



Investor Presentation

September 2025



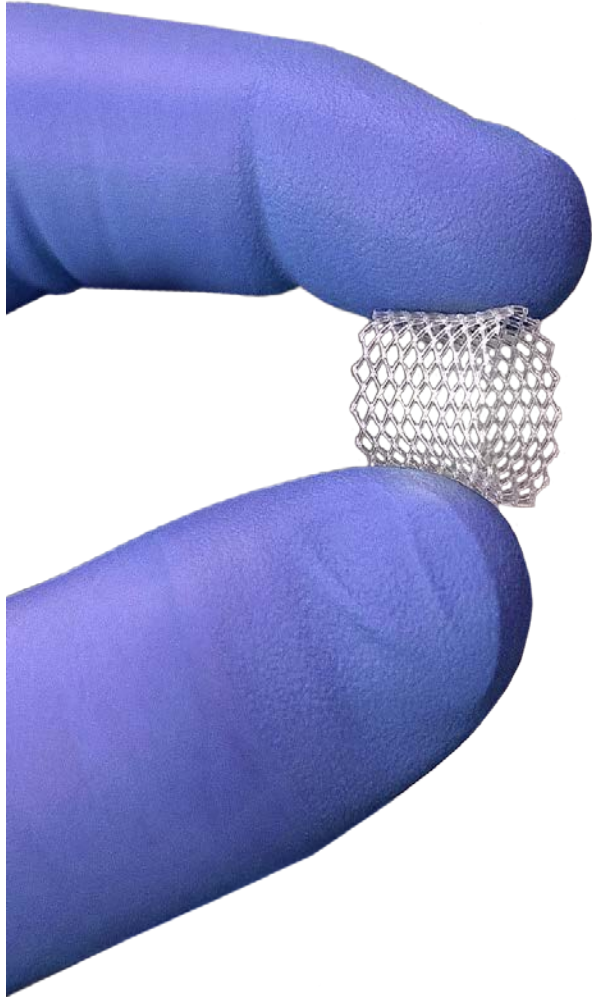
Forward Looking Statement

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. The words “believe,” “may,” “will,” “estimate,” “continue,” “anticipate,” “intend,” “expect,” and similar expressions are intended to identify forward-looking statements. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including statements regarding the significant market opportunity in both polyp and non-polyp CRS populations, whether the majority of patients with CRS are not served by current treatments, our evaluation and investigation of the ENLIGHTEN 1 and ENLIGHTEN 2 results and how they inform our path forward, our planned regulatory interaction and path for LYR-210, our ability to correctly interpret feedback received from FDA in December 2024 and September 2025 as well as our belief we have clarity on the regulatory path for LYR-210, whether patients with PAR was a significant confounder in the results of ENLIGHTEN 1, our expectations on the need, size and timing for any pivotal trial for LYR-210, our ability to raise money to fund another pivotal trial for LYR-210, our ability to design, implement and complete a new Phase 3 trial, if necessary, our ability to be targeted in our go to market strategy, whether LYR-210, if advanced, would be positioned to align with current ENT practices, and statements regarding the potential market opportunity for LYR-210.

These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause the Company's actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, the following: the fact that the Company has incurred significant losses since inception and expects to incur additional losses for the foreseeable future; the Company's need for substantial additional funding, which may not be available, including funding to initiate and complete another Phase 3 trial for LYR-210 in CRSsNP, if necessary; the Company's ability to continue as a going concern; the failure of our ENLIGHTEN 1 Phase 3 trial to meet its primary endpoint has made it more difficult for the Company to raise capital; our loss of personnel from a reduction in force in May 2024 following the failure of our ENLIGHTEN 1 Phase 3 trial to meet its primary endpoint significantly and adversely affects our operations; the Company's limited operating history; the fact that the Company has no approved products; the fact that the Company's product candidates are in various stages of development; the fact that clinical trial data is subject to change until the completion of the applicable clinical study report; the fact that the Company may not be successful in its efforts to identify and successfully commercialize its product candidates; the fact that clinical trials required for the Company's product candidates are expensive and time-consuming, and their outcome is uncertain; the Company's potential inability to obtain required regulatory approvals; effects of recently enacted and future legislation; the possibility of system failures or security breaches; effects of significant competition; the fact that the successful commercialization of the Company's product candidates will depend in part on the extent to which governmental authorities and health insurers establish coverage, adequate reimbursement levels and pricing policies; failure to achieve market acceptance; product liability lawsuits; while we restarted the manufacturing of our product candidates internally, we may face delays and challenges in achieving our desired production level, especially with our limited staff; the fact that the Company must scale our in-house manufacturing capabilities for the manufacture of materials for its clinical trials and commercial supply; the Company's reliance on third parties to conduct its clinical trials; the Company's inability to succeed in establishing and maintaining collaborative relationships; the Company's reliance on certain suppliers critical to its production; failure to obtain and maintain or adequately protect the Company's intellectual property rights; failure to retain key personnel or to recruit qualified personnel; difficulties in managing the Company's growth; effects of natural disasters, terrorism, wars and global pandemics; the fact that the price of the Company's common stock may be volatile and fluctuate substantially; significant costs and required management time as a result of operating as a public company and any securities class action litigation. These and other important factors discussed under the caption "Risk Factors" in the Company's Quarterly Report on Form 10-Q filed with the SEC on August 12, 2025 and its other filings with the SEC could cause actual results to differ materially from those indicated by the forward-looking statements made in this presentation. Any such forward-looking statements represent management's estimates as of the date of this presentation. While the Company may elect to update such forward-looking statements at some point in the future, it disclaims any obligation to do so, even if subsequent events cause its views to change.

This presentation also includes statistical and market data that we obtained from industry, publications and research, surveys and studies conducted by third parties or us. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. All of the market data used in this presentation involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. While we believe these industry publications and third-party research, surveys and studies are reliable, we have not independently verified such data. The industry in which we operate is subject to a high degree of uncertainty, change and risk due to a variety of factors, which could cause results to differ materially from those expressed in the estimates made by the independent partners and by us. Neither Lyra's most advanced product candidate, LYR-210, nor its pipeline product candidate, LYR-220, have been approved by FDA. This presentation does not constitute an offer to sell or a solicitation of an offer to buy securities, nor shall there be any sale of any securities in any state or jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state or jurisdiction.

Company Overview



Late-stage biotechnology company developing long-acting, bioabsorbable, anti-inflammatory sinonasal drug implants for the treatment of chronic rhinosinusitis (CRS)

- **Innovative, proprietary sinonasal drug implant**
 - Designed to deliver 6 months of continuous anti-inflammatory therapy (mometasone furoate) with a single administration
 - Robust clinical data and safety package in over 500 CRS patients with and without nasal polyps treated across six clinical trials
- **Multi-billion dollar market opportunity in both non-polyp and polyp patients with high unmet need**
 - CRS affects ~12% of the US population⁽¹⁾ with ~50% of patients failing medical therapy⁽²⁾
 - CRS without Nasal Polyps (CRSsNP) – complex inflammatory condition that affects ~70% of CRS patients
 - CRS with Nasal Polyps (CRSwNP) – characterized by presence of nasal polyps that affects ~30% of CRS patients
- **Advancing lead program, LYR-210 to approval in non-polyp patients**
 - ENLIGHTEN 2 Phase 3 trial met primary and key secondary endpoints
 - Clarity from FDA on one additional study in CRS without polyps required for approval
 - Pooled nasal polyp data in the ENLIGHTEN program showed consistent improvement over sham control in multiple subjective and objective endpoints
- **Broad pipeline expansion opportunities in ENT**
- **Robust patent portfolio with multiple lineages including one potentially extending coverage to 2042**

Chronic Rhinosinusitis (CRS): An “Unrecognized Epidemic”⁽¹⁾

Significant market opportunity in both polyp and non-polyp CRS populations



CRS Cardinal Symptoms⁽¹⁾



Nasal obstruction and congestion



Nasal discharge



Facial pain and pressure



Reduced sense of smell

CRS in the United States Annually

~8M

CRS patients treated⁽²⁾

~4M

CRS patients failing medical management⁽³⁾

~\$60B

Annual healthcare expenditure⁽⁴⁾

With Nasal Polyps⁽⁵⁾

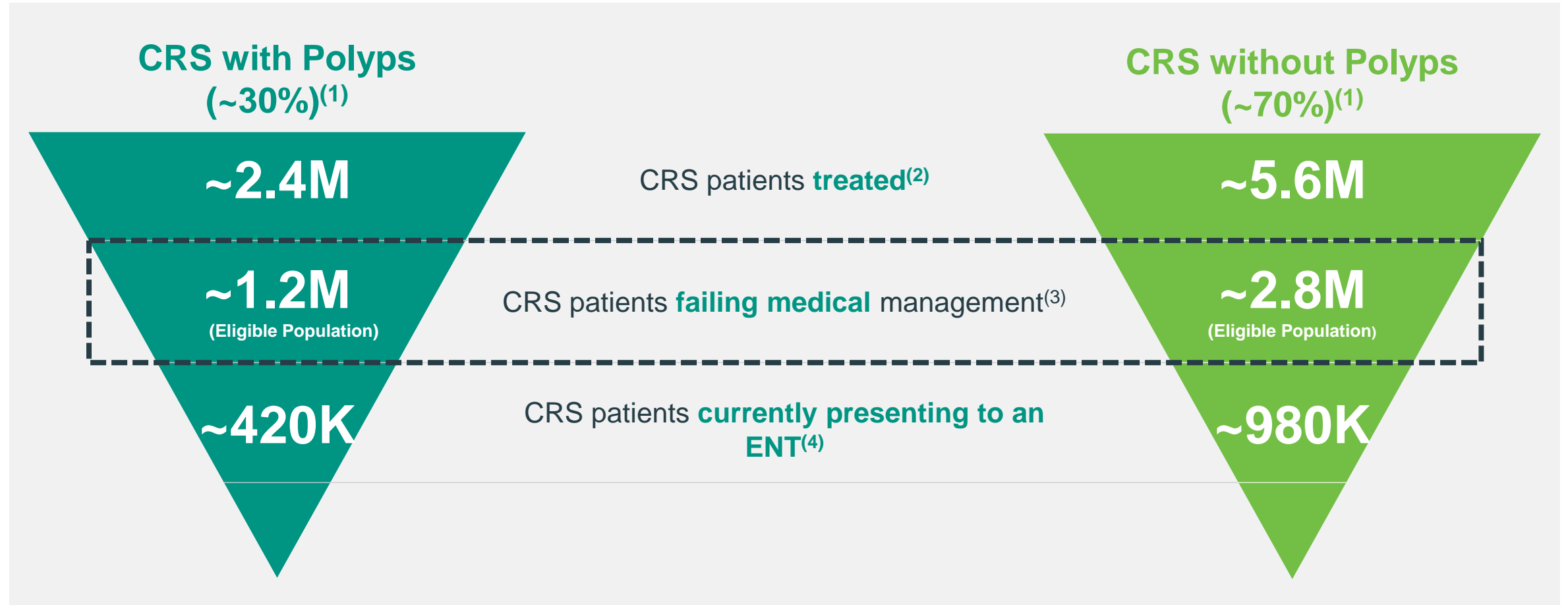
~30%

~70%

Without Nasal Polyps⁽⁵⁾

Annual Incidence of CRS in the U.S. Represents Large Unmet Need

Both polyp and non-polyp CRS includes ~4M eligible patients for Lyra products; current focus on non-polyp patients, which represents 70% of the market



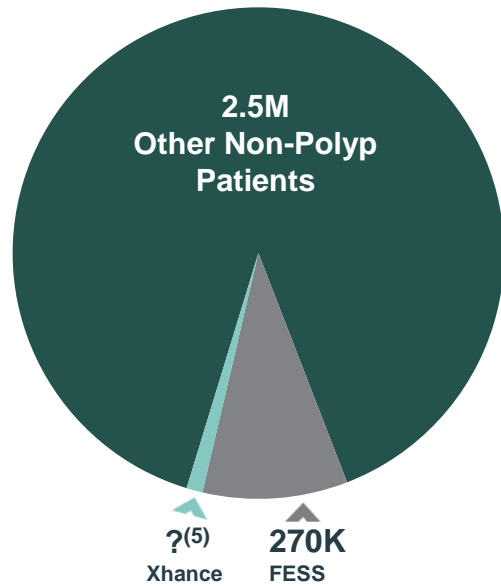
CRS is a Large, Underserved Market

Despite the introduction of biologics for severe polyp patients, the CRS market remains highly underpenetrated with the vast majority of patients not served by current treatments

Market Size

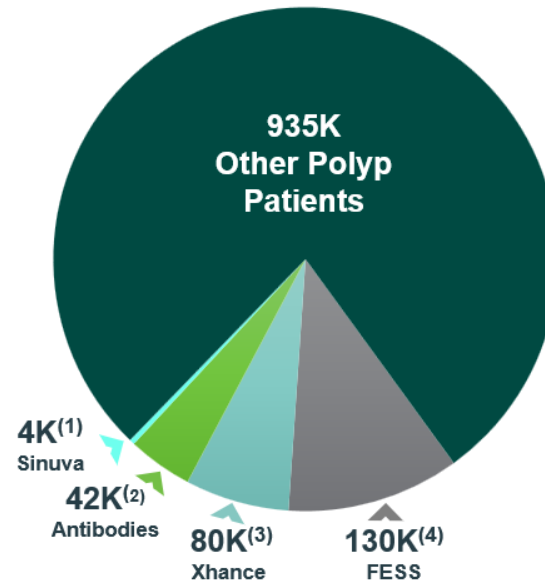
Non-Polyp Market Size

~2.8 Million Failed Non-Polyp Patients



Polyp Market Size

~1.2 Million Failed Polyp Patients



Current Standard of Care & Key Limitations

Medical Management

- ~50% of patients fail topical medical management as a first-line therapy, due to sub-optimal delivery and poor compliance
- Xhance has not been shown to be better than inexpensive, over-the-counter steroid sprays

Surgery

- Non-responders referred to sinus surgery, which does not treat the underlying cause and requires ongoing medical management
- 65% of surgical patients have recurring CRS, with 20% requiring revision surgery

Biologics for Polyps Only

- Given systemic exposure and high cost, reserved for the most severe cases (Grade 3-4 nasal polyps, which represent only 27.5% of patients(6)) and effective only in patients with Type 2 inflammation
- Despite this, Dupixent did >\$1 billion in sales in CRSwNP in 2024

A Novel Drug-Eluting Implant to Deliver 6 Months of Continuous Therapy



Polymer-Drug Complex

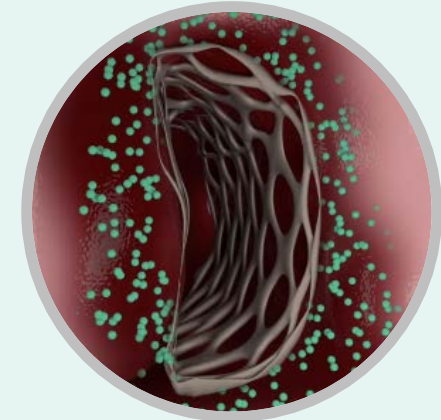
Designed to deliver 6 months of continuous, local drug therapy with a single placement

Engineered Elastomeric Matrix

Shape memory intended to keep implant in place

Bioabsorbable Mesh Scaffold

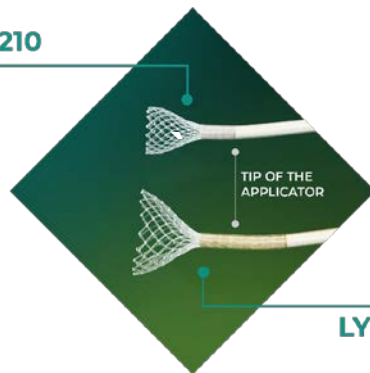
Designed to maximize surface area for drug release while maintaining underlying tissue function



Product Family to Address Full Spectrum of CRS Patients

Smaller dimension for surgery naïve patients or those with previous surgery and narrow ethmoid cavity

LYR-210



Larger dimension for patients with enlarged anatomy including those with previous full ethmoid sinus surgery

LYR-220

Designed to be the New Standard of Care for CRS

- **Only product candidate designed to provide 6 months of CRS therapy with a single treatment**
- FDA-approved steroid: Mometasone furoate
- Designed to provide continuous anti-inflammatory therapy
- Straightforward, office-based procedure with topical anesthesia
- Administered nasally via a single-use applicator
- Potential additional indication as a surgical adjunct to improve outcomes

Strong Clinical Progress in CRS without Nasal Polyps – One Successful Phase 3 Study Completed

- **ENLIGHTEN 2 study met its primary endpoint**
 - Statistically significant improvement over sham in 3CS at Week 24 in the primary population of CRS patients without nasal polyps, with improvement observed as early as Week 8
 - Key secondary endpoints of change in 3CS and SNOT-22 in the full study population were also met
 - Clinically meaningful improvement, more than twice the MCID observed at Week 24 relative to baseline (-22.4 points in SNOT-22)
- **Pooled safety data from ENLIGHTEN 1 and 2 demonstrates positive safety profile, with more than 300 exposures to LYR-210**
- **Clarity from FDA regarding one additional pivotal study for NDA in CRS without Nasal Polyps**

Significant Experience in CRS without Nasal Polyps, with ~300 Patients Treated in ENLIGHTEN Program

ENLIGHTEN 2 met its primary endpoint

ENLIGHTEN Program Design

Criteria

- Two Phase 3 studies of ~180 subjects each, including ~30 polyp patients each⁽¹⁾
- Adult CRS patients without nasal polyps or with nasal polyps, who have failed medical management

Primary Endpoint

- Change from baseline in 3CS⁽²⁾ Score at Week 24 in patients without nasal polyps

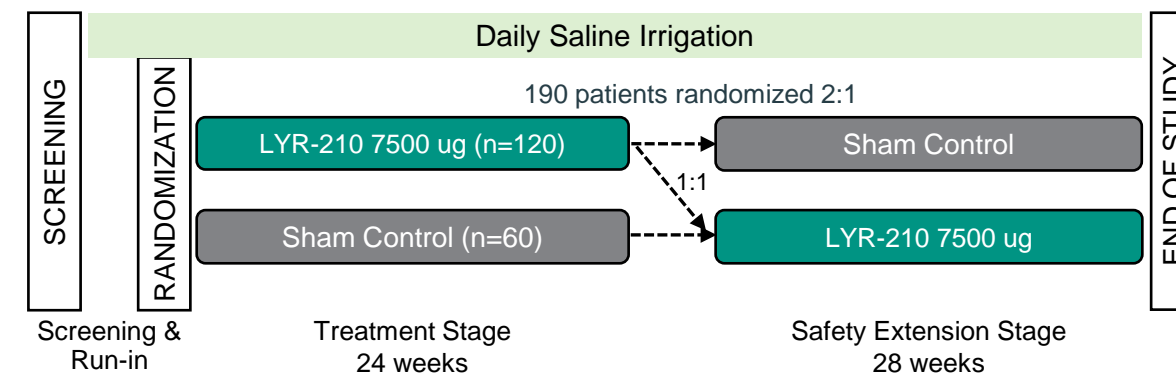
Key Secondary Efficacy Endpoints in All Participants (Polyp and Non-Polyp)

- CFBL in 3CS scores at Week 24
- CFBL in SNOT-22 score at Week 24
- CFBL in ethmoid sinus percent opacification by CT analysis at Week 20
- Rescue treatment use (pooled ENLIGHTEN 1 and ENLIGHTEN 2)

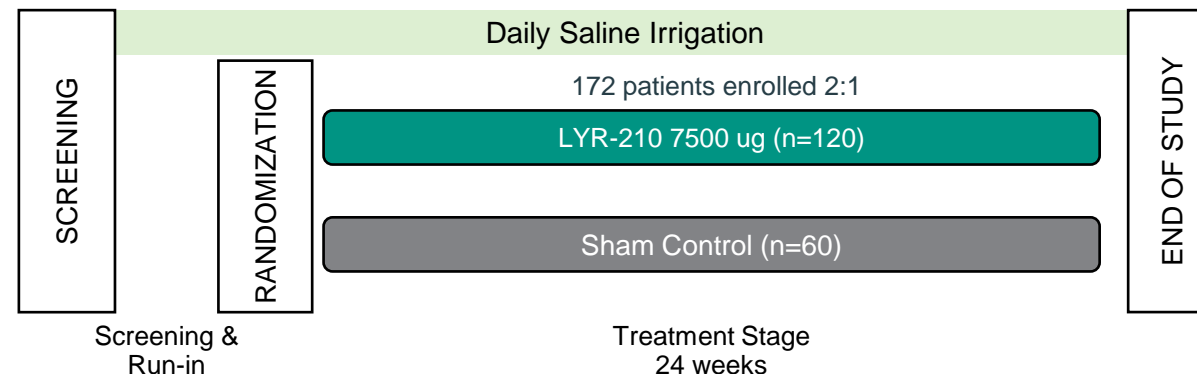
Highlights

- ENLIGHTEN 1: 40 sites in U.S (64% of patients) and Europe (36%)
- ENLIGHTEN 2: 55 sites in U.S (55% of patients) and Europe (45%)

ENLIGHTEN 1⁽⁴⁾



ENLIGHTEN 2⁽⁵⁾



ENLIGHTEN 1 and 2: Patient Demographics & Baseline Characteristics

ENLIGHTEN 1 enrolled nearly double the proportion of patients with perennial allergic rhinitis (PAR) than ENLIGHTEN 2. A statistically significant interaction of PAR by Treatment was detected ($p=0.039$), implying PAR as a confounder in ENLIGHTEN 1.

ITT Analysis Set (all patients with or without nasal polyps)	ENLIGHTEN 1		ENLIGHTEN 2	
	LYR-210 (n=124)	Sham (n=66)	LYR-210 (n=111)	Sham (n=61)
Age in years (mean, SD)	50 (13.7)	45 (14.4)	50 (15.5)	49 (12.99)
Sex (n, %)				
Male	71 (57.3)	35 (53.0)	65 (58.6)	31 (50.8)
Female	53 (42.7)	31 (47.0)	46 (41.4)	30 (49.2)
Race (n, %)				
White	111 (89.5)	54 (81.8)	94 (84.7)	51 (83.6)
Black or African American	5 (4.0)	6 (9.1)	9 (8.1)	5 (8.2)
Region (n, %)				
North America	80 (64.5)	42 (63.6)	63 (56.8)	31 (50.8)
European Union	44 (35.5)	24 (36.4)	48 (43.2)	30 (49.2)
Comorbidity (n, %)				
Seasonal Allergic Rhinitis	27 (21.8)	14 (21.2)	22 (19.8)	12 (19.7)
Perennial Allergic Rhinitis	54 (43.5)	25 (37.9)	23 (20.7)	15 (24.6)
With nasal polyps (n, %)	23 (18.5)	12 (18.2)	17 (15.3)	12 (19.7)
Baseline score (mean, SD)				
3CS Score	6.9 (1.37)	6.7 (1.24)	6.5 (1.29)	7.2 (1.37)
SNOT-22	61.1(19.76)	60.5 (20.00)	56.2 (17.38)	58.8 (22.21)

ENLIGHTEN 2: Most Frequent Adverse Events (≥5% of patients)

Favorable safety profile with no product-related serious adverse events

Safety Analysis Set Preferred Term ¹	ENLIGHTEN 1		ENLIGHTEN 2	
	LYR-210 (n=124)	Sham (n=66)	LYR-210 (n=112)	Sham (n=60)
Any adverse event	95 (76.6%)	41 (62.1%)	67 (60.4%)	27 (44.3%)
Epistaxis ²	23 (18.5%)	7 (10.6%)	18 (16.2%)	1 (1.6%)
Nasal Odour	23 (18.5%)	0	3 (2.7%)	0
Upper respiratory tract infection	10 (8.1%)	10 (15.2%)	10 (9.0%)	5 (8.2%)
Chronic sinusitis (<i>worsened</i>)	14 (11.3%)	3 (4.5%)	8 (7.2%)	6 (9.8%)
Nasopharyngitis	10 (8.1%)	4 (6.1%)	7 (6.3%)	4 (6.6%)
Sinusitis	13 (10.5%)	3 (4.5%)	1 (0.9%)	0
Acute sinusitis	14 (11.3%)	0	9 (8.1%)	3 (4.9%)
COVID-19	10 (8.1%)	4 (6.1%)	5 (4.5%)	4 (6.6%)
Headache	7 (5.6%)	1 (1.5%)	6 (5.4%)	3 (4.9%)

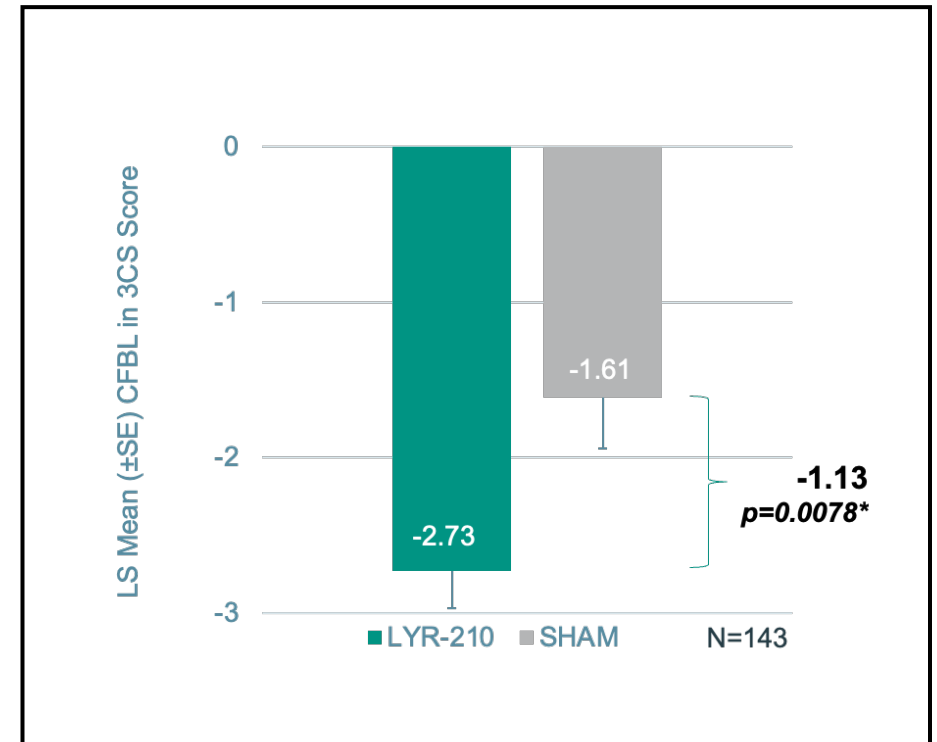
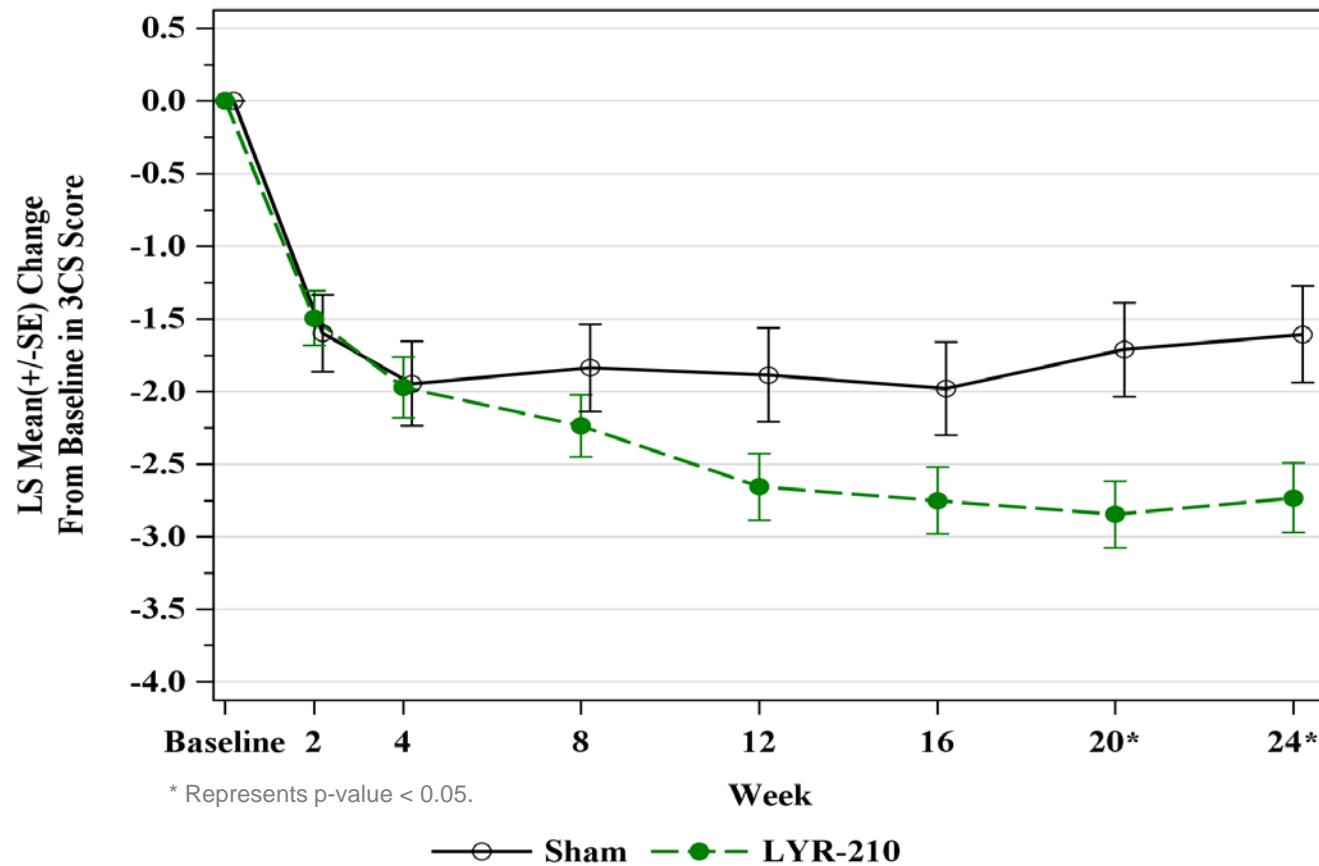
1) Events coded to a standard term using MedDRA coding dictionary

2) Any event with terms such as blood-tinged mucus, nosebleed, etc. are coded to this preferred term and does not indicate a clinical nosebleed requiring intervention

ENLIGHTEN 2 Trial Met Primary Endpoint

Statistically significant improvement in 3CS at 24 weeks, with consistent improvement over Sham control starting as early as Week 8

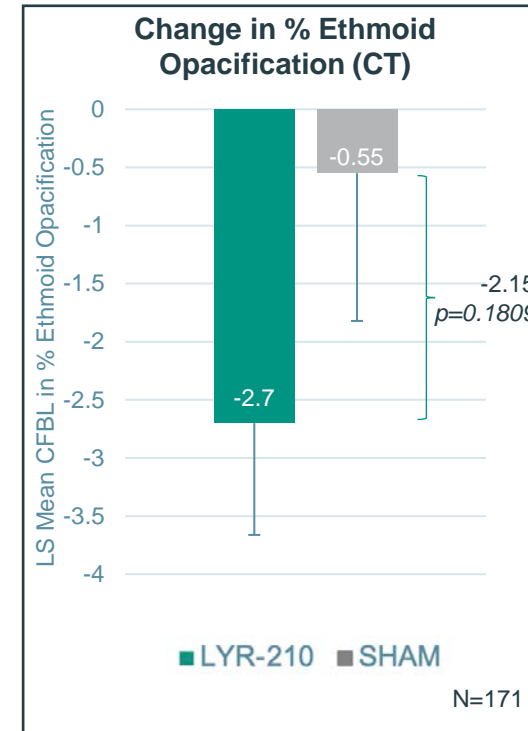
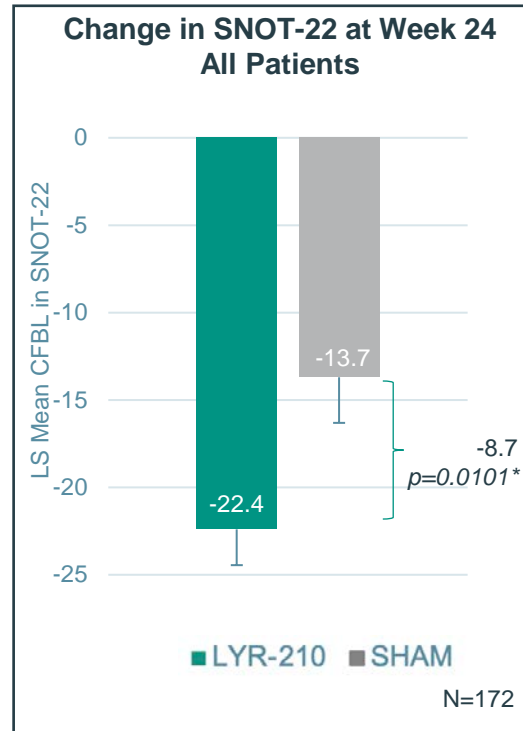
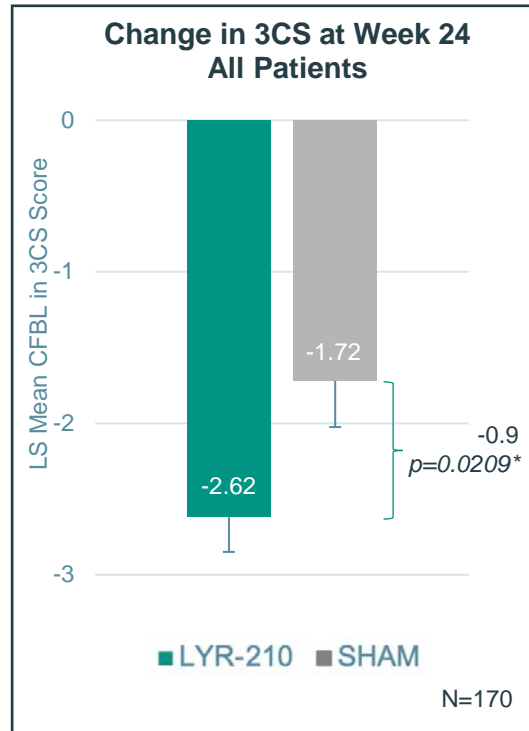
Composite of the 3 Cardinal Symptoms in Non-Polyp Patients



ENLIGHTEN 2 Trial Met Key Secondary Endpoints

Data represent ~40% improvement in 3CS and SNOT-22 scores relative to baseline in ITT population

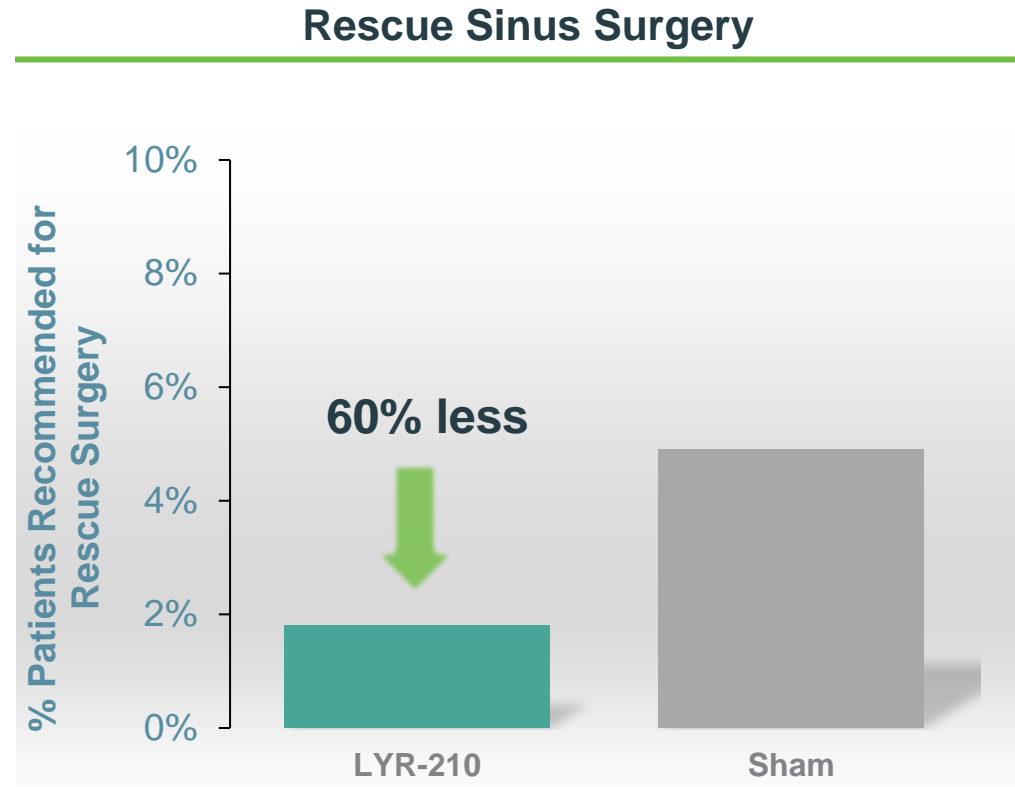
Key Secondary Endpoints



* Statistically significant

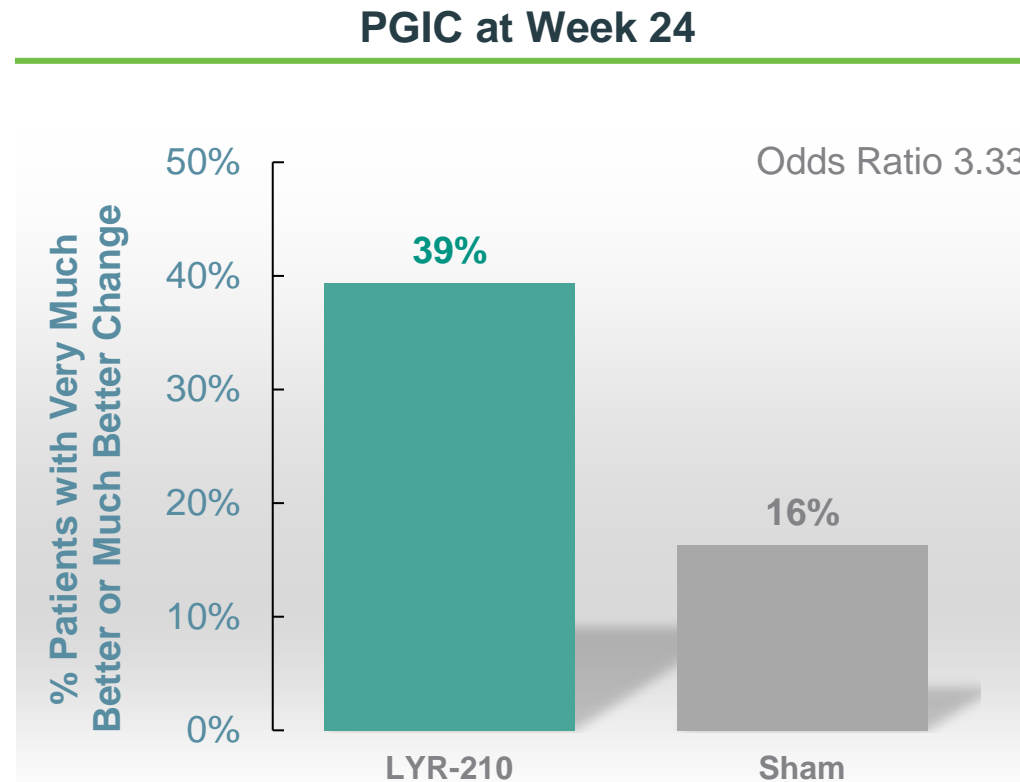
ENLIGHTEN 2: Proportion of Patients Recommended for Rescue Surgery

Treatment with LYR-210 reduced the need for sinus surgery by 60% compared to Sham



ENLIGHTEN 2: Patient Global Impression of Change (PGIC) in Non-Polyp Patients⁽¹⁾

Patients treated with LYR-210 were over 3-fold more likely than Sham-treated to experience a change of “very much better” or “much better”



Clarity on Path to NDA Submission for CRS without Nasal Polyps

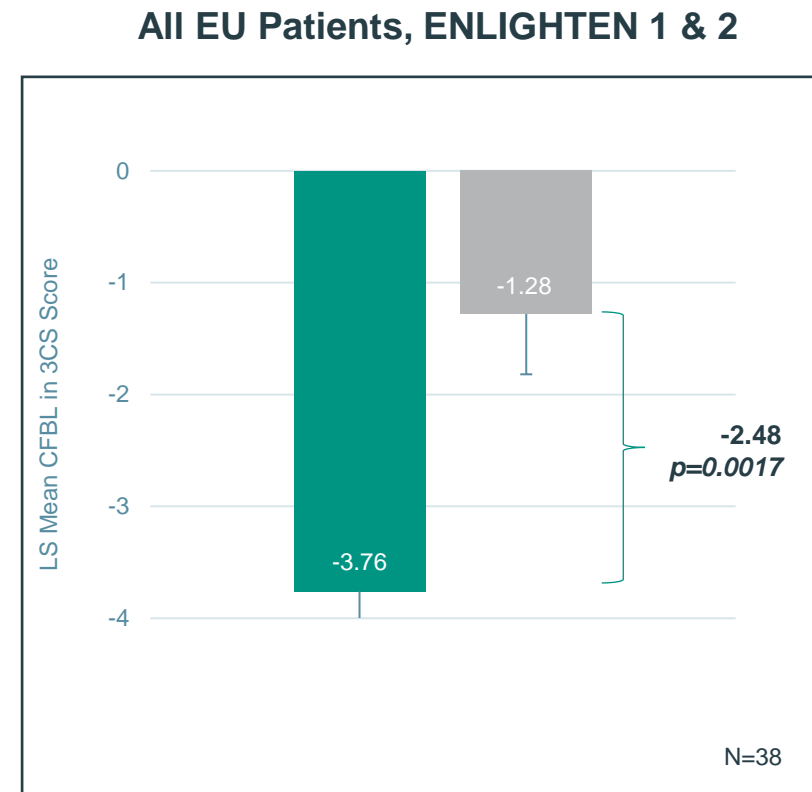
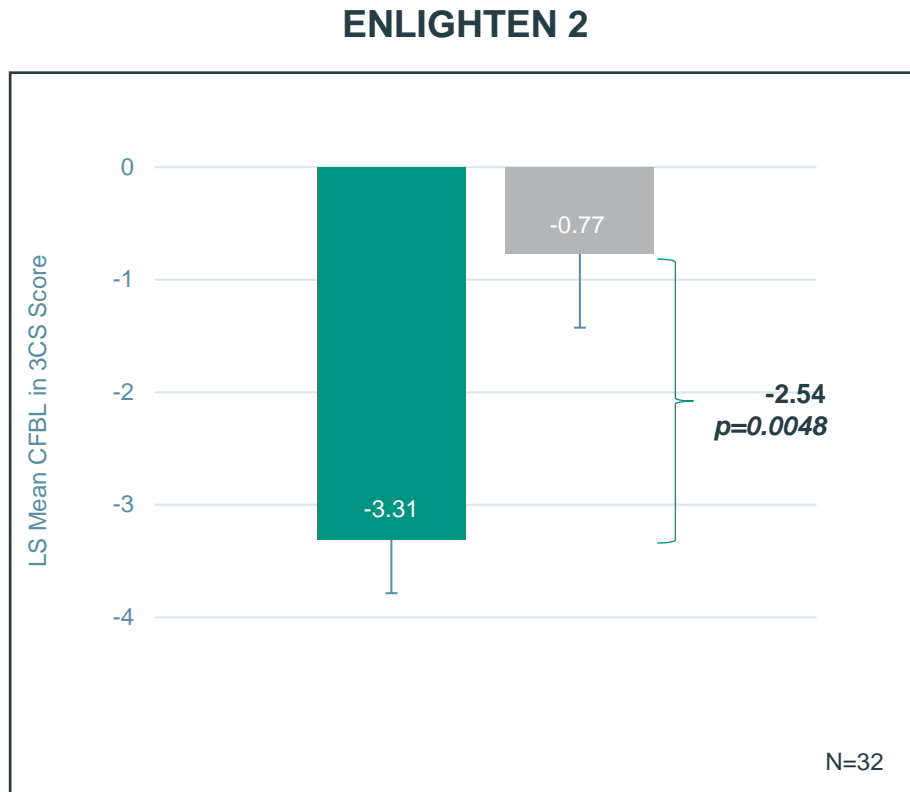
*Met with FDA in September 2025 on NDA requirements for CRS without nasal polyps**

- As expected, an additional clinical study is required to demonstrate substantial evidence of effectiveness in CRS without nasal polyps
- FDA has agreed to single primary endpoint of change from baseline in 3CS at 24 weeks
- FDA is allowing removal of daily saline irrigation for all participants
- FDA has agreed that study can be modified based on the learnings of ENLIGHTEN 1
 - Manage PAR patients with history questionnaire and severity of disease on endoscopy / CT
 - Inclusion criteria of CT opacification greater than or equal to 25% at baseline
- FDA recommends additional safety data on repeat administration of LYR-210

Large Treatment Effect Observed in Patients with Higher CT Opacification

In patient population with greater than 25% CT opacification, treatment effect relative to Sham of 2.5 points in 3CS score

All CRS without Nasal Polyps with Ethmoid Opacification >25%

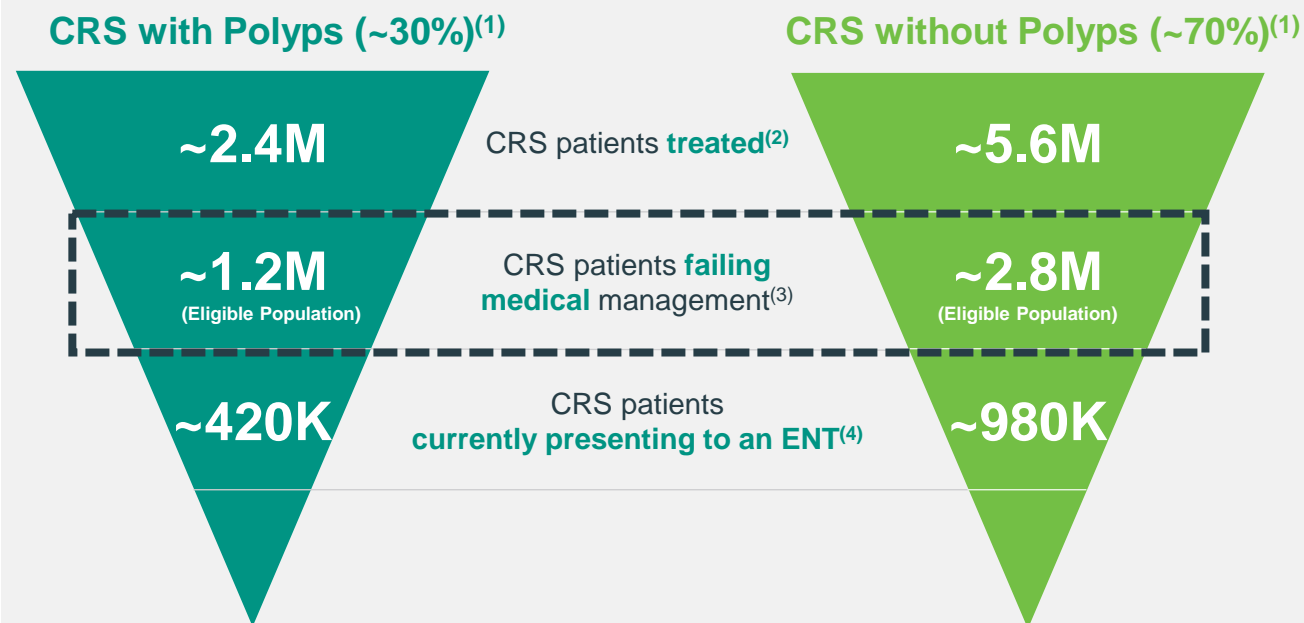


Targeted Go-to-Market Strategy

Significant market opportunity with targeted focus on ENTs specializing in sinus procedures

~4M of Eligible Polyp and Non-Polyp Patients

Annual Incidence of CRS in the U.S.

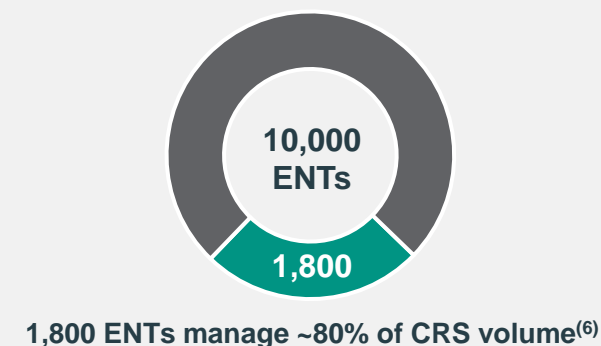


Targeted Patient and Physician Base

Highly Accessible Patients



Specialist Physicians



Key Milestones

- ✓ **May 2024: Data readout from ENLIGHTEN 1**
- ✓ **Q4 2024: Extension study data from ENLIGHTEN 1**
- ✓ **2H 2024: Complete enrollment in ENLIGHTEN 2**
- ✓ **2Q 2025: Data readout from ENLIGHTEN 2**
- ✓ **2H 2025: Clarity from FDA on NDA strategy for CRS without Nasal Polyps**
- ▮ **Est. 1H 2026: Initiation of pivotal phase 3 trial for CRS without Nasal Polyps***

LYRA

THERAPEUTICS

