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ORIGINAL ARTICLE

Long-acting implantable corticosteroid matrix for chronic rhinosinusitis: Results of LANTERN Phase 2 randomized controlled study

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Abstract

Background: Topical steroids are first-line treatment for chronic rhinosinusitis (CRS), but fail to provide adequate symptom control for all patients. Designed for medical treatment failures, LYR-210 is an implantable matrix that locally elutes mometasone furoate to inflamed sinonasal tissue for up to 24 weeks in CRS patients. In an open-label phase 1 study, LYR-210 demonstrated clinically relevant improvement in the 22-item Sino-Nasal Outcome Test (SNOT-22). Safety and efficacy of LYR-210 in CRS were evaluated in the LANTERN Phase 2 study.

Methods: Sixty-seven surgically naive adult CRS patients who were inadequately controlled by previous medical management and seeking an alternative treatment enrolled in a multicenter, blinded, controlled, dose-ranging study. Patients had moderate-to-severe disease based on SNOT-22 and composite 7-day average scores of the 4 cardinal CRS symptoms (4CS), with diagnosis confirmed by nasal endoscopy and magnetic resonance imaging. Patients were randomized (1:1:1) to saline irrigation–only control or bilateral in-office administration of LYR-210 (2500 μg) or LYR-210 (7500 μg). Safety and efficacy were evaluated over 24 weeks.

Results: Both LYR-210 doses were safe and well-tolerated over the 24-week treatment period. LYR-210 demonstrated rapid and durable dose-dependent symptom improvement based on 4CS and SNOT-22, with LYR-210 (7500 μg) achieving statistical significance as early as 8 weeks and out to 24 weeks compared with control. LYR-210 (7500 μg) reduced rescue treatment use and radiographic ethmoid opacification at week 24.

Conclusions: LYR-210 is the first implantable sinonasal treatment to achieve up to 24 weeks of benefit from a single administration in surgically naive CRS patients with and without nasal polyps.

KEYWORDS
chronic sinusitis, local drug delivery, mometasone furoate, nasal polyps, sinus procedure, surgically naive

1 | INTRODUCTION

Chronic rhinosinusitis (CRS) is described in the literature as an "unrecognized epidemic" due to its high prevalence, substantial impact on patient quality of life, and significant limitations of treatment options.[1] CRS can be divided into endotypes defined by molecular mechanisms underlying the pattern of inflammation in the tissue.[2,3] From this perspective, 85% of patients with Western CRS with nasal polyps (CRSwNP) exhibit type 2 (T2) inflammation, with significant eosinophilia, and 50% of patients with Western CRS without nasal polyps (CRSsNP) demonstrate T2 inflammation.[4] The T2 CRS endotype has been associated with severe symptoms and a high rate of treatment failure.[5] There are no current US Food and Drug Administration (FDA)-approved drug therapies to treat CRSsNP, although some drugs approved for nasal polyps are used off label in this population.

Current clinical practice guidelines universally recommend topical corticosteroids as a first-line treatment for CRS patients.[5,6] Corticosteroids reduce inflammation associated with all CRS endotypes and are particularly effective at suppressing T2 inflammation. However, intranasal corticosteroids do not provide adequate symptom control for all patients due to their limited ability to reach inflammation deep within the sinonasal passages, rapid clearance rates, and poor patient compliance.[7,8] Approximately 40% to 60% of CRS patients fail medical management[9] and become candidates for functional endoscopic sinus surgery (FESS). Many of these medical failure patients elect to not undergo surgery as it does not address the underlying inflammation of CRS nor obviate the need for continued medical therapy. Approximately 65% of CRS patients have recurrent symptoms within the first year post-FESS.[10] Therefore, novel therapeutic modalities are needed for CRS patients who fail medical management.

LYR-210 is an implantable drug matrix based on the XTreo drug-delivery platform[11] that is designed to consistently elute mometasone furoate (MF) to local sinonasal mucosa for up to 24 weeks. The unique design of LYR-210 allows it to fit within and dynamically conform to the middle meatus. MF is embedded in bioabsorbable polymers, which aid in the controlled and sustained delivery of MF to the sinonasal mucosa from a single administration. Sustained drug release was confirmed in vitro and in vivo before this study (unpublished data). LYR-210 is in development for the treatment of adult patients with CRS who failed previous medical management. In an open-label phase 1 study (ClinicalTrials.gov identifier: NCT02967731), LYR-210 (2500 μg) was well-tolerated and demonstrated clinically relevant improvement in the 22-item Sino-Nasal Outcome Test (SNOT-22) over 24 weeks in 20 surgically naive CRS patients.[12] To further evaluate the safety and efficacy of LYR-210, we conducted the LANTERN Phase 2 study (ClinicalTrials.gov identifier: NCT04041609).

2 | PATIENTS AND METHODS

2.1 | Investigational products

LYR-210 is an investigational product designed and manufactured by Lyra Therapeutics, Inc (Watertown, MA). LYR-210 has a tubular mesh configuration with a repeat diamond pattern throughout that is composed of biocompatible and bioabsorbable polymers formulated to precisely control the gradual release of up to 2500 μg or 7500 μg of MF over 24 weeks, and gradually soften over time. The engineered elastomeric properties allow LYR-210 to dynamically expand to target anatomy, promoting continuous apposition to the surrounding mucosa for effective and consistent local MF delivery over the 24-week period. LYR-210 is placed bilaterally within the middle meatus, which has not been distorted by previous surgical intervention, in CRS patients with a single-use applicator in an office-based procedure under endoscopic visualization after topical anesthesia. Figure 1 shows LYR-210 self-expanding from a constrained state upon deployment from the applicator. LYR-210 is intended to be removed at 24 weeks or earlier at the physician's discretion using standard instruments.

FIGURE 1 LYR-210 matrix self-expands from a constrained state when deployed from an applicator.

2.2 | Study design

CRS patients who were inadequately controlled by previous medical management and seeking an alternative treatment were enrolled in the multicenter, randomized, blinded, controlled, dose-ranging LANTERN Phase 2 trial to evaluate the efficacy, safety, and tolerability of LYR-210 (2500 μg) and LYR-210 (7500 μg). Patients were recruited and enrolled by 14 otolaryngology practices in Poland, the Czech Republic, Australia, and New Zealand. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol and patient informed consent were reviewed and approved by the ethics committees of each study center in accordance with the regulatory requirements of each country. All patients signed informed consent documentation before participating in the study.

Inclusion criteria were patients ≥18 years of age with at least 2 of the 4 cardinal symptoms (4CS) of CRS for a minimum of 12 weeks[5,6] and a baseline average 4CS composite score over the preceding 7 days of ≥7 on a 0 to 12 scale. Patients exhibited purulence, inflammation, and/or nasal polyps on nasal endoscopy and had radiologic evidence of sinusitis on paranasal magnetic resonance imaging (MRI). Enrolled patients had at least 2 previous trials of medical treatment for CRS, independent of the LANTERN study, including at least one course of intranasal corticosteroid sprays (INCS) for a minimum of 4 weeks—a duration based on the 2016 International Consensus Statement on Allergy and Rhinology (ICAR-2016) guidance for the "Length of appropriate medical therapy prior to ESS."[13] Enrolled patients in this trial reported to have used an average of 1.9 courses of INCS (median, 2; maximum, 5) before screening in the past year alone.

Exclusion criteria were history of previous FESS, nasal endoscopic evidence of significant mucosal injury (eg, ulceration or erosion), nasal septal perforation, severe nasal blockage by nasal polyps that prevented access to or visualization of the middle meatus, concurrent seasonal allergic rhinitis (if onset of symptoms was anticipated within 4 weeks of randomization), perennial allergic rhinitis (if well controlled by regular use of INCS), or severe asthma. Patients were excluded if they exhibited a bilateral Zinreich score of <4 in all 3 pairs of the posterior ethmoid, frontal, and sphenoid sinuses (0-5 scale for each of sinuses) on screening MRI. Patients were excluded if they were intolerant of topical anesthesia or corticosteroids; had received systemic corticosteroids (SCS) within 1 month before screening; or had a history or evidence of immunodeficiency, intracranial or orbital complications, evidence of mycetoma/fungal ball, sinus mucocele, or invasive fungal rhinosinusitis.

Certain medications that could potentially interfere with study evaluations were not permitted from the screening visit until the end of the study, except for their use as rescue treatment. Such medications included INCS, oral/intramuscular corticosteroids (apart from a stable regimen of inhaled corticosteroids for asthma taken for a minimum of 3 months before screening and would be maintained throughout the study), oral decongestants, and monoclonal antibodies. Non-sedating antihistamine medications were only allowed if patients continued such medication at a consistent dose from the screening visit through the study duration.

After screening assessment, patients underwent a 14-day minimum washout period. Patients were provided with and instructed to use nasal saline irrigations daily starting from the washout period to the end of the 24-week treatment period. Patients received no other active treatment for CRS during the washout period. On the day of the procedure (day 1), patients were randomized (1:1:1) to 1 of the 3 study arms: bilateral administration of LYR-210 (7500 μg) into the middle meatus; bilateral administration of LYR-210 (2500 μg) into the middle meatus; or daily saline-irrigation-only control. To ensure patients remained blinded to study treatment assignment, patients randomized to the control arm also received a sham procedure, wherein the applicator was inserted into and withdrawn from the middle meatus. All patients received topical anesthetic and decongestant before the procedure and wore a blindfold. The clinical study investigator and clinical staff were unblinded to LYR-210 vs control; however, they were blinded to the LYR-210 dose administered. The sponsor was blinded to the study.

Patients returned to the clinic for follow-up assessments at weeks 4, 12, and 24, and had telephone follow-ups at weeks 8, 16, and 20 to record any adverse events (AEs) and concomitant medications/procedures. All patients wore an eye mask at all postscreening clinic visits only during endoscopies to remain blinded to the study treatment

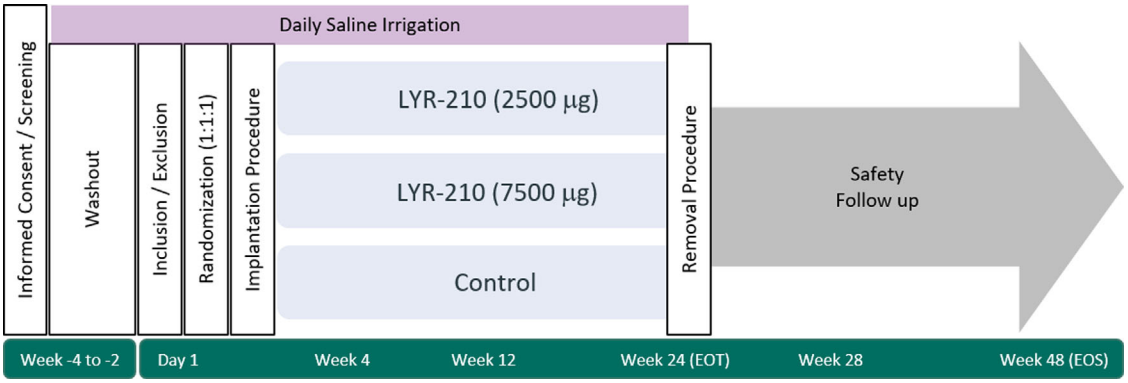

FIGURE 2 LANTERN Phase 2 study design schematic.

assignment. At the week 24 (end-of-treatment) visit, LYR-210 (2500 μg) or LYR-210 (7500 μg) were removed using standard instruments, and control patients underwent a sham-removal procedure. After the end-of-treatment visit, patients underwent a posttreatment follow-up period lasting approximately 24 weeks. The LANTERN Phase 2 study design is summarized in Figure 2.

2.3 | Safety assessments

Safety was assessed by rates of AEs and changes in laboratory tests, vital signs, morning serum cortisol levels, nasal endoscopy assessment, intraocular pressure (IOP), and slit-lamp examination of the crystalline lens for presence of lens opacification. AEs were coded using the Medical Dictionary for Regulatory Activities version 23.0. All AEs were recorded throughout the study and reported for seriousness and relationship to study treatment or procedure. Severity of AEs was graded by the investigator as mild, moderate, or severe.

Ocular safety was assessed via measurement of IOP and dilated slit-lamp examination at baseline and week 24. Lens opacity was graded using the Simplified Cataract Grading System of the World Health Organization Prevention of Blindness and Deafness. All ocular assessments were conducted by ophthalmologists blinded to the study treatment received by patients.

2.4 | Efficacy assessments

Patient-reported symptoms and daily use of saline irrigation were captured using an electronic patient-reported outcome (ePRO) system. Patients reported the score for each of the 4CS of CRS on the ePRO each morning, beginning at least 7 days before the day 1 visit and continuing throughout the 24-week treatment period. Each of the 4CS (nasal blockage, facial pain/pressure, nasal discharge, and loss of smell) was rated on a 0 to 3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Patients recorded the severity of their symptoms and social/emotional consequences of CRS via the SNOT-22[14] at baseline and at weeks 2, 4, 8, 12, 16, 20, and 24. To evaluate the effect of LYR-210 in reducing sinonasal inflammation, patients underwent sinus MRI at baseline and at the end of treatment (week 24). Both 3-dimensional coronal T2- and T1-weighted fast spin-echo images were acquired. The level of sinus opacification for each anterior and posterior ethmoid sinus was scored by an independent imaging core lab using the Zinreich (modified Lund-Mackay) scoring system, which categorizes the percentage of opacification on a 0 to 5 scale (0 = 0%, 1 = 1%-25%, 2 = 26%-50%, 3 = 51%-75%, 4 = 76%-99%, 5 = 100% or completely occluded).[15,16] The time to first rescue treatment use was evaluated and defined as worsening or acute exacerbation of CRS in an enrolled subject resulting in the investigator recommending INCS, SCS, decongestants, and/or FESS.

2.5 | Data analysis

All patients who underwent an attempted or successful study treatment procedure were included in the safety analyses (the safety population). All efficacy analyses were conducted on the intention-to-treat (ITT) population, which included all patients who underwent a successful study treatment procedure and had at least one post-randomization efficacy assessment. Patients' demographics, medical history, and baseline disease characteristics were reported as frequencies or percentages of patients with the ITT population. Treatment-emergent AEs were reported as counts of patients that experienced the event. For the primary and secondary endpoints of change from baseline (CFBL), an analysis of covariance (ANCOVA) model adjusting for treatment group, baseline score, and stratification variables (nasal allergy, nasal

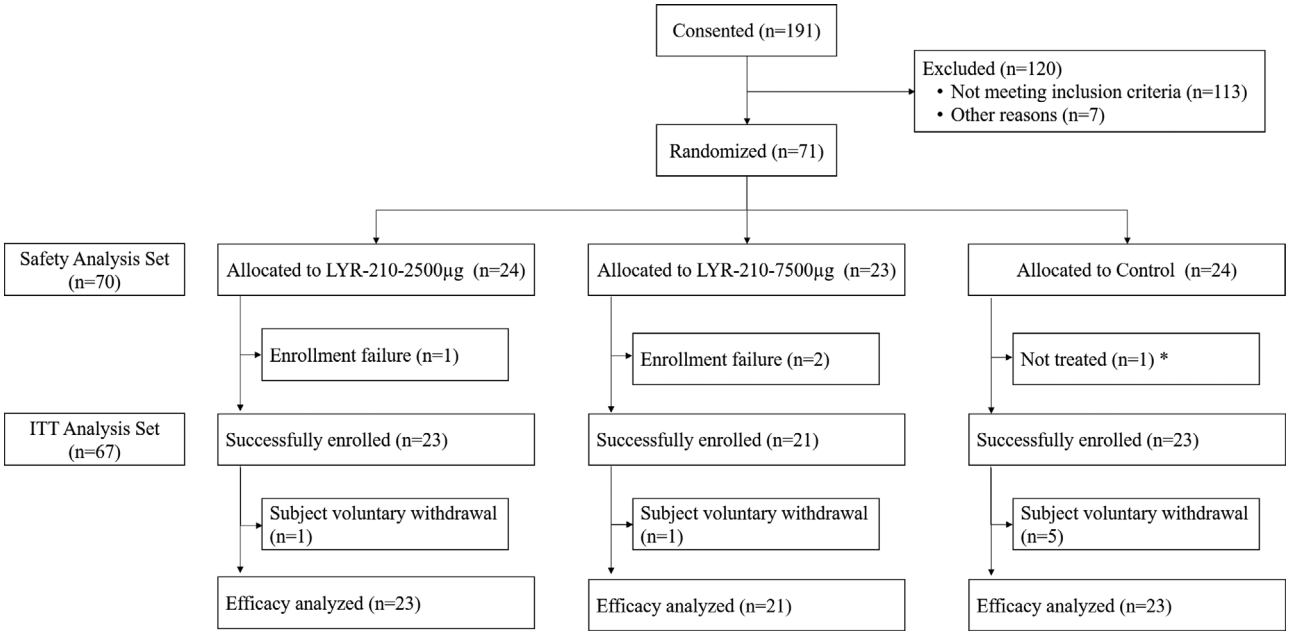

FIGURE 3 Disposition of patients (CONSORT) diagram. ITT = intention to treat.

polyp) was used and tested at a one-sided significance level of 0.05. No adjustments for multiplicity were made. The CFBL means were reported as least-squares means (LSMs) along with standard error (SE) from the ANCOVA model, unless otherwise noted. Time-to-first rescue treatment use was analyzed with the Kaplan-Meier method and hazard ratios. Subjects who did not achieve the event were censored at the end of treatment date or at the early termination date. Hazard ratios, two-sided 90% confidence intervals (CIs), and *p* values tested at a one-sided significance level of 0.05 were obtained from a Cox proportional hazards model. For symptom-based endpoints, if a patient dropped out of the trial or otherwise did not report data for a particular timepoint during the treatment period, the last-observation-carried-forward (LOCF) approach was used to impute the missing values. For patients who required a rescue treatment during the treatment period, the post-rescue data were set to missing and values for the post-rescue timepoints were imputed using the LOCF method. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) or higher.

3 | RESULTS

3.1 | Patients' characteristics

The LANTERN Phase 2 study investigators planned to enroll up to 150 adult CRS patients who were inadequately controlled by previous medical management and had not undergone sinus surgery. Patient enrollment was curtailed early due to the COVID-19 global pandemic. Between May 2019 and March 2020, 71 patients were randomized, 70 underwent an attempted study treatment procedure, and 67 were successfully enrolled. Of these, 23 patients were bilaterally administered LYR-210 (2500 μg), 21 were bilaterally administered LYR-210 (7500 μg), and 23 had a bilateral sham procedure (saline irrigation only control). One patient in each of the LYR-210 (2500 μg) and LYR-210 (7500 μg) arms and 5 patients in the control arm voluntarily withdrew before completing the planned 24 weeks. The matrix retention rate at week 22 was 80%. The drug matrices that dislodged in this study were expelled through the nose and none were swallowed. Disposition of patients is illustrated in Figure 3.

Of the 67 enrolled patients, 35 (52.2%) were male and 37 (55.2%) were diagnosed with bilateral nasal polyps by endoscopy, each representing approximately half the patients in each study arm. All patients reported moderate-to-severe CRS symptoms[17] at baseline, with a mean ± standard deviation SNOT-22 score of 68.2 ± 18.4 (range, 25-107) and a 4CS score of 9.7 ± 1.59 (range, 7-12). In addition, all patients exhibited sinonasal inflammation based on their baseline Zinreich scores (mean, 20.3 ± 12.3 [median 17; range, 1-53]). All patients had at least 1 trial of INCS before screening, whereas 19.4%, 49.2%, and 73.1% of patients had also previously used oral corticosteroids, antibiotics, and saline irrigations for CRS, respectively. Patients' demographics, CRS medical history, and baseline clinical disease severity measures are summarized in Table 1.

TABLE 1 Patients' demographics, medical history, and baseline characteristics*

	LYR-210 (2500 μg) (*n* = 23)	LYR-210 (7500 μg) (*n* = 21)	Control (*n* = 23)	Total (*n* = 67)	*p* value
Gender (male), n (%)	11 (47.8)	13 (61.9)	11 (47.8)	35 (52.2)	0.565
Age (years)					
Mean ± SD	42.3 ± 12.72	46.9 ± 12.72	41.3 ± 14.68	43.3 ± 13.44	0.357
Median (range)	41.0 (18-72)	43.0 (28-75)	43.0 (21-78)	42.0 (18-78)	
Comorbidity, n (%)					
Seasonal allergic rhinitis	0 (0)	2 (9.5)	2 (8.7)	4 (6.0)	0.453
Perennial allergic rhinitis	2 (8.7)	1 (4.8)	4 (17.4)	7 (10.4)	0.431
Concurrent asthma	3 (13.0)	5 (23.8)	4 (17.4)	12 (17.9)	0.670
COPD	1 (4.3)	0 (0)	0 (0)	1 (1.5)	1.000
Sensitivity to NSAIDs	2 (8.7)	2 (9.5)	1 (4.3)	5 (7.5)	0.734
Current smoker	2 (8.7)	5 (23.8)	3 (13.0)	10 (14.9)	0.353
Nasal polyps, n (%)	13 (56.5)	11 (52.3)	13 (56.5)	37 (55.2)	1.000
Baseline SNOT-22 score					
Mean ± SD	70.0 ± 19.92	62.9 ± 18.39	71.2 ± 16.57	68.2 ± 18.4	0.277
Median (range)	74.0 (41-97)	65.0 (25-92)	71.0 (47-107)	69.0 (25-107)	
Baseline 4CS score					
Mean ± SD	9.9 ± 1.61	9.3 ± 1.60	9.8 ± 1.58	9.7 ± 1.59	0.357
Median (range)	10.0 (7.0-12.0)	8.9 (7.1-12.0)	10.4 (7.3-12.0)	9.7 (7.0-12.0)	
Baseline modified Zinreich MRI score					
Mean ± SD	19.6 ± 12.3	23.7 ± 12.4	17.6 ± 12.0	20.3 ± 12.3	0.268
Median (range)	16.0 (5-52)	24.0 (5-53)	15.5 (1-49)	17.0 (1-53)	
CRS medical treatment history, n (%)					
Intranasal corticosteroid sprays	23 (100)	21 (100)	23 (100)	67 (100)	1.000
Oral corticosteroids	5 (21.7)	5 (23.8)	3 (13.0)	13 (19.4)	0.689
Antibiotics	13 (56.5)	12 (57.1)	8 (34.8)	33 (49.2)	0.267
Saline irrigations	15 (65.2)	17 (81.0)	17 (73.9)	49 (73.1)	0.543

*Analysis of variance used to compare means of continuous variables between groups. Fisher's exact test is used to compare categorical variables between groups.

4CS = composite score of 7-day average scores of 4 four cardinal symptoms of chronic rhinosinusitis; COPD = chronic obstructive pulmonary disease; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test.

TABLE 2 summary of treatment-emergent AEs and SAEs

Event, system organ class, preferred term[a]	LYR-210 (2500 μg) (n = 24)	LYR-210 (7500 μg) (n = 23)	Control (n = 23)
AEs			
Infections and infestations			
Chronic sinusitis[b]	4	4	7
Rhinitis	1	4	0
Upper respiratory tract infection	2	1	1
Respiratory, thoracic, and mediastinal disorders			
Epistaxis	4	3	2
Rhinorrhea	4	2	1
Oropharyngeal pain	0	1	2
Nasal congestion	2	0	0
Nervous system disorders			
Headache	2	1	3
Dizziness	2	0	0
General disorders and administration site conditions			
Facial pain	1	2	0
Metabolism and nutrition disorders			
Hyperkalemia	0	0	2
SAEs			
Infections and infestations			
Acarodermatitis	1	0	0
Treatment-related AEs			
Infections and infestations			
Rhinitis	1	3	0
Respiratory, thoracic, and mediastinal disorders			
Epistaxis	3	1	0
Rhinorrhea	2	0	0
Nervous system disorders			
Headache	0	0	2
Procedure-related AEs			
Respiratory, thoracic, and mediastinal disorders			
Epistaxis	2	1	1

[a]The preferred terms were summarized for AEs reported by more than 1 patient in any study group. If a patient reported an AE more than once within that system organ class/preferred term, the patient was counted only once for that system organ class/preferred term. The relatedness of an AE to study treatment or procedure was attributed by the treating physician.

AEs were coded using MedDRA version 23.0.

[b]MedDRA preferred term for exacerbation/worsening of chronic sinusitis.

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.

3.2 | Safety

Table 2 summarizes treatment-emergent AEs reported by more than 1 patient in any study arm. The most common AEs reported in the LYR-210 (2500 μg) arm were chronic sinusitis, epistaxis, and rhinorrhea (n = 4 each); in the LYR-210 (7500 μg) arm they were chronic sinusitis and rhinitis (n = 4 each); and in the control arm they were chronic sinusitis (n = 7). Other less common AEs included upper respiratory tract infection, oropharyngeal pain, nasal congestion, facial pain, dizziness, and hyperkalemia. There was only 1 serious adverse event (SAE) reported in this study, in which a patient in the LYR-210 (2500 μg) arm had acarodermatitis that was determined by the treating physician to be unrelated to the study treatment.

The mean CFBL in IOP at week 24 was reduced in the LYR-210 (7500 μg) arm (−0.5 ± 2.8; range, −5.5 to 7.5) and in the LYR-210 (2500 μg) arm (−0.1 ± 2.5; range, −6.3 to

4.0) and was increased in the control arm (0.9 ± 2.7; range, −4.0 to 9.5). None of the patients in this study had an elevated IOP (>21 mm Hg) or a clinically significant increase of IOP (>10 mm Hg from baseline) in 1 or both eyes. One patient in the control arm developed a clinically significant nuclear cataract while in the study.

There was no significant decrease of morning serum cortisol levels at weeks 4, 12, or 24. No AEs indicative of adrenal insufficiency were reported.

3.3 | Efficacy

The treatment effect of LYR-210 was evaluated over 24 weeks based on patient symptom improvement, reduction in sinonasal inflammation, and reduction in the need for rescue treatment. LYR-210 demonstrated dose-dependent improvement in nasal blockage, facial pain/pressure, and nasal discharge in CRS patients throughout the 24-week treatment period (Fig. 4A-C). Specifically, LYR-210 (7500 μg) achieved statistically significant improvement compared with control in nasal blockage (weeks 16, 20, and 24) (Fig. 4A), facial pain/pressure (weeks 12, 16, 20, and 24) (Fig. 4B), and nasal discharge (weeks 16, 20, and 24) (Fig. 4C). In enrolled patients who exhibited moderate-to-severe anosmia at baseline (≥2 in loss of smell score), LYR-210 (7500 μg) showed a numerical improvement in smell over the control but this was not statistically significant (Fig. 5).

The 4 cardinal symptoms were analyzed throughout the 24-week treatment period as a composite score (4CS), which is the primary efficacy endpoint. LYR-210 demonstrated dose-dependent improvement in 4CS score that became more pronounced over 24 weeks (Fig. 6A). LYR-210 (7500 μg) demonstrated statistically significant improvement from baseline compared with control at weeks 16, 20, and 24. As only a subset of patients exhibited moderate-to-severe anosmia at baseline, we conducted a post-hoc analysis of the composite score of the 7-day average scores from nasal blockage, facial pain/pressure, and nasal discharge (ie, 3 cardinal symptoms [3CS]). LYR-210 demonstrated a dose-dependent treatment effect, with LYR-210 (7500 μg) achieving significant improvement in the 3CS score compared with control at weeks 12 through 24 (Fig. 6B).

The SNOT-22 questionnaire is the most widely used measurement of CRS patient burden and quality of life. As shown in Figure 7A, a dose response was observed between LYR-210 (7500 μg), LYR-210 (2500 μg), and control over the 24-week treatment period. LYR-210 demonstrated rapid, durable, and clinically meaningful improvement in SNOT-22 scores from baseline. Patients

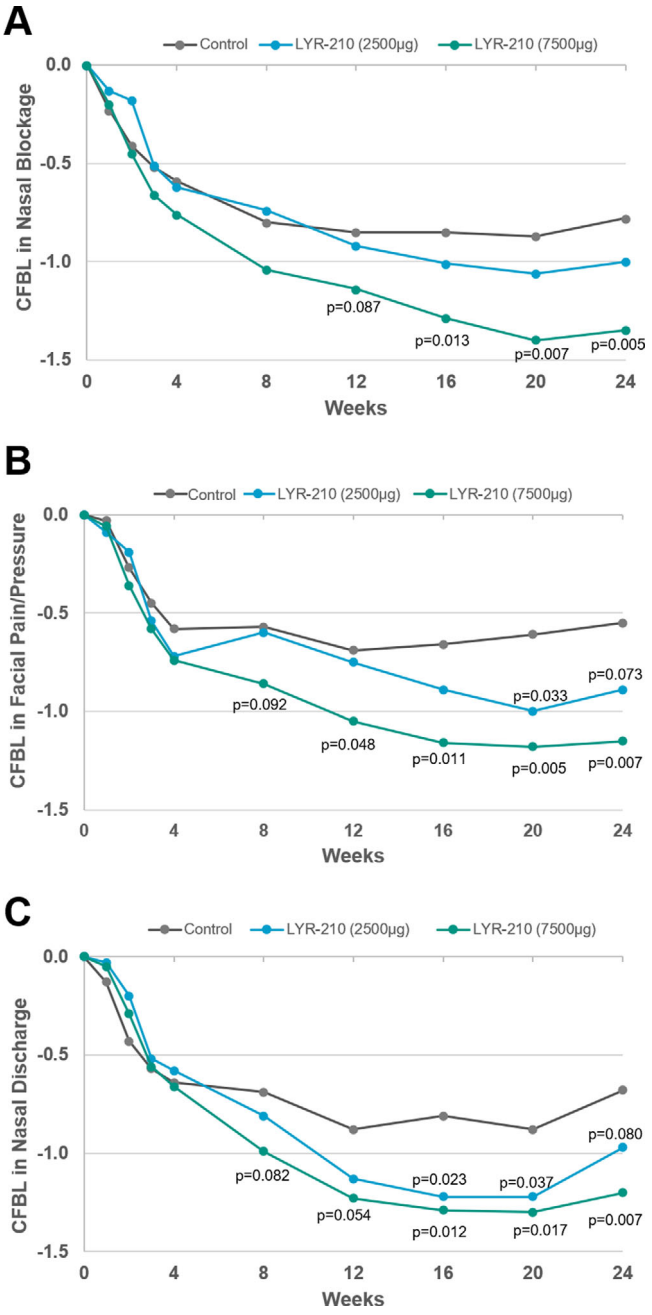

FIGURE 4 Patient symptom improvement in nasal blockage, facial pain/pressure, and nasal discharge. Mean change from baseline (CFBL) in the 7-day average score in (A) nasal blockage, (B) facial pain/pressure, and (C) nasal discharge (anterior/posterior). Data are presented as LSM. $p < 0.05$ considered statistically significant compared with control.

administered bilateral LYR-210 (7500 μg) exhibited statistically significant improvement compared with control at weeks 8, 16, 20, and 24. Notably, LYR-210 (7500 μg) achieved a 19-point improvement in SNOT-22 over control at week 24, which was >2-fold the minimal clinically important difference (MCID) of 8.9 points.[14] SNOT-22 responder analysis revealed that all patients administered

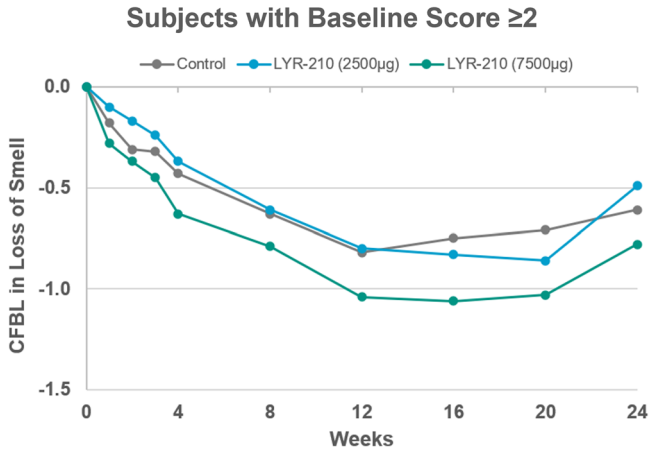

FIGURE 5 Patient-reported loss-of-smell scores in patients with moderate-to-severe baseline anosmia. Mean change from baseline (CFBL) in the 7-day average score in loss of smell for patients with moderate-to-severe baseline anosmia (≥2 baseline score in loss of sense of smell). Patients per group: LYR-210 (7500 μg), n= 15; LYR-210 (2500 μg), n = 20; and control, n = 20. Data are presented as LSM.

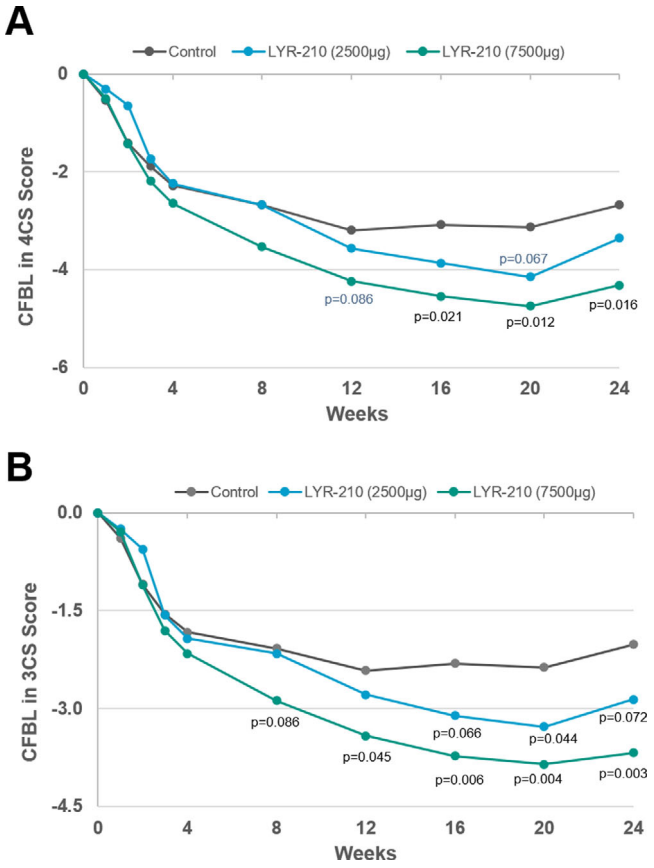

FIGURE 6 Patient symptom improvement as measured by composite score of (A) 4 cardinal symptoms (4CS) and (B) 3 cardinal symptoms (3CS). Mean changes from baseline (CFBL) in 7-day average score in 4CS include nasal blockage, facial pain/pressure, nasal discharge (anterior/posterior), and loss of smell. For 3CS, these include nasal blockage, facial pain/pressure, and nasal discharge (anterior/posterior). Data are presented as LSM. $p < 0.05$ considered statistically significant compared with control.

LYR-210 (7500 μg) achieved MCID for SNOT-22 total score at week 24 compared with 70% in the LYR-210 (2500 μg) and 65% in the control arms (Fig. 7B). The polyp vs non-polyp subgroup analysis showed that 69% of CRSwNP and 70% of CRSsNP patients in the LYR-210 (2500 μg) arm and 62% CRSwNP and 70% of CRSsNP patients in the control arm achieved at least MCID in SNOT-22 total score at week 24 (Fig. 7C). By contrast, 100% of patients administered LYR-210 (7500 μg) achieved at least MCID in SNOT-22, regardless of polyp status (Fig. 7B,C).

To evaluate the treatment effect of LYR-210 on sinonasal mucosal inflammation, patients underwent paranasal sinus MRI at baseline and at the end of treatment (week 24). Because LYR-210 was placed in the middle meatus and is designed to locally deliver MF to the surrounding nasal tissue, we examined the effect of LYR-210 on the inflammation in the ethmoids, the nearest sinus to the middle meatus. LYR-210 demonstrated improvement in bilateral ethmoid Zinreich MRI scores at week 24 in a dose-dependent manner, with LYR-210 (7500 μg) demonstrating significant improvement compared with control (Fig. 8).

The time to first rescue treatment use was also assessed, with the need for rescue treatment at the physician's discretion. Use of LYR-210 showed a dose-dependent reduction in the need for rescue treatment, with the LYR-210 (7500 μg) arm requiring significantly less rescue treatment than control (hazard ratio, 0.1; $p < 0.05$). Only 1 patient administered LYR-210 (7500 μg) and 2 patients administered LYR-210 (2500 μg) required a rescue treatment compared with 7 patients in the control arm over the 24-week treatment period (Fig. 9). The rescue treatments used were as follows: in the LYR-210 (7500 μg) arm, 1 patient used INCS; in the LYR-210 (2500 μg) arm, 2 patients used decongestants; and, in the control arm, 2 patients used oral steroids + INCS, 1 patient used INCS + decongestants, 2 patients used INCS alone, and 2 patients used decongestants alone. The first incidence of rescue treatment in the control arm occurred at week 2, whereas the only LYR-210 (7500 μg) patient who received rescue treatment did not require it until after 18 weeks of treatment.

4 | DISCUSSION

This is the first report of global symptom improvement in surgically naive CRS patients treated with a local drug-delivery implant placed in the middle meatus. Both doses of LYR-210 were safe and well-tolerated throughout the 24-week treatment period. No treatment-related SAEs

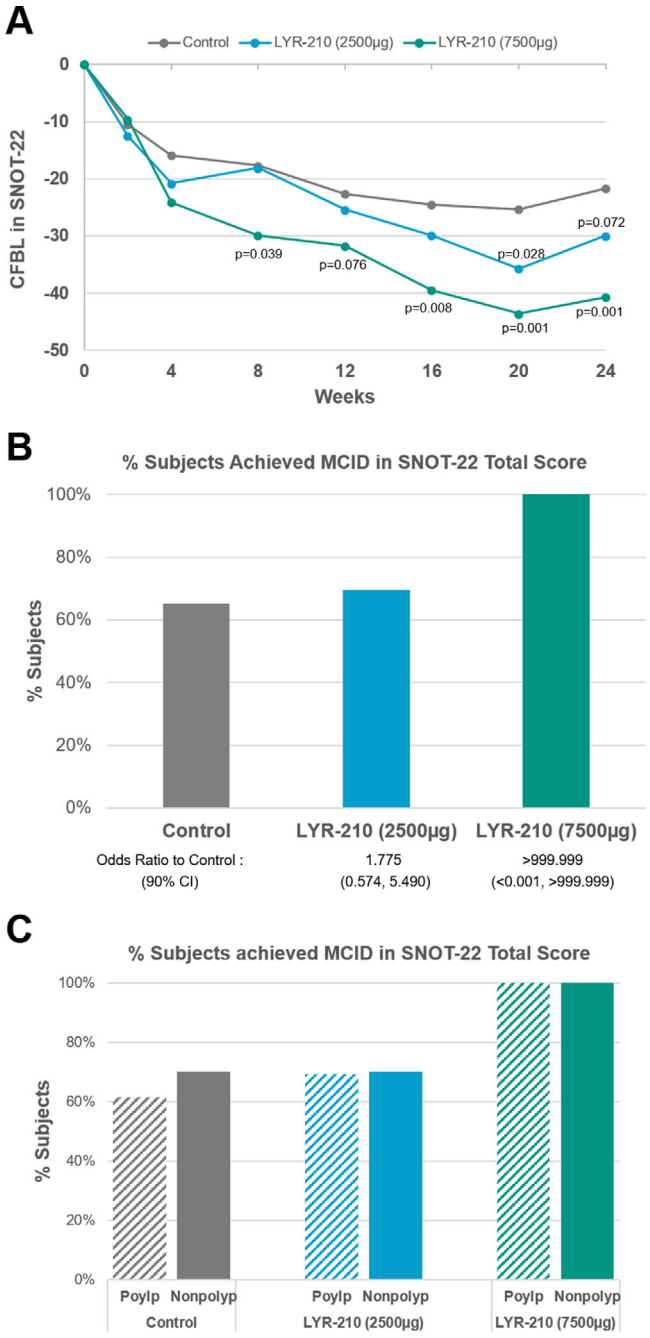

FIGURE 7 Patient symptom improvement as measured by SNOT-22. (A) Mean change from baseline (CFBL) in SNOT-22 total score. Data presented as LSM. $p < 0.05$ considered statistically significant compared with control. (B) Percentages of patients administered bilateral LYR-210 (2500 μg), bilateral LYR-210 (7500 μg), or control who achieved minimal clinically important difference (MCID) in SNOT-22 total score at week 24. (C) Percentages of patients with nasal polyps vs without nasal polyps administered bilateral LYR-210 (2500 μg), bilateral LYR-210 (7500 μg), or control who achieved MCID in SNOT-22 total score at week 24.

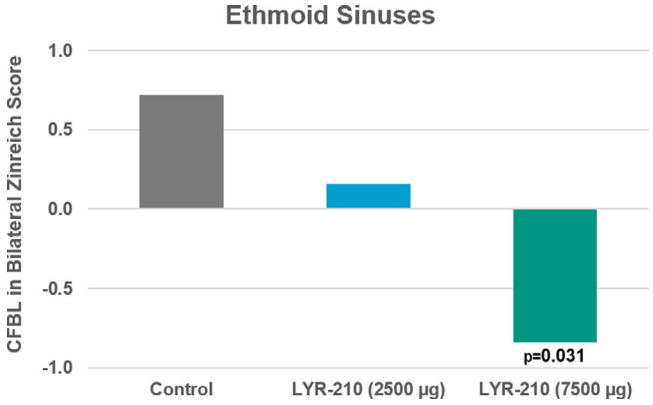

FIGURE 8 Reduction in ethmoid sinus opacification as measured by bilateral Zinreich MRI scores. Mean change from baseline (CFBL) in the bilateral ethmoid Zinreich score (composite score of anterior ethmoid and posterior ethmoid Zinreich scores) at 24 weeks. Data are presented as means. $p < 0.05$ considered statistically significant compared with control.

were reported and all treatment-related AEs that occurred were in line with the known safety profile of MF.[18]

A composite score focused on the cardinal symptoms of CRS and the SNOT-22 provide information on the impact of CRS on patients and the effectiveness of treatments. In this study, LYR-210 (7500 μg) demonstrated significant improvement in nasal blockage, facial pain/pressure, and nasal discharge at weeks 16, 20, and 24 compared with saline irrigation control. Although LYR-210 (7500 μg) showed a numerical improvement in loss-of-smell scores, it was not statistically significant compared with control. As only a subset of enrolled patients in this study had impaired sense of smell, the 3CS composite score of nasal blockage, facial pain/pressure, and nasal discharge may be a more appropriate endpoint for measuring symptom improvement in surgically naive CRS patients both with and without nasal polyps, as they are more reliably present in this study population. LYR-210 (7500 μg) demonstrated improvement in the 3CS composite score that was statistically significant compared with saline irrigation control at weeks 12, 16, 20, and 24. LYR-210 (7500 μg) also achieved significant improvement in SNOT-22 score at weeks 8, 16, 20, and 24 compared with saline irrigation control. Moreover, LYR-210 (7500 μg) significantly reduced ethmoid sinus opacification and the need for rescue treatment compared with control.

The primary efficacy endpoint of the LANTERN study is the mean CFBL in the 4CS score at week 4, which was −2.2 points for LYR-210 (2500 μg) and −2.5 points for LYR-210 (7500 μg). The rationale for selecting week 4 as the primary efficacy endpoint was to be in accordance with the regulatory precedent at the time of the LANTERN study design, which was 4 weeks for FDA-approved

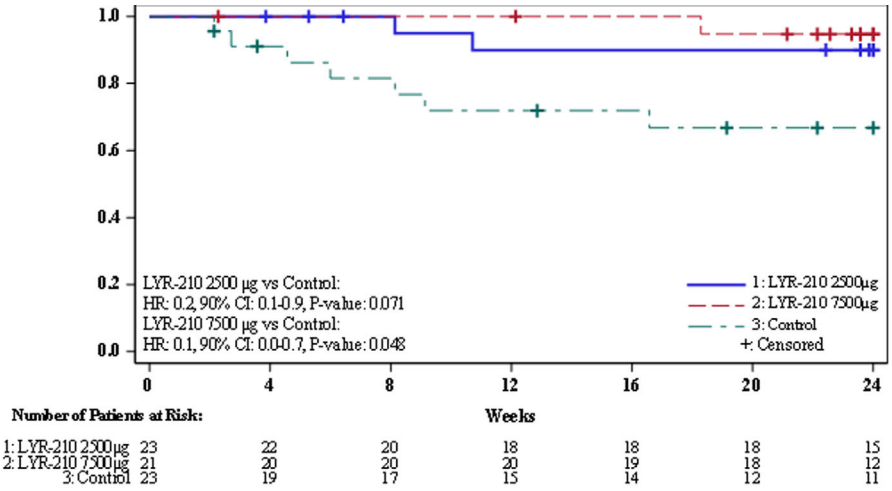

FIGURE 9 Time to first rescue treatment use over 24 weeks. An event is when rescue treatment was used. Patients who did not achieve the event were censored at the end of treatment date or at the early termination date. Use of rescue treatment over the 24-week treatment period was as follows: LYR-210 (7500 μg), 1 patient; LYR-210 (2500 μg), 2 patients; and saline irrigation control, 7 patients.

steroid-eluting sinonasal implants for nasal polyps.[19,20] Although neither dose achieved statistical significance at week 4 compared with saline irrigation control, a clinically meaningful treatment effect was observed for both doses of LYR-210 at week 4, as demonstrated by an improvement greater than half of the standard deviation of the baseline value (−0.8 point in CFBL in 4CS score), a statistical rule that is widely accepted for quality-of-life (QOL) assessments.[21–24] Importantly, LYR-210 (7500 μg) demonstrated significant improvement in 4CS score at weeks 16, 20, and 24 compared with saline irrigation control, indicating a long-acting and durable treatment effect.

The control arm in this study reported symptom improvement from baseline based on the 4CS and SNOT-22 assessments, particularly within the first 4 weeks. This response may be attributed to the procedure, wherein all patients received decongestant and underwent nasal suctioning, but is perhaps more likely due to compliance with daily patient-administered nasal saline irrigations. Nasal saline irrigation is a mainstay guideline-driven standard of care therapy in CRS[5,6,13] and has been shown to improve SNOT-22 scores by approximately 20 points from baseline when used as a monotherapy.[25] Importantly, all patients in this study demonstrated high compliance (mean, 82.6% ± 26.7%; median, 94.6%) with the nasal saline irrigation regimen throughout the 24-week treatment period, much higher than in real-world use.[8]

The LANTERN study was designed to assess the safety and efficacy of LYR-210 as a stand-alone treatment compared with a control in CRS patients who have a history of inadequately responding to INCS based on their own evaluation. The inclusion criteria for a previous trial of INCS for a minimum of 4 weeks were based on ICAR-2016 guidance on the length of appropriate medical therapy before ESS.[13] Enrolled patients in this trial actually reported to have used an average of 1.9 courses of INCS (median, 2; maximum, 5) before screening in the past year alone. Although escalation of therapy can include cumulative additions of therapies in the real world, the purpose of this study was not to evaluate LYR-210 as an add-on therapy to INCS or any other therapy. Therefore, it is not yet known how LYR-210 may work in concert with other therapies, such as INCS, in patients with CRS. However, LYR-210 (7500 μg) achieved clinically significant improvements up to 24 weeks without INCS compared with control, supporting its potential use as a monotherapy, if approved. Thus, a potential advantage for LYR-210, based on this study, is the opportunity to eliminate patient compliance issues with INCS in the real world and lessen treatment burden.

Unlike the 4CS score, which has not yet been validated, the SNOT-22 has an established MCID for symptom improvement in CRS. In this study, all patients administered LYR-210 (7500 μg) achieved MCID on the SNOT-22 at week 24, superior to both the LYR-210 (2500 μg) and control arms. Although the data from our study were analyzed using 8.9 points as the MCID for SNOT-22,[14] an MCID of 12 points has also been used in a study of medically managed CRS patients.[26] Using this alternative MCID of 12 points, in our study 90% of patients administered LYR-210 (7500 μg) achieved this MCID at week 24 compared with 65% of patients in the control arm. A larger multicenter, randomized, blinded, controlled clinical study has been planned to further evaluate the efficacy of LYR-210 (7500 μg) in CRS.

Despite curtailed enrollment at 67 patients, LYR-210 demonstrated rapid and durable dose-dependent

symptom improvement throughout 24 weeks. The LANTERN Phase 2 study is the first clinical trial to show a dose response with an implantable sinonasal treatment in CRS patients that can provide sustained corticosteroid therapy over 24 weeks from a single administration. LYR-210 demonstrated a reproducible treatment effect in surgically naive CRS patients regardless of polyp status in 2 different clinical studies. The CFBL on the SNOT-22 over the 24-week treatment period observed for LYR-210 (2500 μg) in the LANTERN Phase 2 study is consistent with that of LYR-210 of the same dose in a phase 1 study,[12] which further validates the findings of the present study.

Current FDA-approved steroid-eluting sinonasal implants provide up to 90 days of treatment but only for CRSwNP patients who have already undergone FESS.[19,20] This neglects the vast majority of patients with CRS, particularly those patients, regardless of polyp status, who have never had sinus surgery. Consistent high-dose drug delivery to the inflamed sinonasal mucosa over an extended period with patient-independent actuation has been identified as a key factor for achieving adequate symptom control in CRS.[27,28] LYR-210 (7500 μg) improves upon current FDA-approved steroid-eluting sinonasal implants by having an approximately 5.5-fold higher total steroid dose, and demonstrating up to 24 weeks of clinical benefit in a single administration in CRS patients. Moreover, LYR-210 enables long-acting therapy directly to the site of CRS inflammation, which may address limitations of INCS. As LYR-210 can be used early in the treatment of CRS, it represents a promising new therapy for optimizing medical management to control symptoms.

5 | CONCLUSION

LYR-210 is the first anti-inflammatory implantable drug treatment to demonstrate up to 24 weeks of benefit in surgically naive CRS patients, independent of polyp status. This data demonstrates that targeted delivery of MF to the middle meatus of a surgically naive CRS patient results in global symptom improvement. LYR-210 appears to be a promising treatment option in the medical management of CRS patients.

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