Phase 1 clinical study to assess the safety of a novel drug delivery system providing long-term topical steroid therapy for chronic rhinosinusitis

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Background: **Chronic rhinosinusitis (CRS) patients who fail medical management have few treatment options other than endoscopic sinus surgery (ESS). A novel biodegradable mometasone furoate drug delivery system (LYR-210) providing continuous topical steroid therapy to sinonasal mucosa over 24 weeks was developed to treat unoperated CRS patients who have failed medical management prior to ESS. LYR-210 was designed to slowly expand in the middle meatus, ensuring efficient drug delivery as mucosal swelling reduces.**

Methods: **A prospective, multicenter, open-label study was conducted in 20 CRS subjects who were determined to be candidates for ESS. Under endoscopic guidance and topical anesthesia, LYR-210 was placed in both middle meatuses. The primary endpoint was product-related serious adverse events (SAEs) at 4 weeks. Additional assessments included plasma drug concentration, morning serum cortisol levels, intraocular pressures (IOPs), and Sino-Nasal Outcome Test (SNOT-22) scores.**

Results: **LYR-210 was successfully placed bilaterally in 20 subjects (12 without nasal polyps and 8 with polyps) in an office setting. There were no product-related SAEs through 24 weeks, at which point 86% of LYR-210 depots were still retained in the middle meatus. Serum cortisol, IOP, and plasma drug concentrations supported systemic safety at all time points tested. Subjects experienced significant reductions in their SNOT-22 scores as early as week 1, and this reduction persisted through week 24 ($p < 0.01$). Significant symptom improvement was achieved in the SNOT-22 rhinologic, extranasal rhinologic, ear-facial, psychological, and sleep dysfunction subdomains at 24 weeks ($p < 0.05$).**

Conclusion: **LYR-210 is safe and well-tolerated in ESS-naive CRS patients and leads to sustained symptom improvement in patients.** © 2019 ARS-AAOA, LLC.

Key Words:
mometasone furoate; intranasal drug, local drug delivery; in-office procedure; biodegradable

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Chronic rhinosinusitis (CRS) is a common condition defined by symptomatic inflammation of the paranasal sinuses lasting longer than 12 weeks. CRS affects 12.5% of the U.S. population,[1] 10.9% of the European population,[2] and is the fifth most common condition in people under age 65 years.[3] CRS results in ~18 annual office visits,[4] and the economic implications are at more than $9 billion each year in the United States alone.[5] Common symptoms of CRS include nasal blockage/obstruction, facial pressure or fullness, nasal discharge, and sense of smell dysfunction.[6,7] The underlying cause of CRS-related symptoms is

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inflammation of mucosal tissue leading to impairment of mucociliary clearance.

Despite the high prevalence of the disease, no U.S. Food and Drug Administration (FDA)-approved drug therapy for the treatment of CRS is available. Evidence-based medical management supports the use of an oral or topical corticosteroid therapy with or without antibiotics. The most common first-line therapy is topical corticosteroids with adjunctive use of daily saline irrigation.[8] However, inefficient drug delivery to the inflamed mucosal tissues[9] and/or poor patient compliance limit the effectiveness of such therapy.[10] Second-line medical therapy, generally used for management of flare-ups and worsening inflammation or severe nasal polyps, includes a short course (1 to 3 weeks) of oral corticosteroids.[6,7] Although effective initially, improvements are not sustained for more than 3 months.[11,12] 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.[13,14] Approximately one-half (40-60%) of CRS patients do not benefit from this recommended medical regimen, and so become potential candidates for endoscopic sinus surgery (ESS).[15] However, many surgical candidates opt out of surgical treatment for clinical or nonclinical reasons.[16]

LYR-210 is a biodegradable intranasal drug delivery system specifically designed to treat CRS patients who have failed medical management. It combines mometasone furoate (MF) with a polymeric matrix that gradually releases a constant daily dose of MF over 24 weeks. The administration of LYR-210 is office-based and performed with topical anesthesia.

LYR-210 was tested in an open-label phase 1 clinical study (clinicaltrials.gov ID: NCT02967731) in CRS patients who were deemed candidates for ESS. The primary objective of this study was to assess the safety and tolerability of LYR-210 in CRS patients, and to explore the effect on patients' symptoms.

Patients and methods

Investigational product

LYR-210 is an investigational product manufactured by Lyra Therapeutics, Inc. (Watertown, MA). Its miniaturized design allows for atraumatic placement within an intact middle meatus of unoperated CRS patients in the office. LYR-210 is administered with a single-use applicator under endoscopic visualization after topical anesthesia. Each LYR-210 gradually delivers up to 2500 μg MF over 24 weeks to the inflamed mucosal tissue from a single administration. LYR-210 has a tubular mesh configuration with a repeat diamond pattern throughout for uniform drug delivery to underlying mucosal tissue (Fig. 1). It is made of biodegradable polymers formulated to precisely control the release of MF over a 24-week treatment period. Additionally, the elastomeric design of LYR-210 enables the depot to actively expand over time as inflammation recedes, providing a fixation mechanism for the duration of the 24-week treatment period. The elastomeric design also ensures the drug depot is continuously apposed to the surrounding mucosa for the duration of treatment, facilitating effective and prolonged MF transfer. LYR-210 gradually softens over time and was removed at 24 weeks or earlier, at the physician's discretion, using standard instruments.

Study design

This multicentered, prospective, open-label, single-arm study enrolled 20 adult CRS patients with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP) who had failed medical management and were determined to be surgical candidates. Patients were recruited from 5 rhinologic practices (R.G.D., A.J.P., J.R., A.C., and T.K.) in New Zealand and Australia between June 2017 and November 2017. The study protocol and patient informed consent were reviewed and approved by Ethics Committees of each study center and regulatory authorities of each country. All patients signed informed consent before participating in the study.

Inclusion criteria included patients who fulfilled the diagnostic criteria for CRS as per the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2012[7] or the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis 2016 (ICAR:RS) guidelines,[6] were 18 years or older, and had at least 1 trial of topical corticosteroid spray and saline spray/irrigation for a minimum of 1 month in the past.

Exclusion criteria included age less than 18 years, pregnancy, and low CRS disease burden as determined by a 22-item Sino-Nasal Outcome Test (SNOT-22) score[17] of <20 or a nasal congestion score <2 rated on a 0 to 5 scale, and a subtotal Lund-Mackay score of maxillary, anterior ethmoid, and posterior ethmoid sinuses <2 on either side assessed on a screening computed tomography (CT). Patients were also excluded if on baseline endoscopic examination they had evidence of previous ESS, significant mucosal injury (eg, ulceration or erosion), nasal septal perforation, or severe nasal blockage by nasal polyps that prevented access to or visualization of the middle meatus. Additionally, patients were excluded if they were intolerant of topical anesthesia or corticosteroids, or had an oral-steroid dependent condition, immunodeficiency, intracranial or orbital complication, evidence of mycetoma/fungal ball, sinus mucocele, or invasive fungal rhinosinusitis.

Medications that could potentially interfere with study evaluations were not permitted from the screening visit until the end of the study. Such medications included intranasal steroids, oral/intramuscular corticosteroids (apart from a stable regimen of oral inhaled corticosteroids for asthma that had been taken for a minimum of 1 month prior to screening visit and would be maintained throughout the study), chronic use of ocular steroidal or nonsteroidal anti-inflammatory drugs, and biologics for asthma

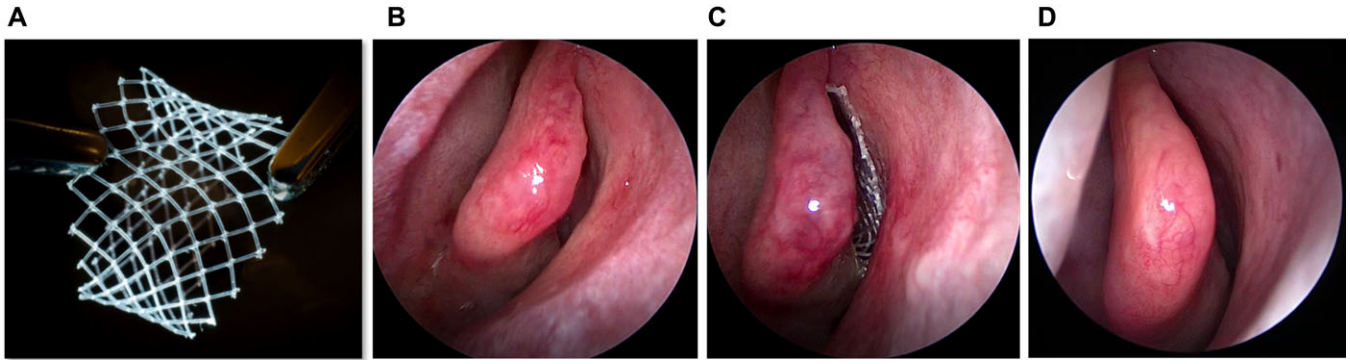

FIGURE 1. (A) A photograph of LYR-210 demonstrating elasticity of depot and (B-D) endoscopy images of a study patients before and after LYR-210 treatment. Endoscopic images show left middle meatus of a patient (B) before and (C) after depot administration and (D) at 1 week post–depot removal.

TABLE 1. Schedule of assessment

	Screening	Baseline	Follow-up							
Visit number	1	2	3	4	No clinic visit	5	No clinic visit	No clinic visit	6	7
Study day	At least 2 weeks prior to baseline	Day 1 (depot administration)	1 week (±2 days)	4 weeks (±3 days)	8 weeks (±3 days)	12 weeks (±7 days)	16 weeks (±3 days)	20 weeks (±3 days)	24 weeks (±7 days) (depot removal)	End of study (7–14 days postremoval)
Adverse events	X	X	X	X	X	X	X	X	X	X
Plasma PK		X	X	X		X				
Morning serum cortisol	X			X		X			X	
Intraocular pressure	X			X					X	
SNOT-22 questionnaire	X	X	X	X	X	X	X	X	X	X

PK = pharmacokinetics; SNOT-22 = 22-item Sino-Nasal Outcome Test.

or sinusitis. Antiallergic medications were only allowed if subjects would continue their antiallergy medication at a consistent dose from the screening visit through study duration. Patients were encouraged to use saline irrigations according to clinic guidelines.

After the screening assessment, patients underwent a 14-day washout period, during which time patients received no active treatment for the study indication. Following the washout period, patients attended the clinic for bilateral placement of LYR-210 under topical anesthesia with endoscopic guidance. Topical anesthesia consisted of applying 3 sprays of co-phenylcaine in each nostril, followed by inserting a pledget soaked in 5% lidocaine in the middle meatus for approximately 2 minutes prior to administration of LYR-210. Patients returned to the clinic for follow-up assessments at weeks 1, 4, 12, and 24 post–LYR-210 placement. At the week 24 visit, LYR-210 was removed using standard instruments. Patients exited the study by attending an end-of-study visit at 7 to 14 days post–depot removal. Table 1 summarizes the study schedule of assessments.

Safety assessments

The primary objective of the study was to evaluate the safety of bilateral LYR-210 depot treatment. Safety assessments included monitoring adverse events (AEs). All AEs were recorded throughout the study and reported for seriousness. Severity was graded as mild, moderate, severe, or life-threatening. Plasma drug concentration was determined at pretreatment, after 1 hour, and at week 1, week 4, and week 12 visits by a liquid chromatography tandem mass spectrometry assay (LC/MS/MS) that has a lower limit of quantification (LLOQ) of 20 pg/mL. Morning serum cortisol level was assessed at screening, week 4, week 12, and week 24 visits. Intraocular pressure (IOP) examination was performed at screening, week 4, and week 24 visits.

Efficacy assessments

Patients completed a CRS-specific quality of life questionnaire (SNOT-22) containing 22 questions[17] at pretreatment and at week 1, week 4, week 8, week 12, week 16,

TABLE 2. Patient demographics and baseline characteristics

Gender (male), n (%)	15 (75)
Age (years)	
Mean ± SD	39.9 ± 14.7
Median (range)	37.1 (23.5–66.9)
Seasonal allergic rhinitis, n (%)	9 (45)
Concurrent asthma, n (%)	4 (20)
Current smoker, n (%)	3 (15)
Bilateral nasal polyps, n (%)	8 (40)
Baseline SNOT-22 score	
Mean ± SD	50.9 ± 15.2
Median (range)	53 (30–76)
Baseline Lund-Mackay score	
Mean ± SD	12.6 ± 4.5
Median (range)	12 (6–22)

SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test.

week 20, and week 24, as well as 1-week post–LYR-210 removal. Patient symptom improvement was analyzed in the total SNOT-22 scores and in 5 subdomains as defined by DeConde et al.[18]

In vivo drug release assessment

Depots were collected from patients after removal or spontaneous dislodgement. The mass of MF remaining on the depot was determined by extracting any remaining drug from the depot using an organic solvent and then measuring the concentration of the drug using a reversed-phase high-performance liquid chromatography (HPLC) assay.

Data analysis

Subject demographics, clinical information, and procedural characteristics were reported as frequencies or percentages of subjects. Continuous variables were presented as mean, standard deviation, and standard error or 95% confidence interval for the mean. Two-tailed paired *t* test was used to compare changes from baseline (CFBL). Values of $p < 0.05$ were considered statistically significant. Study results were reported as intention-to-treat (ITT) analysis. For patients who withdrew from the study, symptom improvement data after patient withdrawal used the last observation carried forward (LOCF).

Results

Patient characteristics

Twenty (20) patients were enrolled, 8 of whom were diagnosed with bilateral nasal polyps by endoscopy. All 20 patients received bilateral administration of LYR-210 in an office setting. Baseline demographics, clinical characteristics, and clinical disease severity measures are summarized in Table 2. The study population was predominantly male with a mean age of 39.9 years (range, 23.5 to 66.9 years). All patients reported moderate-to-severe CRS symptoms with a mean SNOT-22 score of 50.9, of which 9 patients reported severe symptoms (SNOT-22 score >50) as defined by Toma and Hopkins.[19] All patients complained of nasal obstruction and the need to blow their nose. Nasal congestion is the most prevalent and severe individual symptom in preoperative CRS patients as reported by Abdalla et al.[20] The baseline nasal congestion score was 3.8 ± 0.5 on a 0 to 5 scale, in line with what was reported for preoperative CRS patients in Abdalla's study.[20] The mean Lund-Mackay score for the patients in this study was 12.6 ± 4.5 (range, 6 to 22) based on the CT at screening. All patients showed maxillary and anterior ethmoid sinus disease on CT. A majority of the patients also showed sinus disease in the ostiomeatal complex (OMC) region (90% of patients) and the remaining sinuses (85%, 65%, and 75% of patients for posterior ethmoid, frontal, and sphenoid sinuses, respectively).

Depot placement and retention

Forty LYR-210 depots were successfully administered in all 20 patients with topical anesthesia, resulting in a 100% procedural success rate. Although all 20 patients were successfully enrolled, 7 of the 40 middle meatuses required removal of the initial depot and use of a second depot to ensure optimal placement within the middle meatus. Figure 1 shows endoscopic views of the left middle meatus of a study patient before and after LYR-210 administration and at 1 week postremoval (end-of-study visit). Placement procedures were well-tolerated by patients. Five patients noted AEs including facial pain (1 patient), postprocedural discomfort (1 patient), procedural headache (2 patients), and nasal discomfort (1 patient); all were either mild (4 patients) or moderate (1 patient) in severity and resolved shortly after the procedure without need for medical attention.

There were 18 patients who completed follow-up visits through 25 weeks. Two patients withdrew early from the study, 1 after 17 weeks of treatment because of a recurrence of sinus infection, and the other after 21 weeks of treatment for complaints of memory loss. These 2 early withdrawals resulted in a reduction of the total number of evaluable depots for retention analysis to 40 depots at week 12 and 36 depots at week 24. Five depots dislodged spontaneously before the planned removal procedure at the week 24 visit, resulting in a depot retention rate of 97.5% and 86.1% at week 12 and week 24 postplacement, respectively.

In vivo drug release

Thirty-five depots were collected after removal or dislodgement and tested for remaining MF in the depot. Five

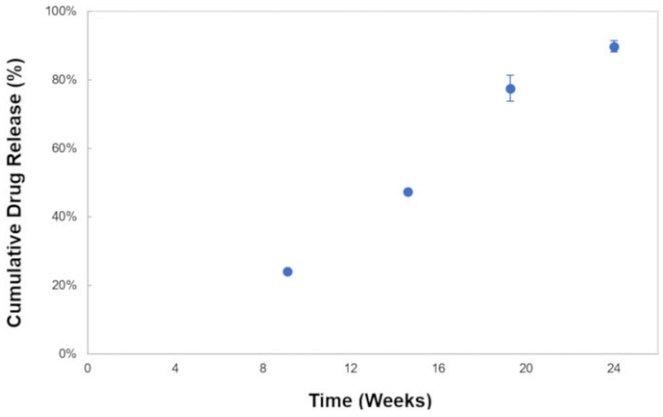

FIGURE 2. In vivo drug release of LYR-210. Cumulative percentage of MF released is shown as a function of time. Data represent mean and standard error for the mean. Data at week 19 were the mean value of 6 depots collected between week 17 and week 21. Data at week 24 were the mean value of 27 depots collected at week 24 visit. MF = mometasone furoate.

samples were excluded from analysis due to fragmentation of the depot at removal or failure to return depot from clinic. Figure 2 shows the cumulative percentage of MF released as a function of time. Two dislodged depots showed 24.0% and 47.3% of MF had been released at week 9 and week 15, respectively. The average percentage of MF release was 77.5% from 6 depots that were removed or dislodged between week 17 and week 21 and 89.8% at week 24 from 27 depots that were removed per study protocol.

Safety

Sixteen patients reported a treatment-emergent AE of any type in this study. Table 3 summarizes the AEs that were reported by more than 1 patient (>5% rate) including nasopharyngitis, sinusitis, upper respiratory tract infection, nasal odor, nasal discomfort, facial pain, and procedural headache. There was only 1 serious adverse event (SAE) reported in the study, in which the patient had an episode of angina pectoris that was determined to be an exacerbation of a preexisting condition. The remaining AEs were mild or moderate in severity. One patient experienced a recurrence of sinus infection that was moderate in severity, in which the depots were removed as stated previously in the "Depot placement and retention" section. This patient received antibiotics and oral steroid treatment to manage the recurrent sinus infection and reported resolution of the AE after 3 days of medical treatment. The only other depot removal resulted from a patient complaining of memory impairment that was determined to be mild in severity. This AE was determined by the site investigator and adjudicated by the independent medical reviewer as not related to LYR-210 due to the negative blood test results for MF systemic exposure and the fact that the depot was not near the memory center of the patient. The patient was referred to a neurologist for further diagnosis.

Despite the use of a highly sensitive assay with a lower limit of quantification (LLOQ) of 20 pg/mL, plasma MF concentrations were below the LLOQ in 11, 10, 16, and 10 of the 20 plasma samples collected after 1 hour, 1 week, 4 weeks, and 12 weeks of treatment, respectively. The remainder of the plasma MF concentrations was near the LLOQ at all time points tested (values ranging from 20.2 to 34.8 pg/mL). Figure 3 shows a low yet constant systemic MF plasma concentration as a function of time, supporting consistent daily MF dosing through at least 12 weeks.

There was no evidence of impact of systemic corticosteroid on serum cortisol or IOP. Morning serum cortisol concentration was not significantly different at all follow-up visits from that before treatment, with mean CFBL in serum cortisol levels of –23.1 nmol/L ($p = 0.33$), –16.0 nmol/L ($p = 0.52$), and 7.5 nmol/L ($p = 0.83$) after 4, 12, and 24 weeks of treatment with LYR-210, respectively. No patient had IOP >22 mmHg and no AEs indicative of high IOP were reported. The mean CFBL in IOP was –0.03 mmHg ($p = 0.96$) and –0.75 mmHg ($p = 0.34$) after 4 and 24 weeks of treatment with LYR-210, respectively.

TABLE 3. Summary of treatment-emergent AEs and serious AEs

Event[a]	Patients with event(n)[b]
All treatment-emergent AEs	16
Common AEs (>1 patient)	
General disorders and administration site conditions	
Facial pain	2
Infections and infestations	
Nasopharyngitis	7
Sinusitis	4
Upper respiratory tract infection	5
Injury, poisoning, and procedural complications	
Procedural headache	2
Respiratory, thoracic, and mediastinal disorders	
Nasal discomfort	2
Nasal odor	4
All serious AEs	
Cardiac disorders	
Acute myocardial infarction	1

[a] AEs were coded using the MedDRA dictionary, version 21.0. Event is the systemic organ class preferred term.
[b] N = 20 total patients. Patients experiencing the same AEs were counted only once.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

Efficacy

Subjects experienced significant reduction in their SNOT-22 scores as early as week 1; this reduction persisted through week 24, and was maintained 1 week post–LYR-210 removal (Fig. 4A). All CFBLs in SNOT-22 score were

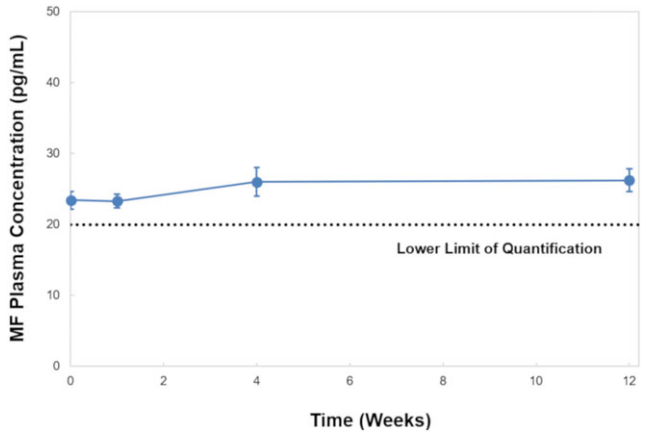

FIGURE 3. Plasma MF concentration indicates a safe but steady daily dosing for a minimum of 12 weeks assessed. Plasma drug concentrations were determined from 20 patients at each time point. Data represent mean and standard error for the mean of patients whose plasma MF concentrations were equal to or greater than the LLOQ of 20 pg/mL (n = 9, 10, 4, and 10 patients at day 1, week 1, week 4, and week 12, respectively). Dashed line indicates LLOQ. LLOQ = lower limit of quantification; MF = mometasone furoate.

statistically significant ($p < 0.01$). There was a moderate linear correlation between the baseline SNOT-22 and posttreatment SNOT-22 scores at week 4 (correlation coefficient = 0.70) and week 8 (correlation coefficient = 0.50). The correlation was weak at the remaining time points (correlation coefficient ranged between 0.21 and 0.40). There were 75% or more of patients who experienced symptom improvement at all time points assessed (Fig. 4B). Sixty percent of patients reported at least a minimal clinically important difference (MCID) in SNOT-22 scores (reduction greater than 8.9 points), as defined by Hopkins et al.,[17] by as early as 1 week posttreatment and 70% of patients reported symptom improvement achieving MCID in SNOT-22 scores by end-of-study visit. Significant symptom improvement was achieved in the SNOT-22 rhinologic, extranasal rhinologic, ear-facial, psychological, and sleep dysfunction subdomains, through week 24 (Fig. 5).

Subgroup analysis of CRSsNP (n = 12) and CRSwNP (n = 8) indicated symptom improvement in both subgroups of patients. The mean CFBL in SNOT-22 scores in CRSsNP was –18.1 after 1 week of treatment ($p < 0.005$) and was maintained throughout the duration of the study (mean CFBL ranged from –17.3 to –23.6, $p < 0.03$ at all time points) (Fig. 6A). The mean CFBL in SNOT-22 scores in CRSwNP was only –5.3 after 1 week of treatment but reached –16.8 after 4 weeks of treatment ($p < 0.03$) and was maintained throughout the remainder of the study (mean CFBL ranged from –16.8 to –31.5, $p < 0.04$ at all time points) (Fig. 6A). There was no significant difference at all time points between these 2 subgroups ($p > 0.05$). Nasal blockage and decreased sense of smell have been reported to be the most prevalent and severe symptoms in both CRSsNP and CRSwNP.[20] The responder rate, defined as at least 1 point of decrease in symptom severity, in CRSsNP patients was 75% to 92% for nasal obstruction and 50% to 75% for sense of smell at all time points assessed during this study (Fig. 6B). In CRSwNP patients, the responder rate for nasal obstruction was 50% to 88% at all time points assessed during this study; the responder rate for sense of smell it was 38% at week 1 and reached 63% to 88% throughout the remainder of the study (Fig. 6C).

Discussion

This phase 1 clinical study is the first report of an intranasal corticosteroid delivery system for treating CRS patients who have not undergone previous ESS. The results from this study show successful administration and tolerability of LYR-210 in the middle meatus of CRS patients without the need for a prior or concomitant surgical procedure.

Treatment of presurgical CRS patients with a local drug delivery system requires a small-profile product that can fit into the tight anatomy of an unoperated patient without obstructing air flow. The average width of a middle meatus is reported to be 1.69 mm anteriorly, 2.83 mm at the transition angle, and 4.74 mm posteriorly.[21] The LYR-210 depot is a miniaturized local drug delivery system designed to fit within, and conform to, the confined space of a patient's middle meatus. The administration of LYR-210 was performed with topical anesthesia in the otolaryngologists' office. Bilateral administration of LYR-210 was achieved in all enrolled patients.

LYR-210 was well tolerated by patients during the entire duration of treatment. There were no reports of unexpected AEs or local nasal AEs including epistaxis, nasal burning, nasal dryness, nasal irritation, and nasal septal perforation during the 24-week MF local-dosing treatment duration. There were 7 patients reported cold as an AE that was Medical Dictionary for Regulatory Activities (MedDRA)-coded as nasopharyngitis, all mild in severity, during the 25 weeks of follow-up. Nasopharyngitis is a labeled event in the MF products as 1 of the most common AEs.[22,23] The rate of nasopharyngitis reported in this phase 1 study is not unanticipated given the long duration of the follow-up period. In 5 patients, 1 of the bilateral administered depots was expelled through the nose while sneezing or coughing between week 9 and week 21 posttreatment; 4 of the 5 dislodgements occurred after week 14. The final depot retention rate was 86.1% at the week 24 visit, the highest rate reported to date.[24,25] No AEs were associated with these depot dislodgements. No change in morning serum cortisol levels or IOPs was noted, and there were no AEs associated with systemic levels of MF.

Current clinical guidelines recommend topical corticosteroids in combination with nasal saline irrigations as the first-line medical therapies for treating CRS patients.[6,7] Current steroid-eluting sinus implants only provide 2 to 12 weeks of drug delivery to the sinuses of peri-ESS or post-ESS CRS patients.[24,25] LYR-210 is the only topical drug delivery system that provides 24 weeks of continuous MF treatment to unoperated CRS patients with a single

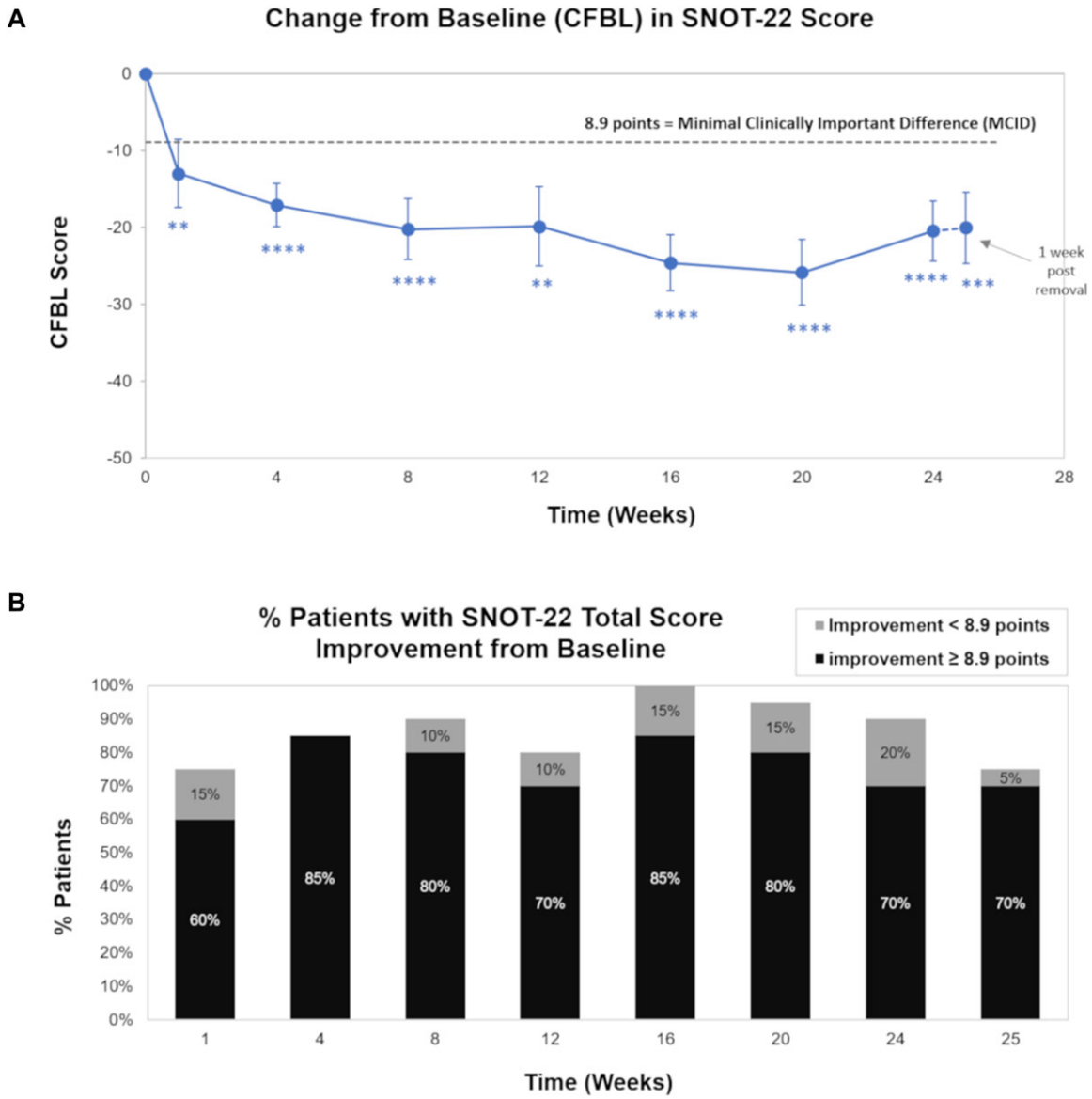

FIGURE 4. Patient symptom improvement measured by SNOT-22 questionnaire. (A) Mean CFBL in SNOT-22 total scores. Data represent mean and standard error for the mean. $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$. (B) Percent of patients achieving symptom improvement at each time point. Percent of patients with or without MCID improvement are shown. CFBL = change from baseline; MCID = minimal clinically important difference; SNOT-22 = 22-item Sino-Nasal Outcome Test.

administration. The in vivo drug release data collected in this study confirmed the constant daily dose through the entire duration of 24 weeks of treatment. Although only a small number of patients were evaluated in this phase 1 clinical study, these data demonstrate early promising results indicating that a single administration of LYR-210 can provide fast-acting and long-lasting symptom relief as measured by the SNOT-22 questionnaire. The average change from baseline in SNOT-22 score was –13.0 points ($p = 0.008$ to pretreatment) by 1 week, already achieving the minimal clinically significant difference of –8.9 points.[17] Symptom relief was sustained through the entire duration of study (–20.5 points at week 24, $p = 0.00005$ to pretreatment). Only 1 patient was prescribed oral steroid therapy during the follow-up period for a recurrence of sinus infection. These changes are notable in that no topical nasal spray was utilized in conjunction with LYR-210. No patients underwent surgical intervention during the 24-week treatment period.

CRS phenotypes can be divided into CRSwNP and CRSsNP based on the presence or absence of nasal polyps via endoscopic findings. Epidemiologic studies across geographic regions indicate CRSsNP is more prevalent in all ages than CRSwNP.[26] However, available topical steroid therapies are only indicated for nasal polyps. This leaves the majority of the CRS patients without an evidence-based treatment. In a clinical study conducted by Abdalla et al.,[20] 789 CRSsNP patients undergoing surgery for CRS were evaluated for SNOT-22 symptom improvement at 3 months postsurgery. They reported that at 3 months

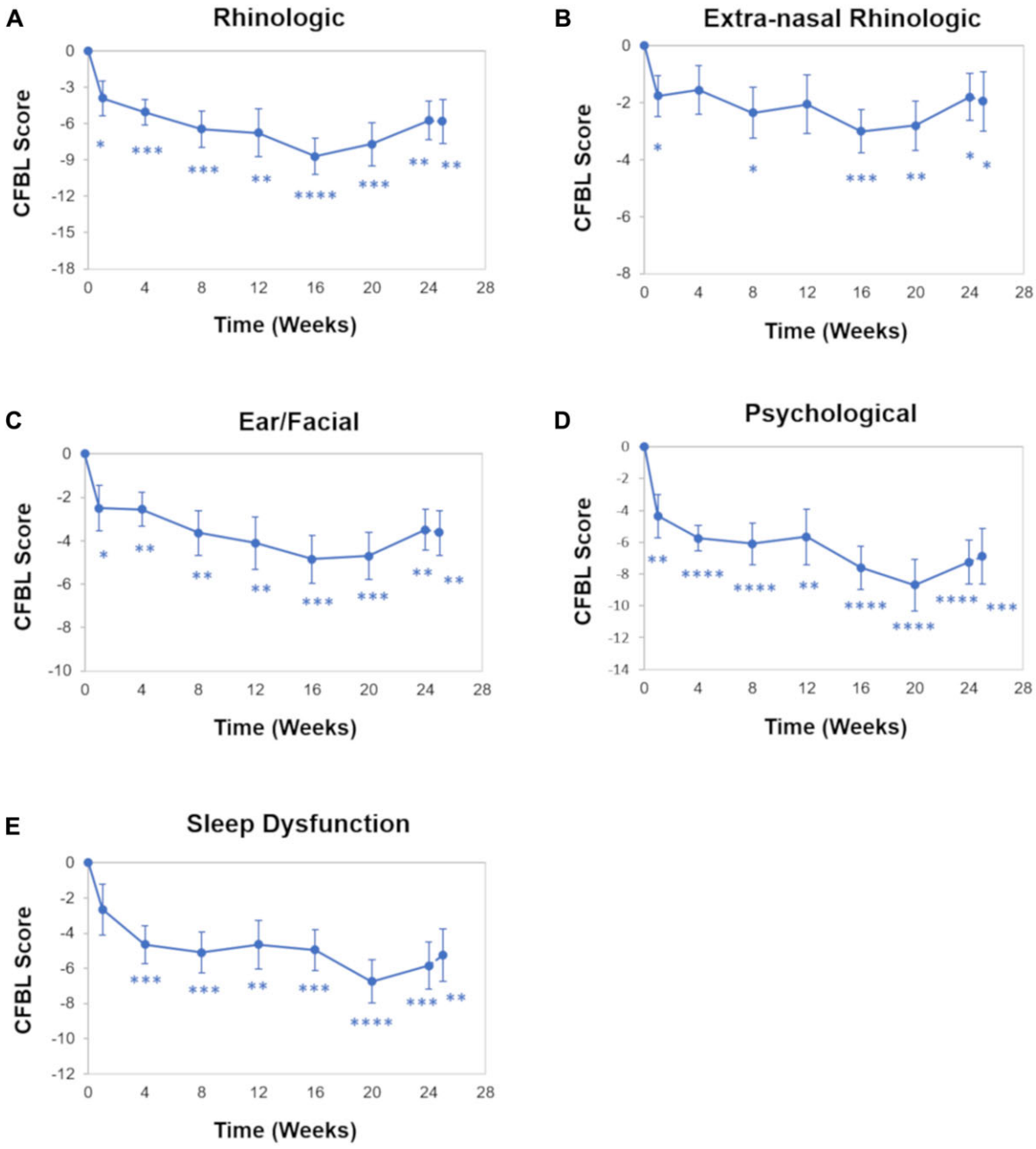

FIGURE 5. Mean CFBL in SNOT-22 (A) Rhinologic, (B) Extra-nasal Rhinologic, (C) Ear/facial, (D) Psychological, and (E) Sleep Dysfunction subdomain symptoms scores. Data represent mean and standard error for the mean. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. CFBL = change from baseline; SNOT-22 = 22-item Sino-Nasal Outcome Test.

postsurgery about 50% to 60% CRSsNP patients had improved nasal blockage and sense of smell scores. The average CFBL in nasal blockage and sense of smell scores were approximately –2.0 and –1.4, respectively. Although our study only included 12 CRSsNP patients, 75% and 58% of these patients reported improvement in nasal blockage and sense of smell, respectively, after 12 weeks of treatment by LYR-210. The mean CFBL in nasal blockage and sense of smell scores were –1.7 ($p = 0.006$) and –1.9 ($p = 0.02$), respectively. Thus, both the responder rate and the level of response in these symptoms were similar to surgery in CRSsNP patients.

Guidance documents recommend a SNOT-22 threshold of 20 and above for ESS in CRS patients who have failed medical management.[6] A strong correlation has been previously shown between CRS patients electing to pursue sinus surgery and higher SNOT-22 scores compared to those electing continued medical therapy, regardless of surgical history or polyp status.[27] An inclusion criterion for this study was a SNOT-22 score of at least 20, ensuring enrolled patients were indeed candidates for ESS. Forty percent and 30% of enrolled patients were converted to nonsurgical candidates at the week 12 and end-of-study visit, respectively, based on a decrease in SNOT 22 score below

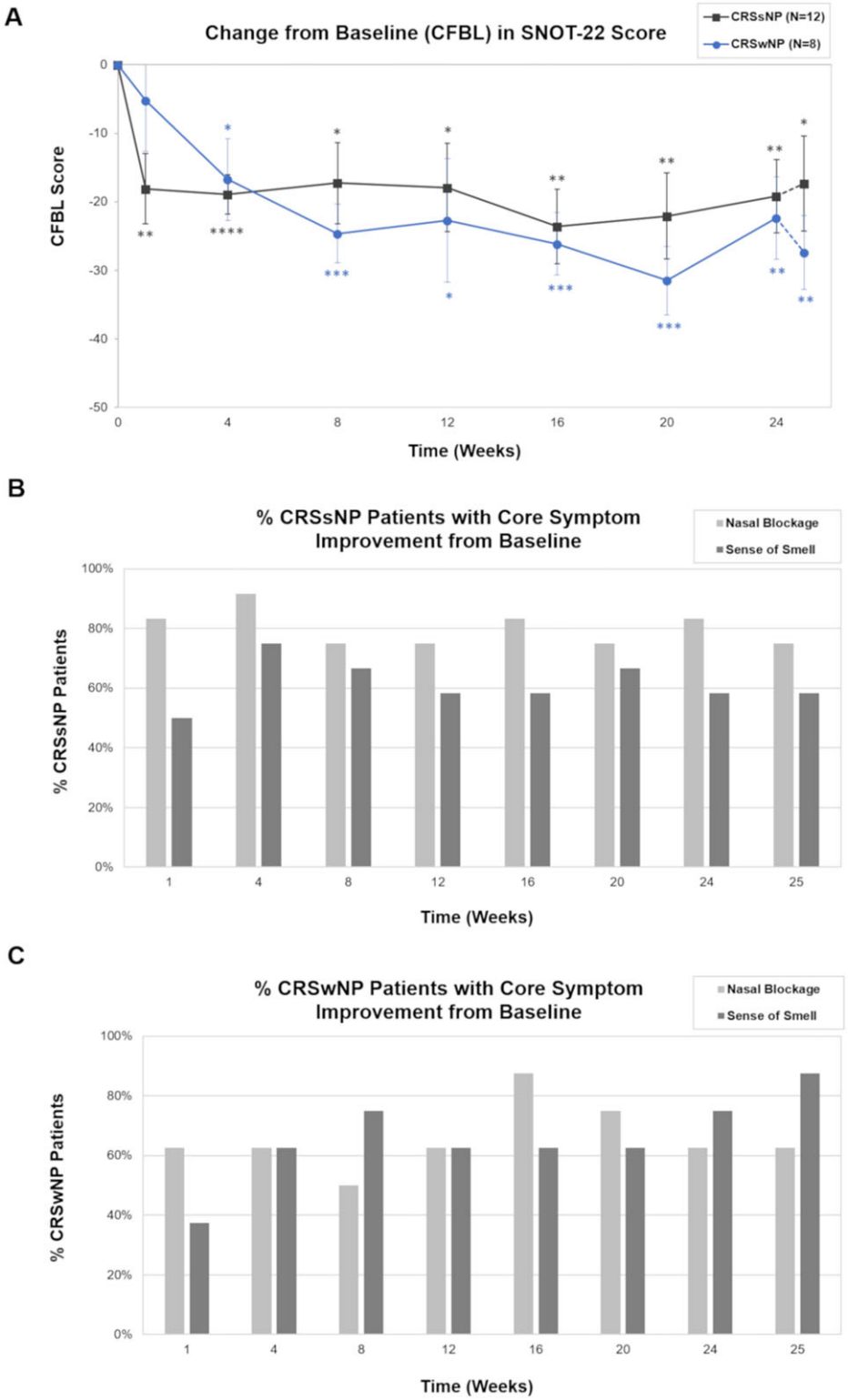

FIGURE 6. Patient symptom improvement in CRSsNP and CRSwNP patients. (A) Mean CFBL in SNOT-22 total scores. Data represent mean and standard error for the mean. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. There was no significant difference between CRSsNP and CRSwNP at all time points ($p > 0.05$). (B) Percent of CRSsNP patients and (C) percent of CRSwNP patients achieving improved nasal blockage and sense of smell at each time point. CFBL = change from baseline; CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; SNOT-22 = 22-item Sino-Nasal Outcome Test.

the threshold of 20. Because nasal congestion is the most prevalent and severe individual symptom of the SNOT-22, a minimum nasal congestion score of 2 was required to be in line with other clinical studies in the field.[28–30] Patients from our study reported a baseline average nasal congestion score of 3.8, in line with that of presurgical patients reported by Abdalla et al.[20] These initial clinical experiences with LYR-210 in CRS patients suggest encouraging clinical benefits without the need for surgery, while avoiding safety risks associated with prolonged oral steroid treatment.

The main limitations in this clinical study 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 that is randomized and blinded to a control treatment will address these limitations.

Conclusion

This small phase 1 trial is a first report of a continuous 24-week steroid delivery system to treat patients with CRS. The study indicates that a biodegradable intranasal drug delivery depot, LYR-210, can be safely placed as an office-based procedure and has an acceptable safety profile for the 24-week duration that it is in place. In addition, initial clinical efficacy data suggest fast-acting and durable symptom improvement during the 24 weeks of treatment duration with bilateral administration of LYR-210. Future randomized clinical trials are warranted.

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