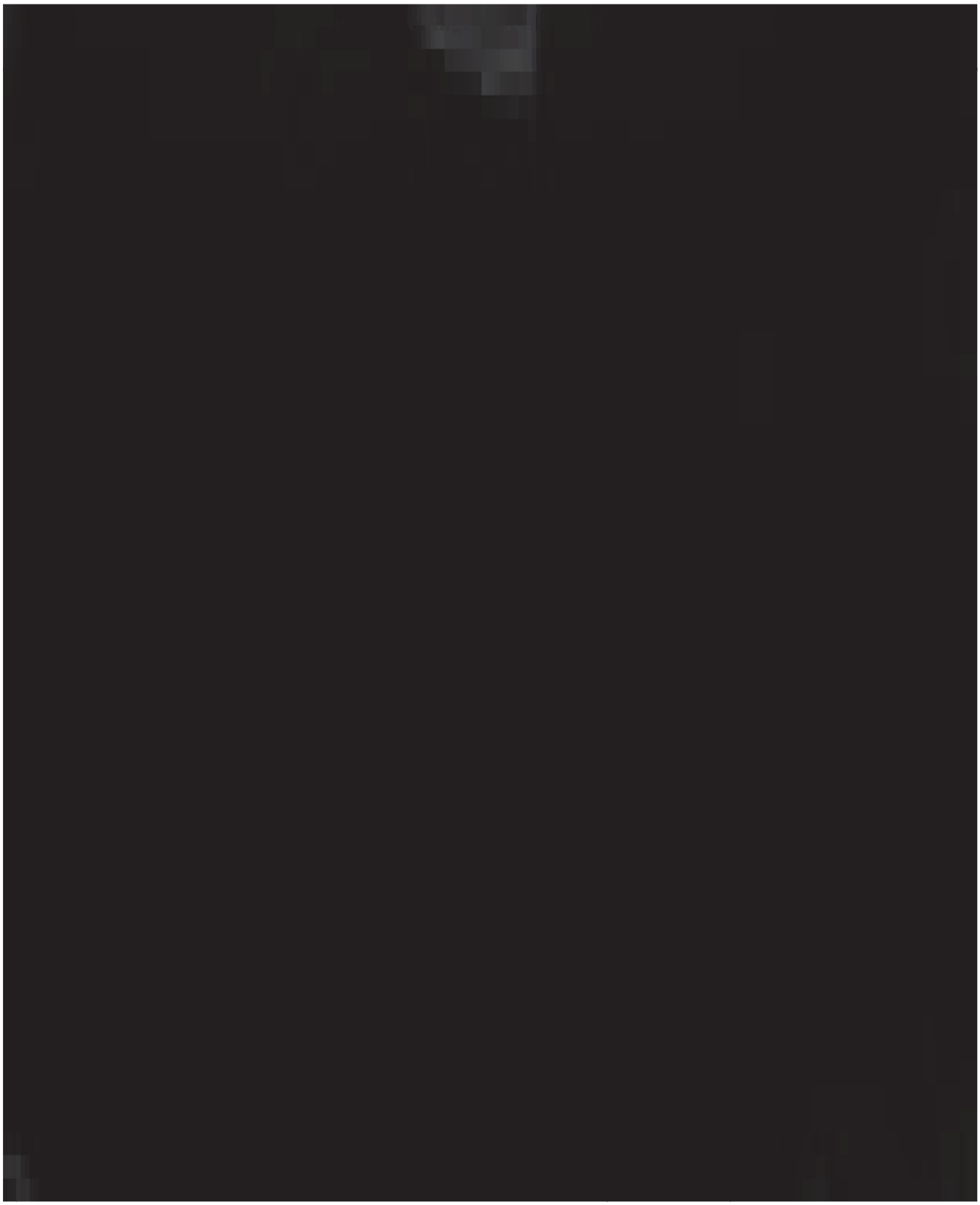
9.1 Safety Rationale of Study Drug Doses and Polymers

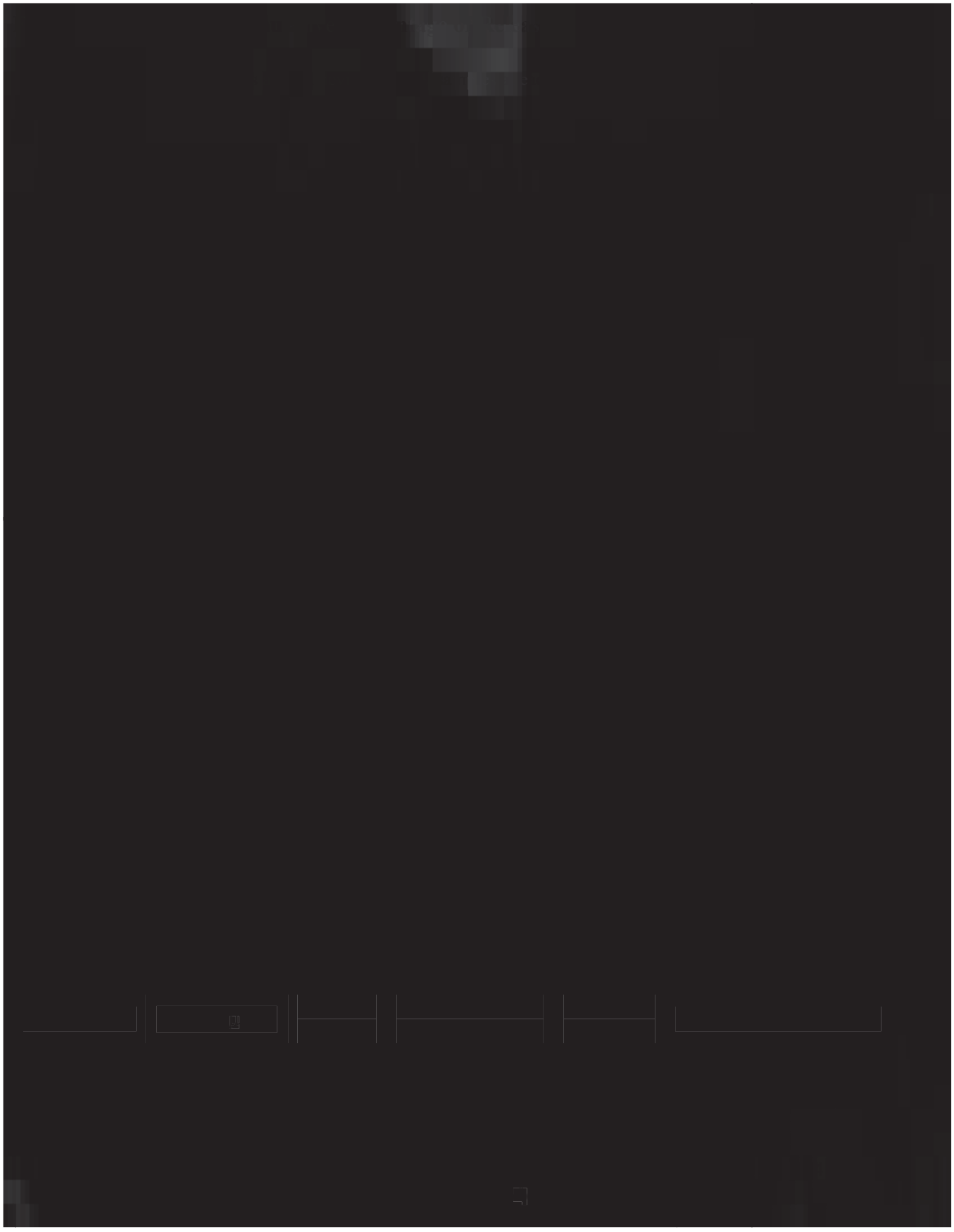
LYR-210 is designed to be administered intranasally under endoscopy visualization via a single use applicator that contains the drug depot. Bilateral placement of LYR-210 (2500 µg) is designed to deliver a total dose of 5000 µg MF over the 24 weeks with an average daily dose of 30 µg MF per subject (or 15 µg MF per nostril). In the case of LYR-210 (7500 µg), a total dose of 15000 µg MF will be delivered over the 24 weeks with an average daily dose of 89 µg MF per subject (or 45 µg MF per nostril). The safety of LYR-210 (2500 µg) and LYR-210 (7500 µg) are supported by the extensive clinical and nonclinical data from existing marketed MF containing pharmaceutical products and medical devices, the non-clinical toxicology assessment of LYR-210, and the Phase I clinical study of LYR-210 (2500 µg) in adult CS subjects.

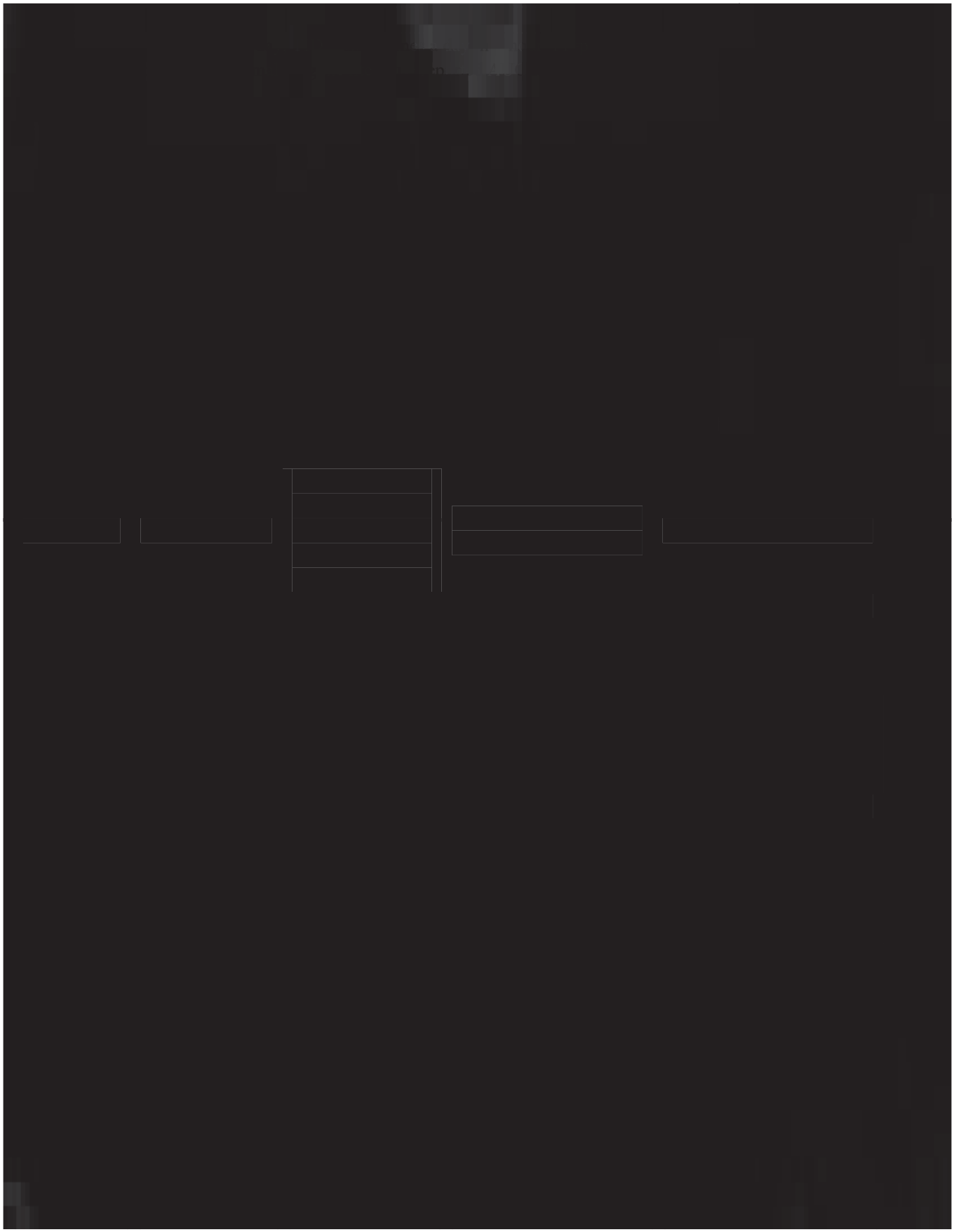


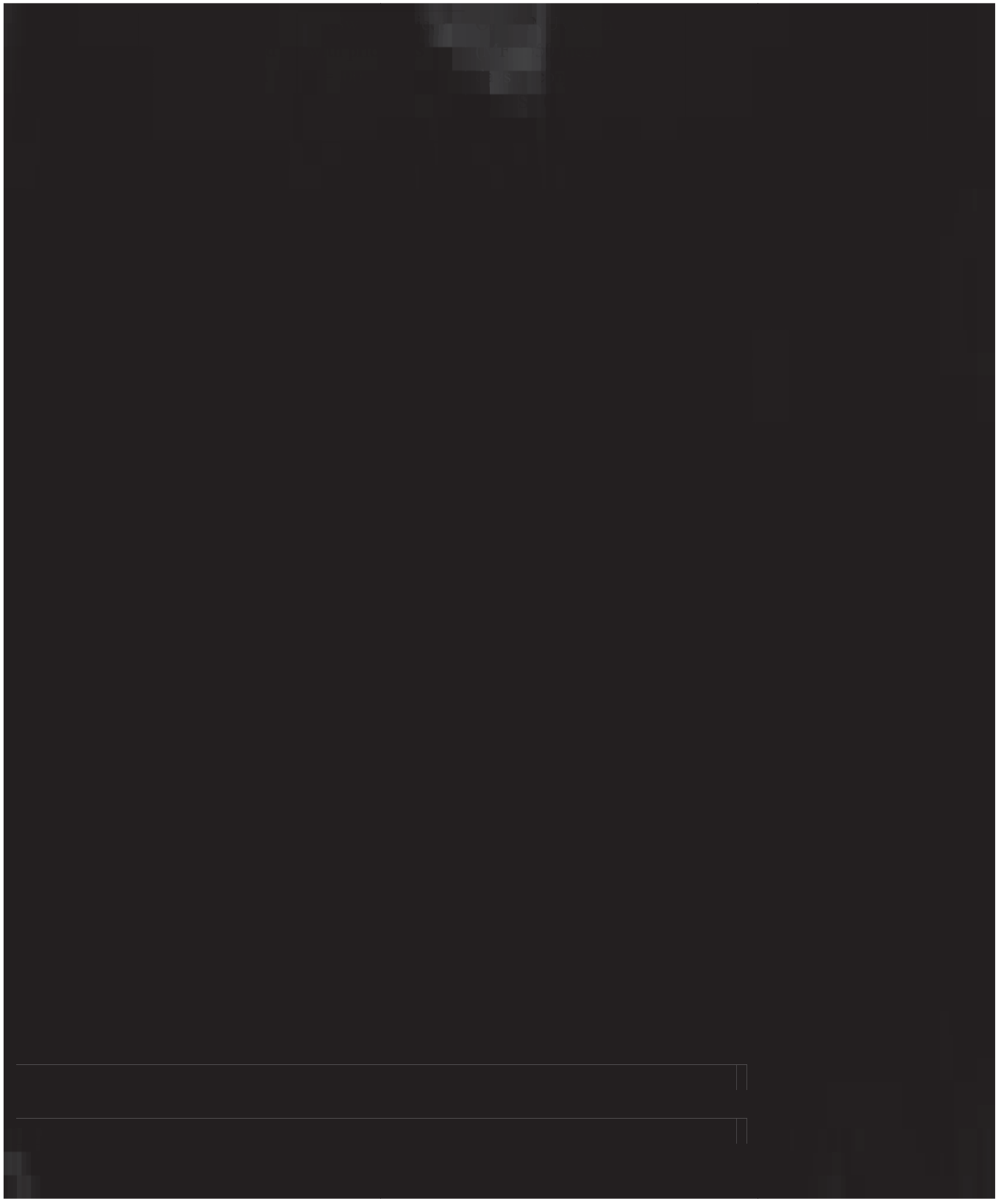


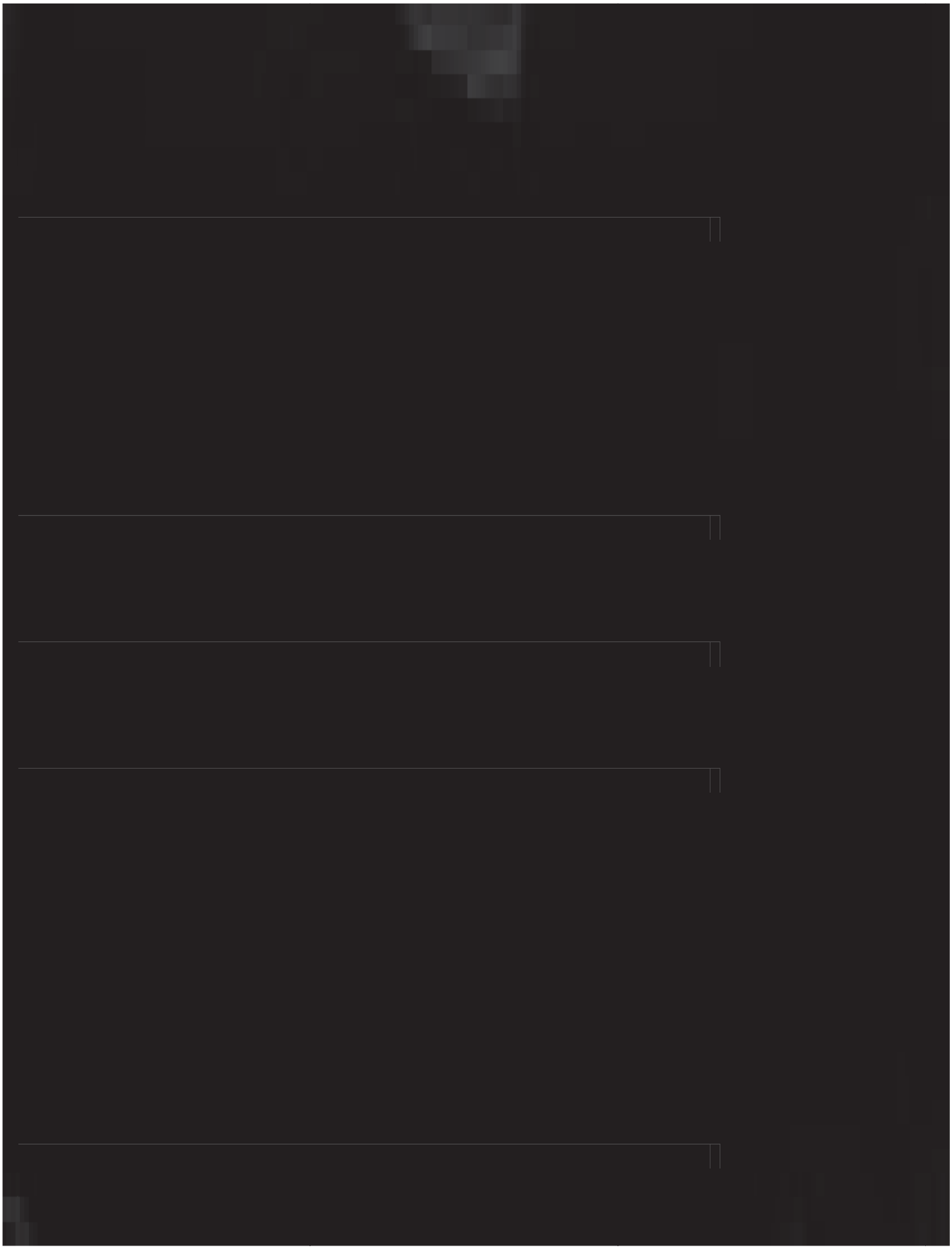


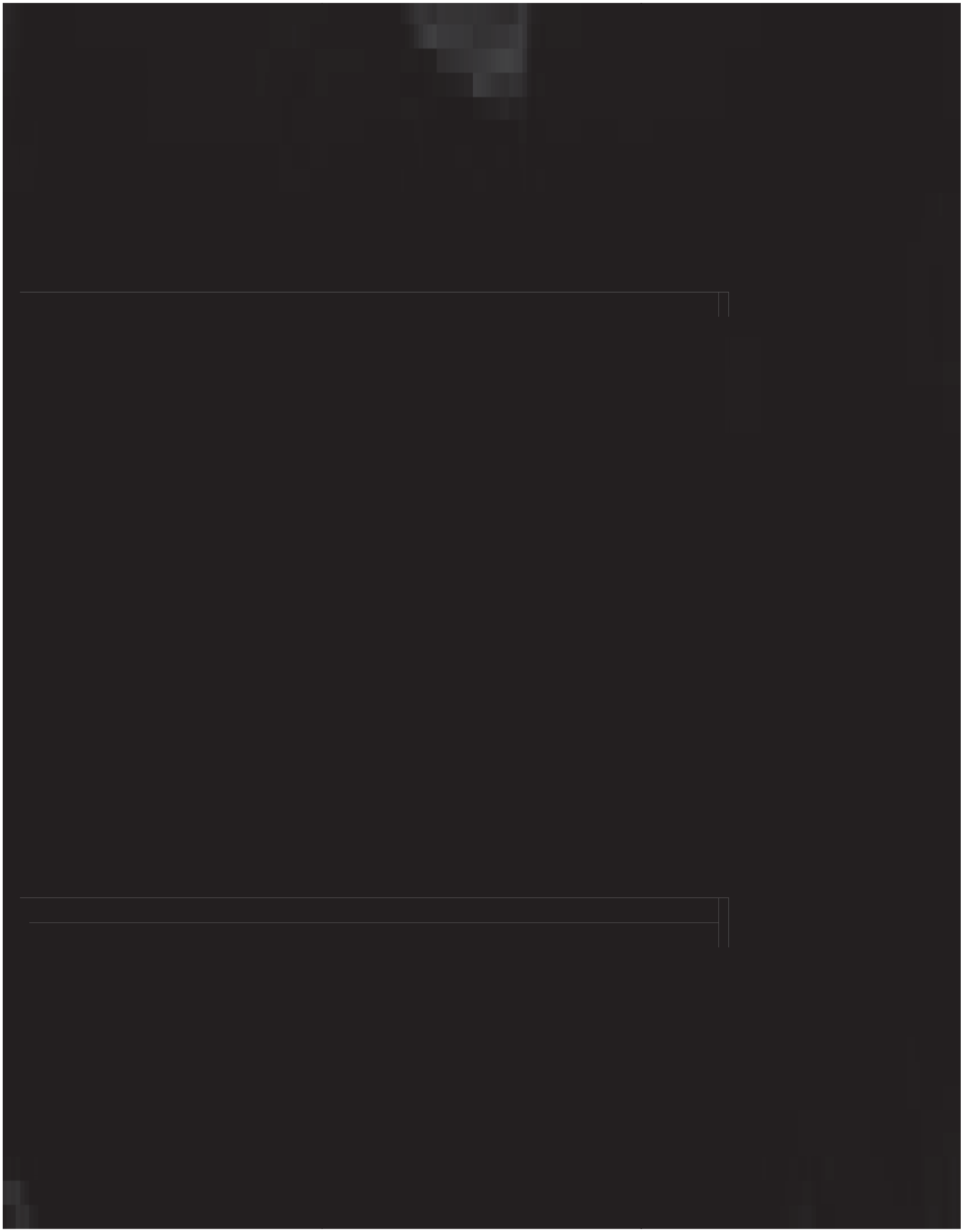












10. STATISTICAL ANALYSIS

A Statistical Analysis Plan (SAP) will be developed and finalized before database lock and will describe the subject analysis sets to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Analyses will be carried out using SAS Version 9.4 or higher.

10.1 Analysis Populations

The following analysis sets are defined for analysis purposes:

- Safety (SAF) analysis set: The SAF analysis set will consist of all randomized subjects who received the study treatment (Sham procedure or a dose of LYR-210) or treatment attempt on Day 1. Subjects will be analyzed according to the treatment actually received or attempted. This is the primary analysis set for safety analyses.
- Intention-to-treat (ITT) set: The ITT analysis will consist of all randomized subjects who received the study treatment (Sham procedure or a dose of LYR-210) or treatment attempt and have post-Day 1 assessments available. Subjects will be analyzed according to the treatment they were assigned to at randomization. This is the primary analysis set for efficacy analyses.
- Per-Protocol (PP) analysis set: The PP analysis set will include all randomized subjects who received the study treatment, have specific post-Day 1 assessments (i.e., non-missing data for the assessment being analyzed), and are without major protocol deviations at the time of the primary analysis. This is a secondary analysis set for the primary, key secondary, and remaining secondary efficacy analyses. Major protocol deviations and the definition of the PP analysis set will be identified and finalized based on blinded review of the data, prior to the data extraction for the primary analysis and unblinding of the treatment code.
- Pharmacokinetic (PK) analysis set: The PK analysis set will include all SAF subjects with at least one evaluable drug concentration post-Day 1. Subjects will be analyzed according to the successful bilateral treatment received ("actual treatment"). As concentration data is required to assign the PK analysis set, this can only be done at study unblinding, at the time of the primary analysis.

10.2 Disposition and Population Assignment

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

10.3 Demographic and Other Baseline Characteristics

All demographic (age, race, ethnicity, height, weight and BMI) and baseline disease characteristics recorded at screening and prior to LYR-210 administration/sham procedure will be summarized, by treatment group, for the SAF and ITT analysis sets. Summaries will include n, mean, standard deviation, median, quartiles, and minimum and maximum for continuous variables, and number and percentage of subjects in each category for categorial variables.

Medical history, serology, and pregnancy test results will only be listed by subject.

10.4 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 one concomitant medication will be presented.

10.5 Safety Analyses

All safety analyses will be performed using the SAF 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 during and after the administration of study treatment.

Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). For each study treatment, numbers of TEAEs and incidence rates (number and percentage of subjects with at least one 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, TEAEs leading to death, and TEAEs leading to discontinuation of study treatment will be tabulated as (a) total number of such TEAEs occurring across all subjects; and (b) number and percentage of subjects with at least one 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, vital signs measurements, morning serum cortisol levels and IOP will be summarized for each treatment group using descriptive statistics by visit for actual value and for percentage change from baseline. The incidence of treatment-emergent abnormal and clinically

significantly abnormal laboratory, vital sign, morning serum cortisol levels, IOP values and slit-lamp examination findings will be summarized by visit for each treatment group using frequency counts and percentages of subjects.

10.6 Efficacy Analyses

All efficacy analyses will be carried out after the last subject completes the Week 28 visit or withdraws study prematurely prior to Week 28. Each efficacy analysis will be performed based on both the ITT and PP analysis sets.

10.6.1 Primary Efficacy Endpoint Analysis

The primary endpoint is CFBL in the composite score of 7-day average scores of the 4 CS cardinal symptoms (CS7DA4S) at Week 4. The 4 cardinal symptoms include nasal blockage /obstruction/congestion score facial pain/pressure, reduction/loss of sense of smell, and anterior/posterior nasal discharge. Specifically, the score for each of the 4 individual components (on a scale of 0-3) of this composite score will be collected each day by daily electronic patient reported outcome (ePRO). The total score across these 4 components will then be calculated each day to create a total composite score for each day. At each of Day 1 (prior to procedure) and Week 4 visits, the average of the total composite score across the preceding 7 days prior to the visit will be calculated for each subject. This 7-day per-subject average total composite score is hereafter referred to as CS7DA4S. The null and alternative hypotheses to be tested are:

$H0: \mu L_{2500} = \mu C$ $H0: \mu L_{7500} = \mu C$

vs. vs.

$H1: \mu L_{2500} < \mu C$ $H1: \mu L_{7500} < \mu C$

where μL_{2500}, μL_{7500} and μC are true mean primary endpoint for the LYR-210 (2500 µg) treatment, the LYR-210 (7500 µg) treatment, and the control (Sham) treatment, respectively. Descriptive statistics (number of observations[n], mean, standard deviation, median, minimum and maximum) of the Baseline CS7DA4S score, the Week 4 CS7DA4S score, and the CFBL to Week 4 CS7DA4S score will be presented for each treatment group.

The primary efficacy analysis will be performed based on subjects in the ITT analysis set with available baseline and Week 4 CS7DA4S score. An analysis of covariance (ANCOVA) model for CFBL in CS7DA4S score at Week 4 will be used to determine which of the two null hypotheses stated above can be rejected. This ANCOVA model will include terms for baseline CSD7A4S score as a covariate and the fixed effects of treatment group (LYR-210 7500 µg, LYR-210 2500 µg, sham procedure) and the randomization stratification variables, presence of nasal allergy and presence of nasal polyps.

Additional secondary analyses of the primary efficacy endpoint will be performed using this ANCOVA model for the following:

- Secondary analyses of the endpoint will also be performed in subjects in the PP analysis set with available data.

- All subjects in the ITT analysis set. Missing Week 4 CS7DA4S data will be imputed as described in Section 10.6.1.1.

- Assessment of treatment effect across study regions, across nasal allergy groups and across polyp groups will be performed as described in Section 10.6.1.2.

10.6.1.1 Handling of Missing Data

The primary efficacy endpoint analysis will be performed based on subjects in the ITT analysis set with available CS7DA4S data at Baseline and Week 4 visit. At each of these visits, a subject is considered as having an available (NON-missing) CS7DA4S score if the daily ePRO score is available (NON-missing) for at least 5 of the preceding 7 days prior to the time point.

For the secondary analyses based on all subjects in the ITT analysis set regardless of available data status, two imputation approaches will be carried out for subjects who have missing Week 4 CS7DA4S data: (a) Last observation carried forward (LOCF) single imputation method; and (b) multiple imputation.

LOCF will be carried out as follows: the CS7DA4S score at each visit will be calculated in a similar manner as described above for the Baseline and Week 4 visits (i.e., 7-day average scores of the 4 CS cardinal symptoms at that visit). If Week 4 CS7DA4S is missing, then the last available CS7DA4S calculated at a post-baseline visit prior to Week 4 will be carried forward and be used as the Week 4 CS7DA4S.

The multiple imputation approach will be carried out as follows:

A. Assuming the missing CS7DA4S pattern at Baseline, Weeks 1, 2, 3 and 4 will not be exactly monotone across visits through Week 4, then a non-monotone missing pattern in CS7DA4S will be imputed 50 times to make 50 copies of a dataset with a monotone missing CS7DA4S data pattern; the Monte Carlo Markov Chain approach will be used for this imputation.

B. For each of these 50 imputed datasets, missing CS7DA4S at Week 4 will be imputed using the monotone linear regression approach: the imputation regression model will include treatment group, study center/region, randomization strata variables, CS7DA4S measured at Baseline and Weeks 1, 2, and 3 scores, and Baseline subject and demographic characteristics that will be fully specified in the SAP.

C. The above-mentioned analysis of covariance comparing treatments on the mean primary endpoint will be carried out on each of the 50 imputed datasets. The estimate of the treatment differences in least square means vs. Sham and their standard errors from each imputed dataset will be combined across the imputed datasets using PROC MIANALYZE in SAS in order to

calculate one overall estimate of treatment effect vs. Sham and its standard error for each Lyra dose group. From these overall estimates, one t-test statistic and its p-value for each LYR-210 dose vs. Sham, assessing whether the above null hypotheses can be rejected, will be calculated and presented.

10.6.1.2 Assessment of Treatment Effect Across Study Regions, Across Nasal Allergy Groups and Across Polyp Groups

To assess consistency of treatment difference across study region, descriptive statistics of the primary endpoint will be presented by treatment group within each region. An exploratory analysis of covariance on the primary endpoint, with independent variables of treatment group, region, baseline CS7DA4S score, and treatment by region interaction, will be carried out on the ITT analysis set with available data.

Similar analyses will be presented to assess consistency of treatment effect across nasal allergy groups (yes/no) and polyp groups (yes/no). Assessment of consistency across subgroups such as baseline CS7DA4S (below median, at or above median), sex and age (below median, at or above median) will be conducted as well. All subgroups to be assessed for treatment effect consistency on the primary endpoint will be detailed in the statistical analysis plan. These analyses will be carried out on the ITT analysis set with available data.

10.6.2 Key Secondary Efficacy Endpoint Analysis

The key secondary endpoints are:

- CFBL in CS7DA4S score at Week 24
- Percentage of subjects with at least 1-point decrease in bilateral Zinreich score in at least one pair of the anterior ethmoid, maxillary, posterior ethmoid, frontal, or sphenoid sinuses at Week 24
- Time to treatment failure: A treatment failure is defined as, after subject enrollment, the subject being recommended by treating physician for oral corticosteroid or ESS due to worsening of CS symptoms, or the subject complaint of persistent CS symptoms with an average CS7DA4S score over the preceding 30 days greater than or equal to the Baseline CS7DA4S score.

For each key secondary endpoint, each LYR-210 dose will be compared to sham at a one-sided 0.05 level of significance. There will be no adjustment of the significance level for multiple comparisons across the secondary endpoints.

10.6.2.1 CFBL in CS7DA4S at Week 24

The first key secondary efficacy endpoint is CFBL in CS7DA4S at Week 24. The primary analysis population for this key secondary efficacy endpoint analysis is ITT subjects with available CS7DA4S data at Baseline and Week 24 visit. At each of these visits, a subject is considered as

having an available (NON-missing) CS7DA4S score if the daily ePRO score is available for at least 5 of the preceding 7 days prior to the time point.

The analysis will be carried out using an ANCOVA model for change from baseline in CS7DA4S score at Week 24 which includes terms for the baseline CS7DA4S score as a covariate, and fixed effects for treatment group and the randomization stratification variables, presence of nasal allergy and presence of nasal polyps.

Additional analyses will be performed for the first key secondary endpoint of CFBL in CS7DA4S at Week 24, using this ANCOVA model for the following:

- Subjects in the PP analysis set with available Baseline and Week 24 CS7DA4S score.
- All subjects in the ITT analysis set. Missing Week 24 CS7DA4S data will be imputed by LOCF and by multiple imputation (details of imputation of missing data are discussed in Section 10.6.1.1).
- Assessment of homogeneity across study regions, across nasal allergy groups and across polyp groups will be performed in the same manner as for the primary endpoint as described in Section 10.6.1.2.

10.6.2.2 Percentage of Subjects with Improved bilateral Zinreich score

The second key secondary endpoint is the percentage of subjects with at least 1-point decrease in bilateral Zinreich score in at least one pair of the anterior ethmoid, maxillary, posterior ethmoid, frontal, or sphenoid sinuses post treatment. Treatment groups will be compared using logistic regression adjusting for the baseline total Zinreich score and randomization strata. This analysis will be performed using subjects in the ITT analysis set with available post-treatment MRI data and repeated with the PP analysis set. There will be no imputation of missing data.

10.6.2.3 Time-to-Treatment Failure

The third key secondary endpoint is the time-to-treatment failure. A treatment failure is defined as, after subject enrollment, the subject being recommended by treating physician for oral corticosteroid or ESS due to worsening of CS symptoms, or the subject complaint of persistent CS symptoms with an average CS7DA4S score over the preceding 30 days greater than or equal to the baseline CS7DA4S score. Time to treatment failure will be analyzed using a Cox proportional hazards model with fixed effects for available baseline CS7DA4S score, treatment group and the randomization stratification variables. Kaplan-Meier plots of time to treatment failure will be presented for each treatment group. There will be no imputation of missing data; subjects without the event through Week 24 will be censored at the end of their follow-up period. This analysis will be performed using subjects in the ITT analysis set with available data and repeated using subjects in the PP set analysis set with available data.

10.6.3 Non-Key Secondary Efficacy Endpoint Analysis

The non-key secondary efficacy endpoints that are continuous variables will be compared between treatments at each post-Day 1 in the same manner as the primary endpoint for the ITT set with available data and the PP set. In addition, for analyses on all ITT regardless of missing data status, LOCF will be used to impute missing secondary efficacy continuous endpoint data. For questionnaires (e.g., SNOT-22) at a given visit, if responses are missing for <50% of the questions at that visit then the missing responses will be imputed with the median of non-missing responses at that visit. Otherwise, if responses are missing for ≥50% of the questions at that visit, the entire questionnaire score at that visit will be considered missing and such missing questionnaire scores will be imputed as missing data in the same manner as for the other non-key secondary endpoints.

For non-secondary dichotomous efficacy endpoints, the number and percentage of subjects with the outcome will be presented for each treatment group. The proportion of subjects will be analyzed using a logistic regression model with effects for baseline CS7DA4S score, treatment group and the randomization stratification variables, presence of nasal allergy and presence of nasal polyps. The analysis will be carried out on the ITT analysis set with available data and repeated using subjects in the PP analysis set with available data.

Secondary efficacy endpoints involving time-to-event endpoints will be analyzed as specified in Section 10.6.2.3.

10.6.4 Exploratory Endpoint Analysis

A one-sided 0.05 level of significance will be used to compare treatments for each exploratory efficacy endpoint at each visit; there will be no adjustment for multiple comparisons. These analyses will be performed in the ITT analysis set with available data and repeated using subjects in the PP analysis set. There will be no imputation of missing data for these analyses.

The exploratory efficacy endpoints that are continuous variables will be compared between treatments at each post-Baseline time point in the same manner as the primary endpoint. For dichotomous efficacy endpoints, treatments will be compared using logistic regression adjusting for baseline score and randomization strata.

As further exploratory analyses on all endpoints measured longitudinally at various visits during the study, generalized estimating equation (GEE) linear regression (for continuous outcomes) and GEE logistic regression (for dichotomous outcomes) will be used to compare treatments over time; the assumed within-subject correlation matrix structure will be unstructured; if the unstructured model does not converge, then an autoregressive (1) structure will be assumed. Included as independent variables for each outcome variable will be treatment group, visit, treatment-by-visit and the baseline value of the variable being analyzed. If the treatment-by-visit interaction is not significant at the 0.10 level of significance, it will be removed from the GEE model. This will be carried out on ITT subjects with available data.

10.6.5 Pharmacokinetic Analyses

The PK analyses will be performed based on subjects in the PK analysis set.

10.6.5.1 Pharmacokinetic Concentrations

PK concentration will be summarized for subjects in the PK analysis set with available 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 dose and nominal time post dose, including number (n), mean, standard error, standard deviation, coefficient of variation (CV), median, minimum, maximum, geometric mean, geometric CV%, and the number of concentrations ≥ LLOQ. The "<LLOQ" values will be set to zero based on the Beal's method M7 [45].

10.6.5.2 Pharmacokinetic Parameters

PK parameters of MF will be estimated using a standard noncompartmental PK approach based on individual plasma concentration-time data as data permit (e.g. the availability of the PK study cohorts at Day 3, 7, 14, and 21). Actual PK sampling times will be used in the derivation of PK parameters. The PK parameters including C_{max} and T_{max} will be calculated from the plasma concentrations versus time profiles. 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. The $AUC_{0\text{-last}}$ will be defined as the area under the concentration time curve from the time of dose until the last concentration above the LLOQ. The $AUC_{0\text{-12h average}}$ is a value derived from $AUC_{0\text{-last}}$ by dividing it by the corresponding total dose time (in hour) and then multiplying by 12.

10.7 Sample Size

The primary endpoint is CFBL in CS7DA4S score at Week 4. The null and alternative hypotheses to be tested are:

$H0: \mu L_{2500} = \mu C$ $H0: \mu L_{7500} = \mu C$

vs. vs.

$H1: \mu L_{2500} < \mu C$ $H1: \mu L_{7500} < \mu C$

where μL_{2500}, μL_{7500} and μC are true mean primary endpoint for the LYR-210 (2500 µg) treatment, the LYR-210 (7500 µg) treatment, and the control (Sham) treatment, respectively. Each null hypothesis will be tested at the one-sided 0.05 level of significance. Under the assumptions that μ_C = -1.30 and μL_{2500} and/or μL_{7500} = -3.00 (conservatively based on the mean of this endpoint for LYR-

210 in Phase I study, and approximately 130% larger decrease than the assumed control mean of -1.30) and that the true standard deviation of the primary endpoint within each treatment group is at most 2.4, then an evaluable sample size of 63 subjects (21 per treatment group) yields 73% power to reject at least one null hypothesis in favor of the alternative at a one-sided 0.05 level of significance. An additional 6-9 subjects will be enrolled to account for potential subject dropout.

11. REGULATORY OBLIGATIONS

11.1 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 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
- A current (i.e. updated no more than 24 months prior) curriculum vitae for the Principal
- Investigator and each sub-investigator listed on the FDA Form 1572. A copy of the current medical license for the investigator and each sub-investigator
- 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 (e.g. 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
- A current laboratory certification for the local reference laboratory and curriculum vitae of the laboratory director
- A list of current laboratory normal values for the reference laboratory

11.2 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.

11.3 Ethics Committee (EC) Approval

The Clinical Protocol and Informed Consent Form (ICF) must have the approval of a properly constituted EC responsible for approving clinical studies prior to commencing the study at that site. Any additional approval requirement(s) of the EC will be followed. Any advertisements used to recruit subjects or any subject facing documents will also be reviewed and approved by the EC 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 and Sponsor. Each site Principal Investigator will advise their EC of the progress of this clinical investigation on a regular basis, according to EC reporting requirements. Approvals for the continuation of the study at each investigational site must be kept current and notifications forwarded to the Sponsor.

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

11.4 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, 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, 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.

The EC-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.

11.5 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 ECs, as required. For non-substantial changes (e.g., 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 and, where appropriate, local Regulatory Authority can be sufficient. The version number and date of amendments shall be documented.

11.6 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. Such deviations shall be documented and reported to the Sponsor and the EC (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 ECs.

The Investigator agrees to inform the EC 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, etc. All subjects with protocol deviations will continue to be followed for safety and performance assessments.

If an Investigator is found to be repeatedly non-compliant 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.

11.7 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 pre-specified 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.

11.8 Data Quality Assurance

The Investigator/designees will maintain accurate source documentation as part of subject case histories. Electronic data capture 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 Standard Operating Procedures. 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 providers 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.

11.9 Record Retention

Each Investigator will maintain all records pertaining to this Clinical Study as required by local regulations, the relevant EC and the Institution. The Investigator will maintain all study related documentation including all correspondence, records of financial interest, individual subject records, informed consent forms, 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 case report forms.

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, however, 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 Agreement (CTA), the Sponsor should be contacted if the Investigator plans to leave the investigational site so that appropriate arrangements can be made for the transfer of the records to the appropriate designee at the study site.

11.10 Auditing

The Investigator will make all pertinent records available including source documentation for inspection by their EC 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 in relation to this Clinical Study, the Investigator will notify the Sponsor immediately and must provide the Sponsor

with copies of any associated correspondence (e.g. EC Audit Reports, warning letters). The Sponsor will provide any necessary support in responding to Regulatory Authority and EC audit requests.

11.11 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 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 Clinical Trial Research Agreement.

11.12 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 (e.g., 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.

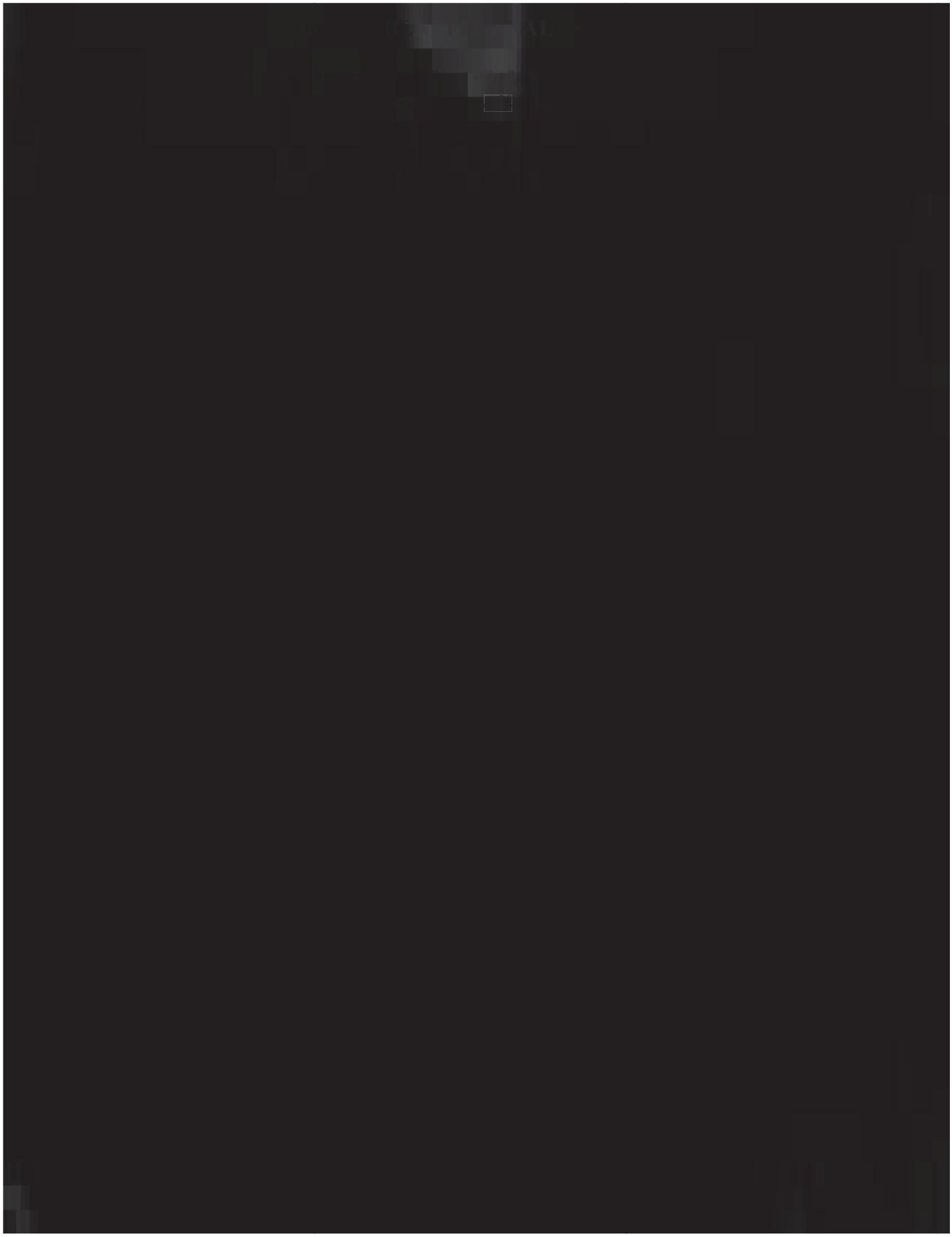
11.13 Early Study Discontinuation

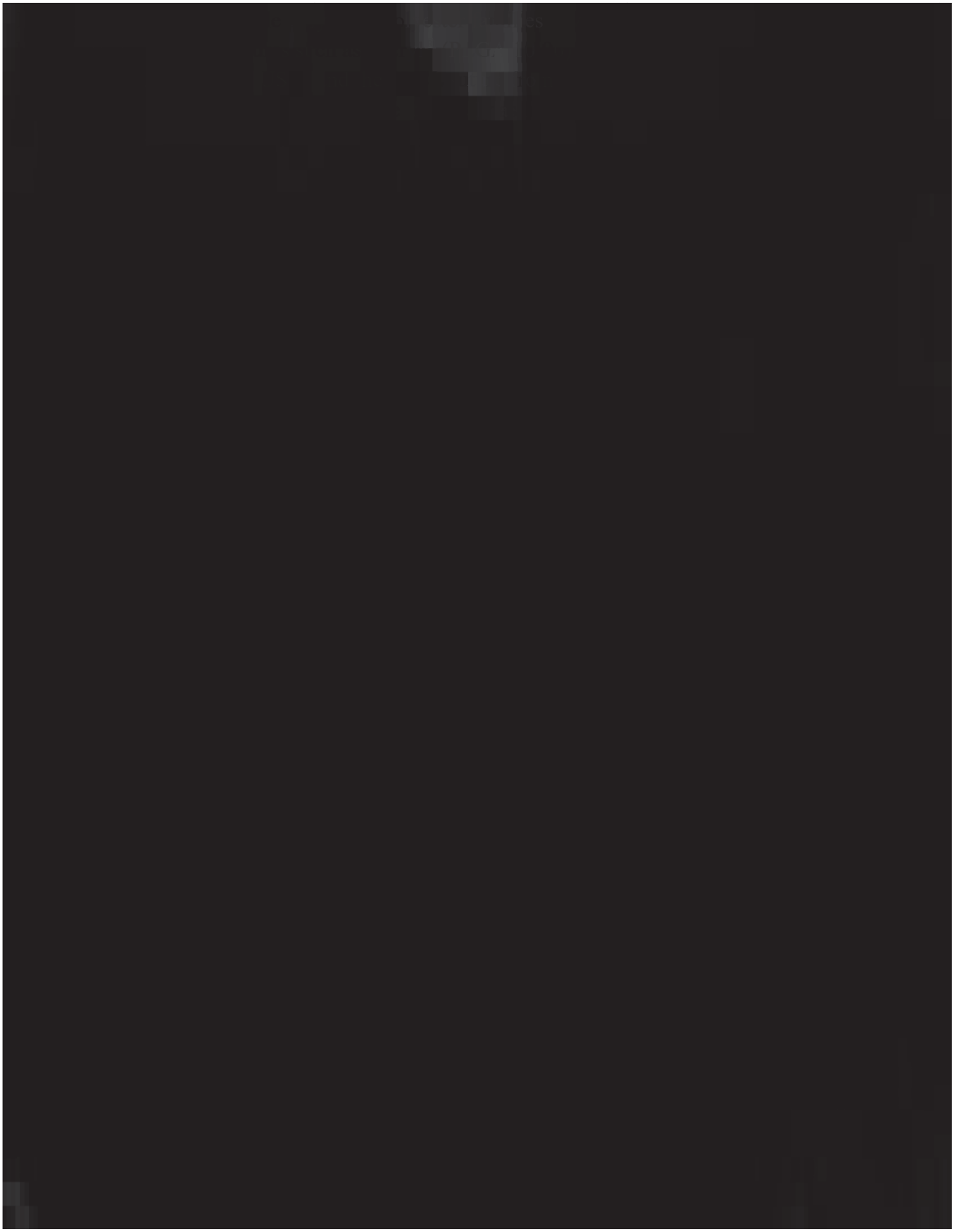
The Sponsor reserves the right to discontinue the Clinical Study at any stage, with suitable written notice to the Investigator. The Investigator may also discontinue participation in the Clinical Study with suitable written notice to the Sponsor.

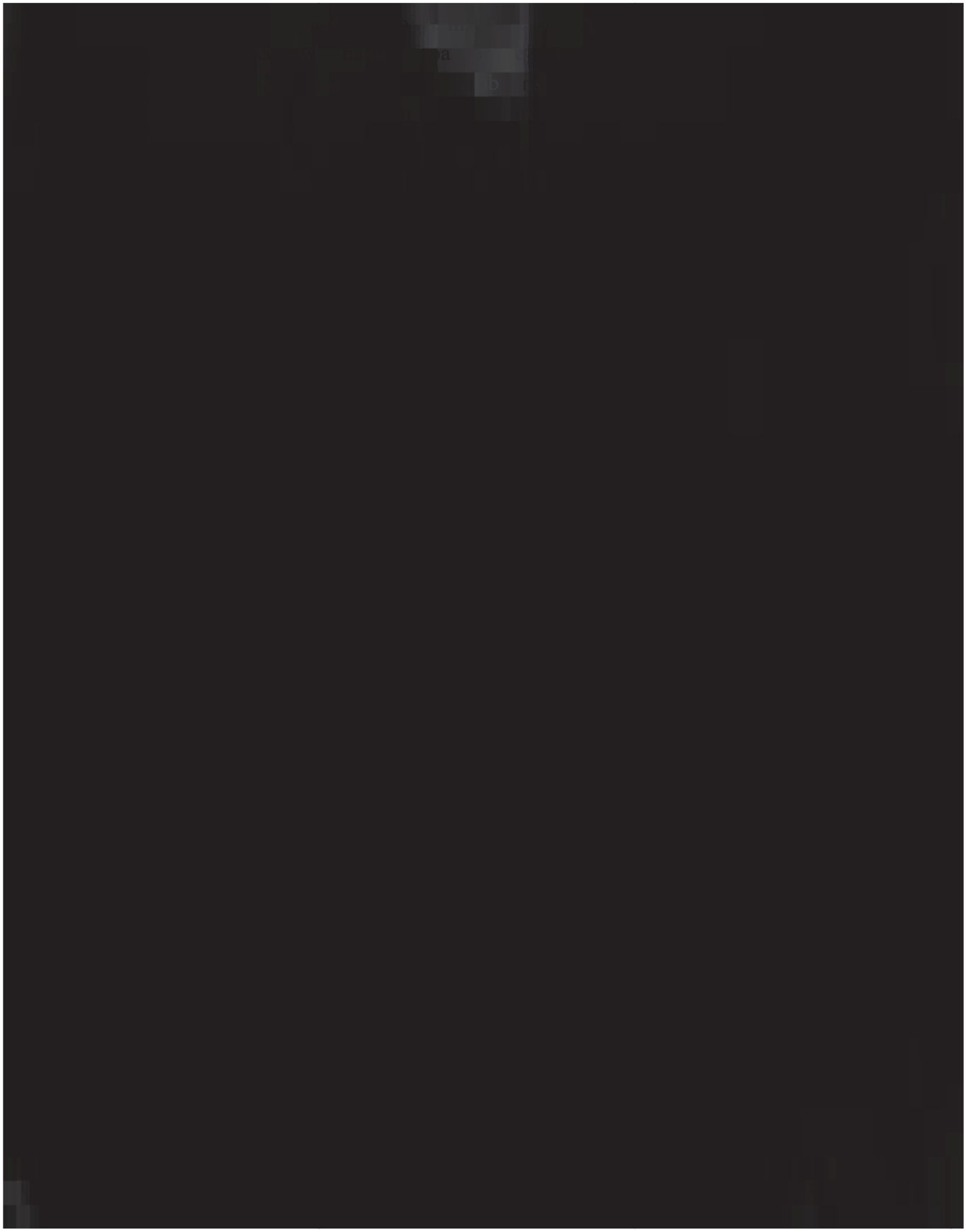
Specific instances that may precipitate site termination include but are not limited to the following reasons:

- 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, [insert AUS / NZ standards], the European Clinical Trial Directive 2001/20/EC, or other relevant national regulations, as appropriate
- Study termination and follow-up will be performed in compliance with the conditions set forth in International Council for Harmonization (ICH) E6(R2) on Good Clinical Practice (GCP) as well as 21 CFR 312.56b, Australian Clinical Trial Handbook, Medsafe guidelines on the regulations of therapeutic products in New Zealand , the European Clinical Trial Directive 2001/20/EC, 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 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.







13. LIST OF REFERENCES

1. Global Initiative for Asthma. 2018 GINA report: Global strategy for asthma management and prevention. Availalble at: Accessed October 2, 2018.
2. Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. Rhinology. 2012; 1-298.
3. Orlandi RR, Kingdom TT, Hwang PH. International consensus statement on allergy and rhinology: Rhinosinusitis executive summary. International Forum of Allergy & Rhinology. 2016; 6:S3-S21.
4. Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in Europe – an underestimated disease. A GA2LEN study. Allergy. 2011; 66:1216-1223.
5. Hamilos DL. Chronic rhinosinusitis: Epidemiology and medical management. The Journal of Allergy and Clinical Immunology. 2011; 128:693-707; quiz 708-9.
6. Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. Otolaryngology–Head and Neck Surgery. 2003; 129:S1-S32.
7. Smith KA, Orlandi RR, Rudmik L. Cost of adult chronic rhinosinusitis: A systematic review. The Laryngoscope. 2015; 125:1547-1556.
8. van Agthoven M, Uyl-de Groot CA, Fokkens WJ, et al. Cost analysis of regular and filgrastim treatment in patients with refractory chronic rhinosinusitis. Rhinology. 2002; 40:69-74.
9. Rudmik L, Hoy M, Schlosser RJ, et al. Topical therapies in the management of chronic rhinosinusitis: An evidence-based review with recommendations. International Forum of Allergy & Rhinology. 2013; 3:281-298.
10. Moeller W, Schuschnig U, Meyer G, et al. Ventilation and aerosolized drug delivery to the paranasal sinuses using pulsating airflow - a preliminary study. Rhinology. 2009; 47:405-12.
11. Nabi S, Rotenberg BW, Vukin I, et al. Nasal spray adherence after sinus surgery: Problems and predictors. Journal of Otolaryngology - Head & Neck Surgery. 2012; 41:S49-55.
12. Vaidyanathan S, Barnes M, Williamson P, et al. Treatment of chronic rhinosinusitis with nasal polyposis with oral steroids followed by topical steroids: A randomized trial. Annals of Internal Medicine. 2011; 154:293-302.
13. Van Zele T, Gevaert P, Holtappels G, et al. Oral steroids and doxycycline: Two different approaches to treat nasal polyps. Journal of Allergy and Clinical Immunology. 2010; 125:1069-1076.e4.
14. Rudmik L, Soler ZM. Medical therapies for adult chronic sinusitis: A systematic review. The Journal of the American Medical Association. 2015; 314:926-939.
15. Poetker DM, Reh DD. A comprehensive review of the adverse effects of systemic corticosteroids. Otolaryngologic Clinics of North America. 2010; 43:753-768.
16. Young LC, Stow NW, Zhou L, et al. Efficacy of medical therapy in treatment of chronic rhinosinusitis. Allergy Rhinol (Providence). 2012; 3:e8-e12.
17. Sanjay P, Dodds A, Miller E, et al. Cancelled elective operations: an observational study from a district general hospital. Journal of Health Organization and Management. 2007; 21:54-58.
18. Merck & Co., Inc. NDA 20762 Drug Approval Package, NASONEX®(mometasone furoate monohydrate) Nasal Spray, 50 mcg. Availalble at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020762_nasonex_toc.cfm. Accessed September 29, 2018.
19. Zitt M, Kosoglou T, Hubbell J. Mometasone furoate nasal spray: A review of safety and systemic effects. Drug Safety. 2007; 30:317-326.

20. Walters T, Bafna S, Vold S. Efficacy and safety of sustained release dexamethasone for the treatment of ocular pain and inflammation after cataract surgery: results from two phase 3 studies. Journal of Clinical & Experimental Ophthalmology. 2016; 7:1-11.
21. Westphal M, Ram Z, Riddle V, et al. Gliadel® wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial. Acta Neurochirurgica. 2006; 148:269-275.
22. Forwith KD, Chandra RK, Yun PT, et al. ADVANCE: A multisite trial of bioabsorbable steroid-eluting sinus implants. Laryngoscope. 2011; 121:2473-2480.
23. Marple BF, Smith TL, Han JK, et al. Advance II: A prospective, randomized study assessing safety and efficacy of bioabsorbable steroid-releasing sinus implants. Otolaryngology - Head and Neck Surgery. 2012; 146:1004-1011.
24. Han JK, Forwith KD, Smith TL, et al. RESOLVE: A randomized, controlled, blinded study of bioabsorbable steroid-eluting sinus implants for in-office treatment of recurrent sinonasal polyposis. International Forum of Allergy & Rhinology. 2014; 4:861-870.
25. Kern RC, Stolovitzky JP, Silvers SL, et al. A phase 3 trial of mometasone furoate sinus implants for chronic sinusitis with recurrent nasal polyps. International Forum of Allergy & Rhinology. 2018; 8:471-481.
26. American Rhinologic Society. ARS position statement on drug-eluting implant. Availalble at: https://www.american-rhinologic.org/index.php?option=com_content&view=article&id=32:drug-eluting-implants&catid=26:position-statements&Itemid=197. Accessed May 15, 2019.
27. Hopkins C, Gillett S, Slack R, et al. Psychometric validity of the 22-item Sinonasal Outcome Test. Clinical Otolaryngology. 2009; 34:447-454.
28. Toma S, Hopkins C. Stratification of SNOT-22 scores into mild, moderate or severe and relationship with other subjective instruments. Rhinology. 2016; 54:129-33.
29. DeConde AS, Bodner TE, Mace JC, et al. Response shift in quality of life after endoscopic sinus surgery for chronic rhinosinusitis. JAMA Otolaryngology-- Head & Neck Surgery. 2014; 140:712-719.
30. Scoggins JF, Patrick DL. The use of patient-reported outcomes instruments in registered clinical trials: Evidence from ClinicalTrials.gov. Contemporary Clinical Trials. 2009; 30:289-292.
31. Optum. PSF-36v2® Health Survey Measurement Model. Availalble at: https://www.optum.com/content/dam/optum/resources/Manual%20Excerpts/SF-36v2-Health-Survey-Measurement-Model.pdf. Accessed June 1, 2020.
32. Likness MM, Pallanch JF, Sherris DA, et al. Computed tomography scans as an objective measure of disease severity in chronic rhinosinusitis. Otolaryngology--Head and Neck Surgery. 2014; 150:305-311.
33. Doty RL, Shaman P, Dann M. Development of the university of pennsylvania smell identification test: A standardized microencapsulated test of olfactory function. Physiology & Behavior. 1984; 32:489-502.
34. Douglas RG, Psaltis AJ, Rimmer J, et al. Phase 1 clinical study to assess the safety of a novel drug delivery system providing long-term topical steroid therapy for chronic rhinosinusitis. International Forum of Allergy & Rhinology. 2019; 9:378-387.
35. Keck T, Leiacker R, Riechelmann H, et al. Temperature Profile in the Nasal Cavity. The Laryngoscope. 2000; 110:651-654.
36. Crim C, Pierre LN, Daley-Yates PT. A review of the pharmacology and pharmacokinetics of inhaled fluticasone propionate and mometasone furoate. Clinical Therapeutics. 2001; 23:1339-1354.
37. Kosoglou T, Hubbell J, Kantesaria B, et al. An evaluation of the systemic bioavailability of mometasone furoate (MF) after oral inhalation from a MF/formoterol fumarate metered-dose inhaler

versus an MF dry-powder inhaler in healthy subjects. Clinical Pharmacology in Drug Development. 2014; 3:229-234.
38. Daley-Yates PT, Kunka RL, Yin Y, et al. Bioavailability of fluticasone propionate and mometasone furoate aqueous nasal sprays. European Journal of Clinical Pharmacology. 2004; 60:265-268.
39. Merck & Co., Inc. NDA 21067 Drug Approval Package, ASMANEX® TWISTHALER® 110 mcg, 220 mcg (mometasone furoate inhalation powder). Availalble at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021067s000_AsmanexTOC.cfm. Accessed October 8, 2018.
40. Kosoglou T, Hubbell J, Xuan F, et al. Comparison of the systemic bioavailability of mometasone furoate after oral inhalation from a mometasone furoate/formoterol fumarate metered-dose inhaler versus a mometasone furoate dry-powder inhaler in patients with chronic obstructive pulmonary disease. International Journal of Chronic Obstructive Pulmonary Disease. 2013; 8:107-116.
41. Minshall E, Ghaffar O, Cameron L, et al. Assessment by nasal biopsy of long-term use of mometasone furoate aqueous nasal spray (Nasonex) in the treatment of perennial rhinitis. Otolaryngology–Head and Neck Surgery. 1998; 118:648-54.
42. Bross-Soriano D, Hanenberg-Milver C, Schimelmitz-Idi J, et al. Effects of three nasal topical steroids in the intraocular pressure compartment. Otolaryngology–Head and Neck Surgery. 2004; 130:187-91.
43. Intersect ENT, Inc. NDA 209310 Drug Approval Package, SINUVA™ (mometasone furoate) sinus implant. Availalble at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209310Orig1s000TOC.cfm. Accessed February 08, 2019.
44. Ozkadif S, Eken E. Three-dimensional reconstruction of multidetector computed tomography images of paranasal sinuses of New Zealand rabbits. Turkish Journal of Veterinary and Animal Science. 2013; 37:675-681.
45. Beal SL. Ways to Fit a PK Model with Some Data Below the Quantification Limit. Journal of Pharmacokinetics and Pharmacodynamics. 2001; 28:481-504.
46. Young LC, Stow NW, Zhou L, et al. Efficacy of medical therapy in treatment of chronic rhinosinusitis. Allergy & Rhinology (Providence, R.I.). 2012; 3:e8-e12.
47. Perloff JR, Palmer JN. Evidence of bacterial biofilms in a rabbit model of sinusitis. American Journal of Rhinology & Allergy. 2005; 19:1-6.
48. Chaubal M. Polylactides/Glycolides - Excipients for injectable drug delivery & beyond. Drug Delivery Technology. 2002; 2:34-36.

14. APPENDICES

APPENDICES HAVE BEEN REMOVED