ENLIGHTEN 2 Study Results

ENLIGHTEN 2: A Phase III, Randomized, Blinded, Controlled, Parallel-Group Trial to Evaluate the Efficacy and Safety of LYR-210 for the Treatment of Chronic Rhinosinusitis (CRS) in Adults

https://clinicaltrials.gov/study/NCT05295459

June 2, 2025

FLS Disclaimer

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 our evaluation and investigation of the ENLIGHTEN 2 results and how they inform our path forward, our planned regulatory interaction and path for LYR-210, our expectations on the need, size and timing for any pivotal trial for LYR-210, our ability to raise money to fund a pivotal trial for LYR-210, our ability to design, implement and complete a new Phase 3 trial, the expected label for LYR-210, whether the pooled results from ENLIGHTEN 1 and 2 would support a path forward to a pivotal study in CRSwNP, our ability to correctly interpret FDA guidance received in December 2024 including on endpoints, inclusion criteria, patient population, background therapy, and assessments, 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 and/or CRSwNP; 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, or 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 are restarting the manufacturing of our product candidates internally, we may face delays and challenges in achieving our desired production level; the fact that the Company must scale its 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 May 6, 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.

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

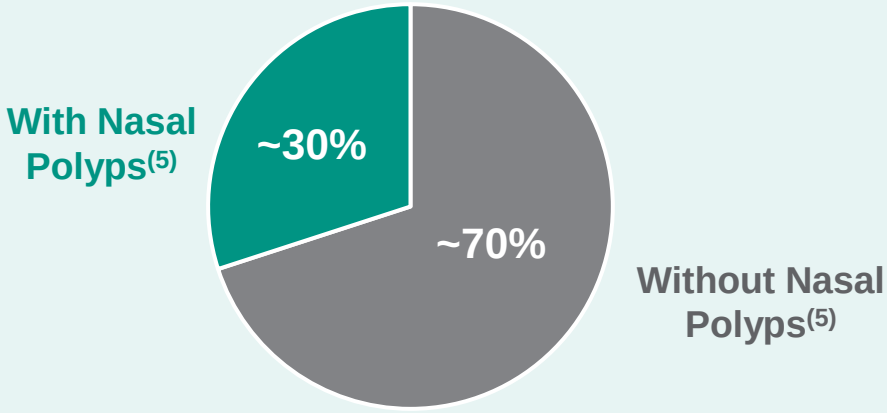
CRS patients **treated**[2]

~4M

CRS patients **failing medical** management[3]

~$60B

Annual healthcare expenditure[4]



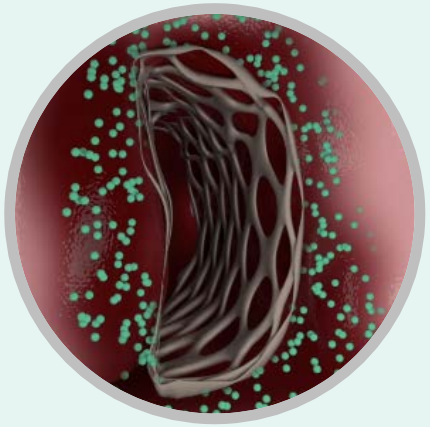
(1) Tan BK et al. Am J Respir Crit Care Med, 2013;188(11):1275–7; (2) Jang et al. Otolaryngol Head Neck Surg, 2018; (3) Baguley et al. Int Forum Allergy Rhinol, 2014;4(7):525-32; (4) Caulley et al. J Allergy Clin Immunol. 2015;136(6):1517-1522; (5) Biomedical Insights Market Sizing Assessment 2020

Lyra's Proprietary Drug-Eluting Implant

Polymer-Drug Complex
Designed to deliver 6 months of continuous, local drug therapy with a single placement

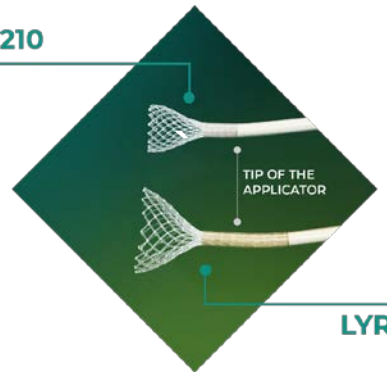
Engineered Elastomeric Matrix
Shape memory intended to keep implant in place

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



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

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

ENLIGHTEN Program Design – LYR-210 Phase 3 Program

Two replicate trials in support of an NDA for the primary indication of CRS without nasal polyps[(1)]

ENLIGHTEN Program Design

Criteria

- Two Phase 3 studies of ~180 subjects each, including a combined 64 polyp patients[(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 the ethmoid sinus percent opacification by CT analysis at Week 20
- Rescue treatment use (pooled ENLIGHTEN 1 and ENLIGHTEN 2)

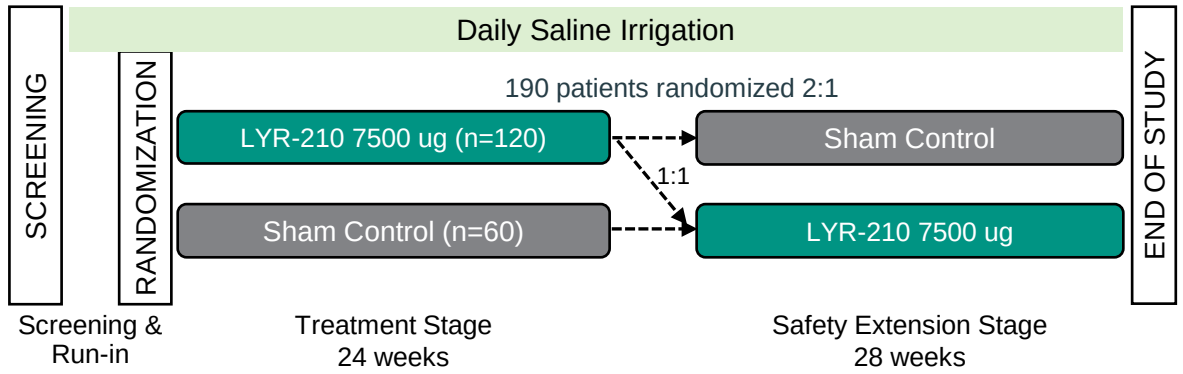
ENLIGHTEN 2 prespecifies a pooled analysis of polyp patients from both ENLIGHTEN 1 and ENLIGHTEN 2

- Pooled analysis included efficacy endpoints of 3CS, SNOT-22, CT, NCS[(3)], NPS[(4)]

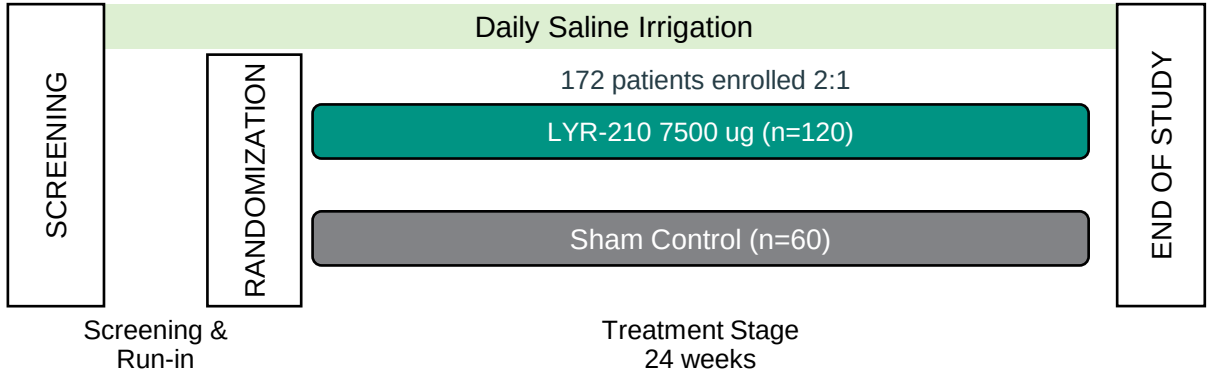
Highlights

- 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[(5)]



ENLIGHTEN 2[(6)]



(1) 35 and 29 patients with grade 1 nasal polyps enrolled in ENLIGHTEN 1 and ENLIGHTEN 2, respectively; study population represents 95% of CRS patients; (2) Three Cardinal Symptom Score is as a composite of nasal blockage/obstruction, facial pain/pressure, and nasal discharge; (3) Nasal Congestion Score; (4) Nasal Polyp Score; (5) NCT05219968; (6) NCT05295459

ENLIGHTEN 2: Patient Demographics & Baseline Characteristics

ITT Analysis Set	LYR-210 (n=111)	Sham (n=61)
Age in years (*mean, SD)*	50 (15.5)	49 (12.99)
Sex *(n, %)* Male Female	 65 (58.6) 46 (41.4)	 31 (50.8) 30 (49.2)
Race *(n, %)* White Black or African American	 94 (84.7) 9 (8.1)	 51 (83.6) 5 (8.2)
Region *(n, %)* North America European Union	 63 (56.8) 48 (43.2)	 31 (50.8) 30 (49.2)
Baseline 3CS Score (*mean, SD)*	6.5 (1.29)	7.2 (1.37)
Baseline SNOT-22 Score (*mean, SD)*	56.2 (17.38)	58.8 (22.21)
Baseline % Ethmoid Opacification Volume (CT) (*mean, SD)*	45.3 (19.28)	45.7 (18.04)

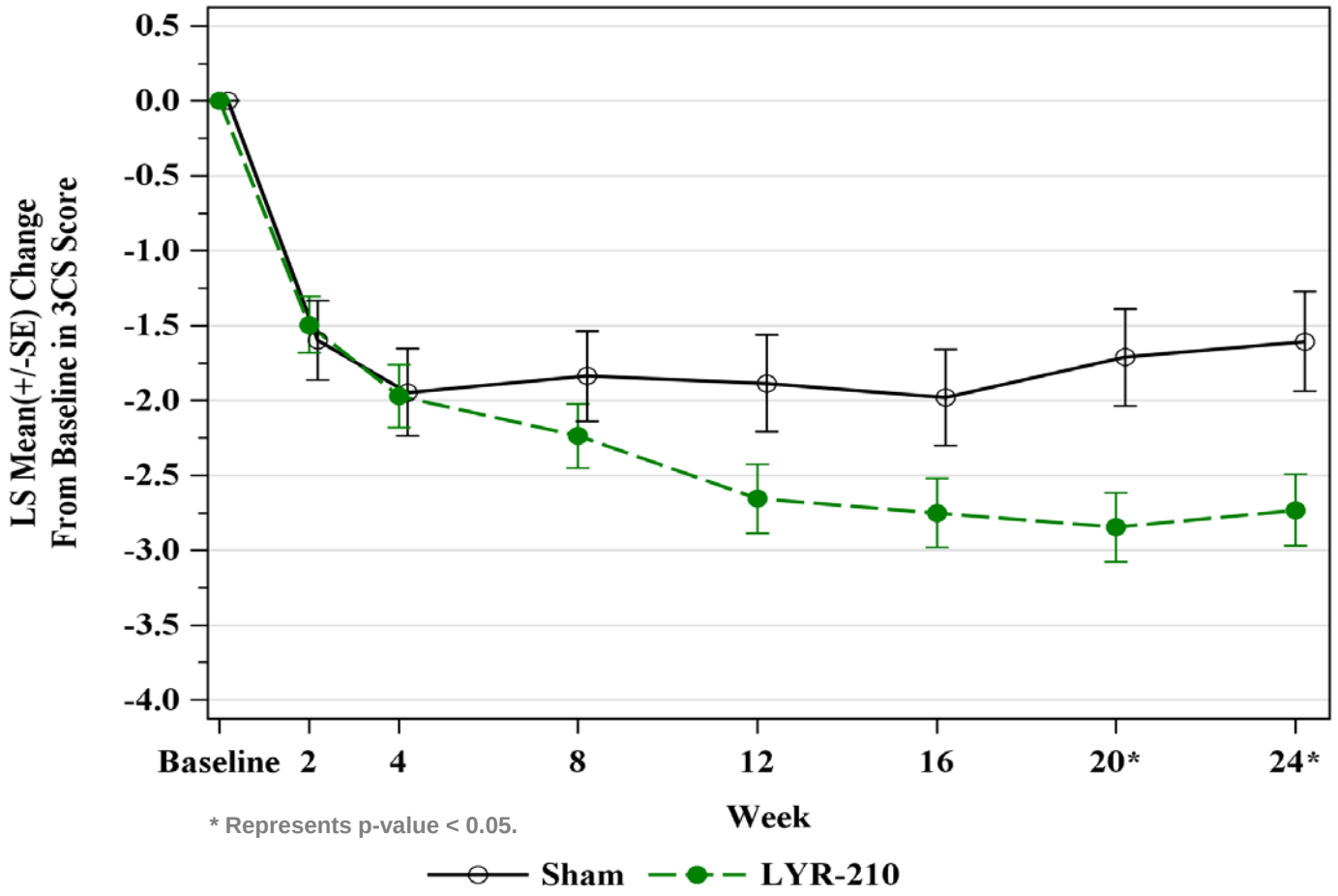
ENLIGHTEN 2: Most Frequent Adverse Events (≥5% of patients)

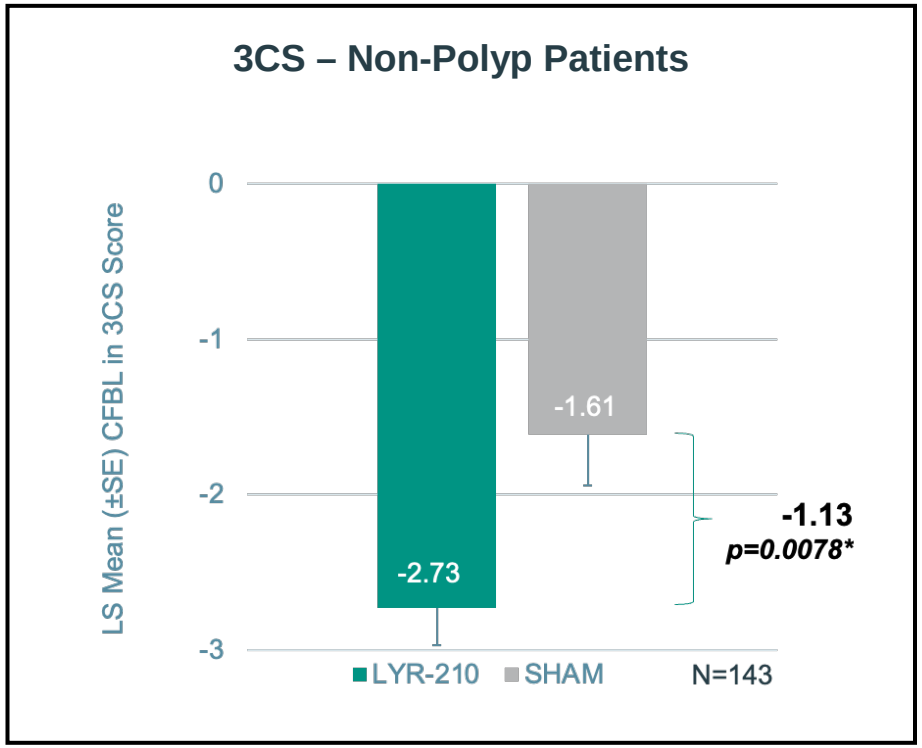
Favorable safety profile with no product-related serious adverse events

Safety Analysis Set (Preferred Term)	LYR-210 (n=111) n (%)	Sham (n=61) n (%)
Any treatment-emergent adverse events (TEAEs)	67 (60.4%)	27 (44.3%)
Epistaxis	18 (16.2%)	1 (1.6%)
Upper respiratory tract infection	10 (9.0%)	5 (8.2%)
Chronic sinusitis	8 (7.2%)	6 (9.8%)
Acute sinusitis	9 (8.1%)	3 (4.9%)
Nasopharyngitis	7 (6.3%)	4 (6.6%)
COVID-19	5 (4.5%)	4 (6.6%)
Headache	6 (5.4%)	3 (4.9%)

ENLIGHTEN 2: Change from Baseline in 3CS at Week 24 (Primary Endpoint)[1]

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



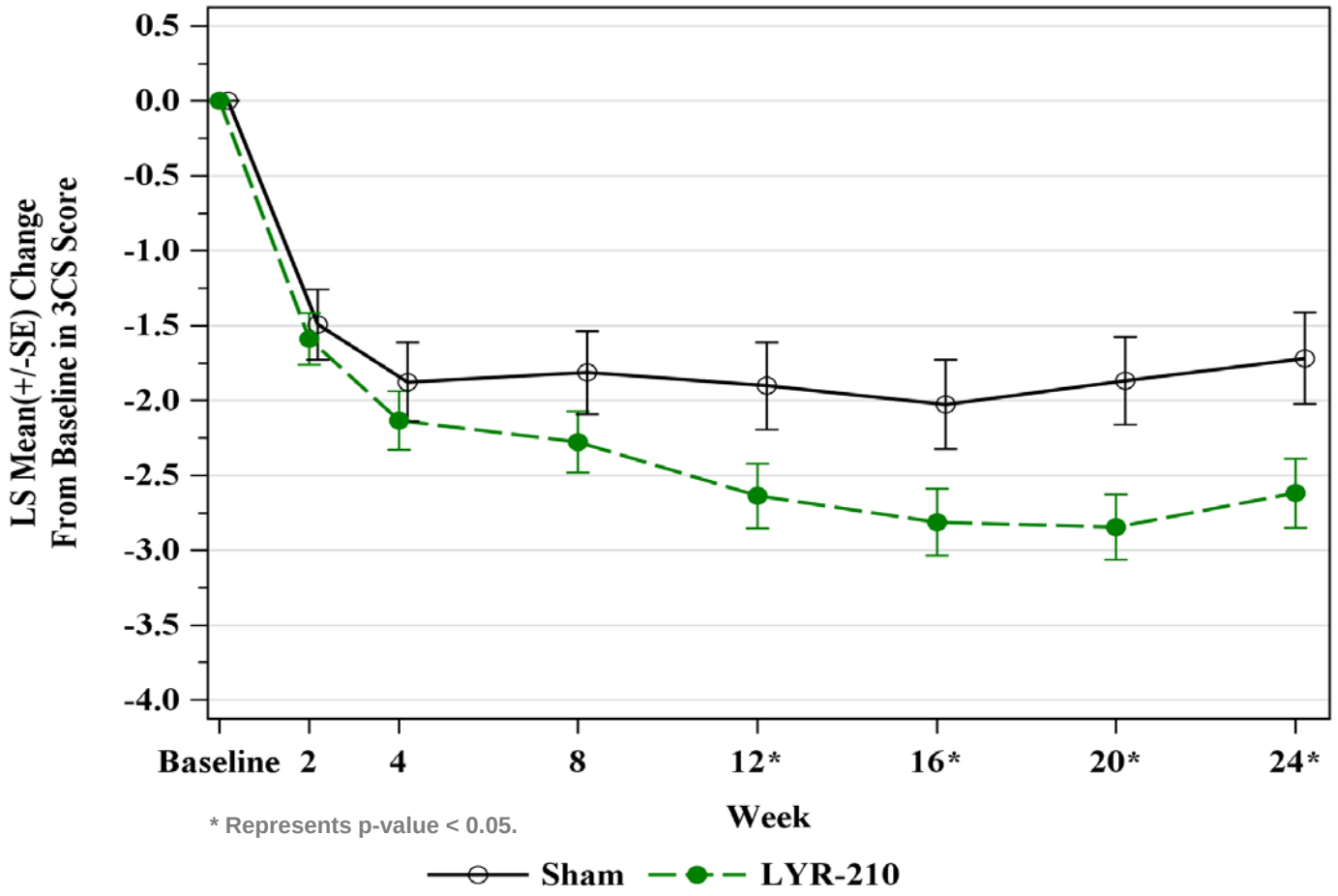


* Statistically significant

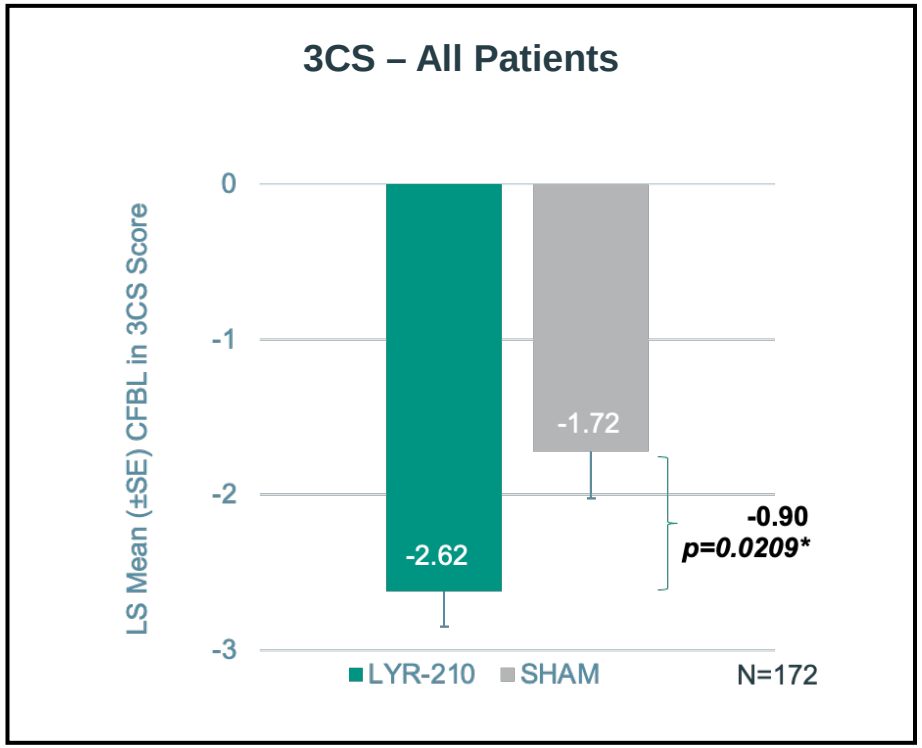
(1) Primary endpoint population is patients without nasal polyps.

ENLIGHTEN 2: Change from Baseline in 3CS at Week 24 for Full Population (1st Key Secondary Endpoint)(1)

Statistically significant improvement in 3CS at 24 weeks, with robust improvement over sham control starting at Week 12



* Represents p-value < 0.05.

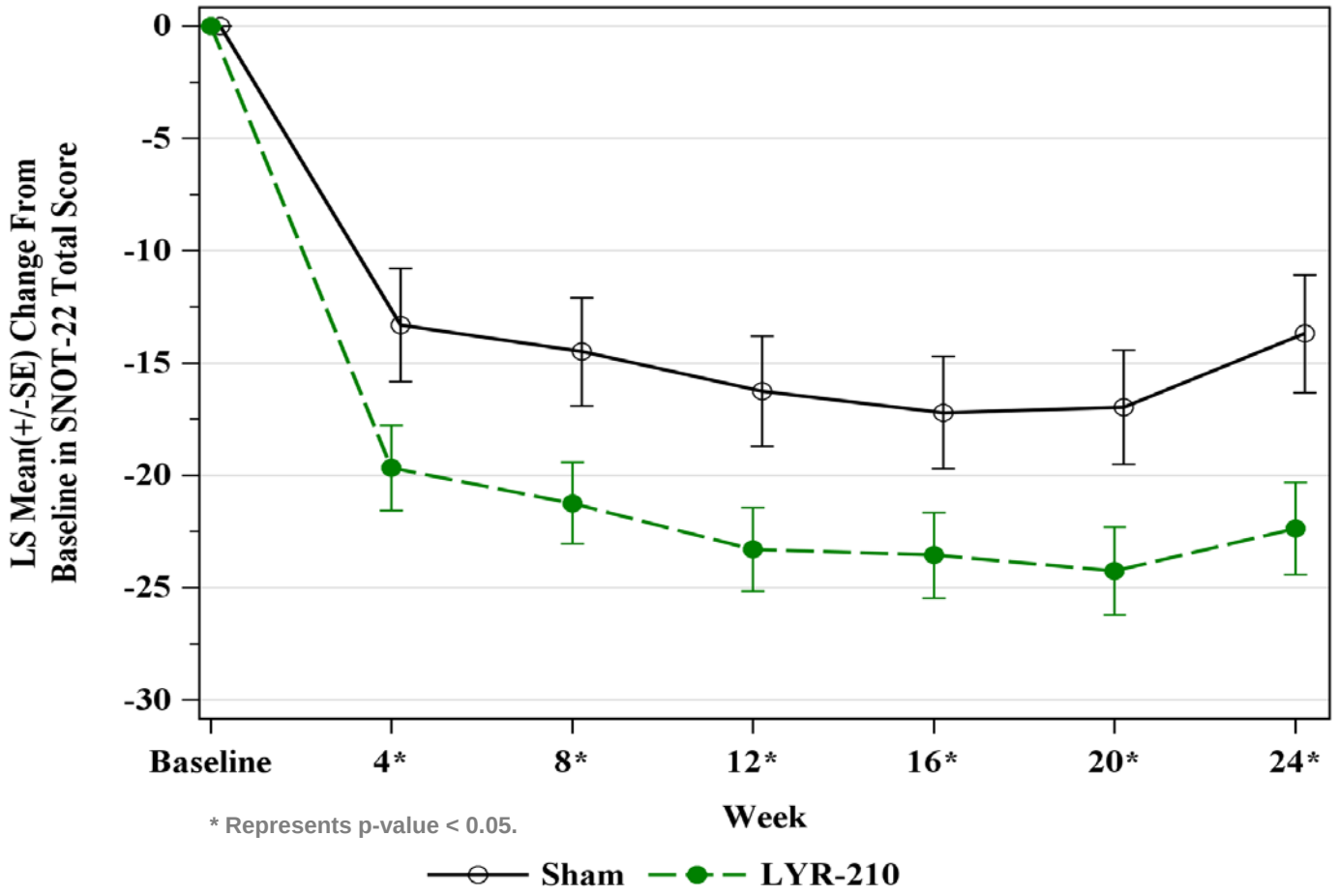


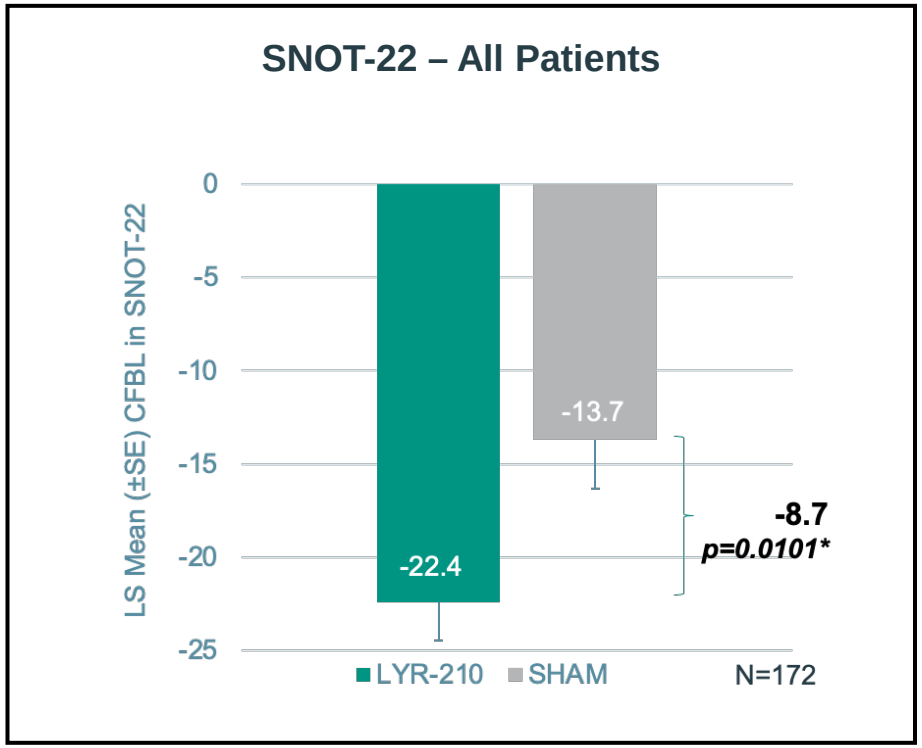
* Statistically significant

(1) Key secondary endpoint population is the intent-to-treat (ITT) analysis set (patients with or without Nasal Polyps).

ENLIGHTEN 2: Change from Baseline in SNOT-22 at Week 24 (2nd Key Secondary Endpoint)(1)

Statistically significant improvement in clinically-validated SNOT-22 score at 24 weeks, with robust improvement over sham control starting at Week 4



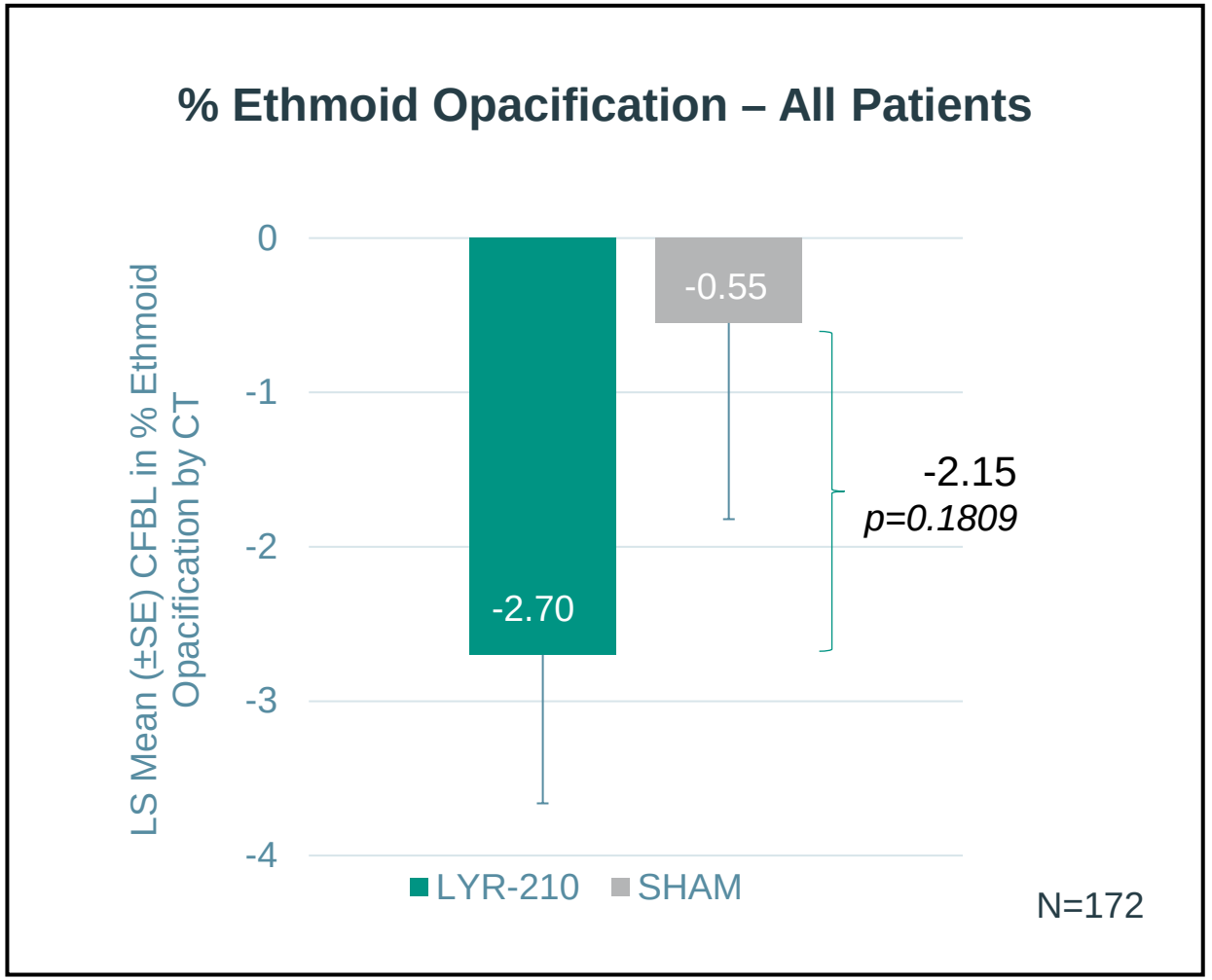


* Statistically significant

(1) Key secondary endpoint population is the intent-to-treat (ITT) analysis set (patients with or without Nasal Polyps).

ENLIGHTEN 2: Change in % Ethmoid Opacification at Week 20 (3rd Key Secondary Endpoint)(1)

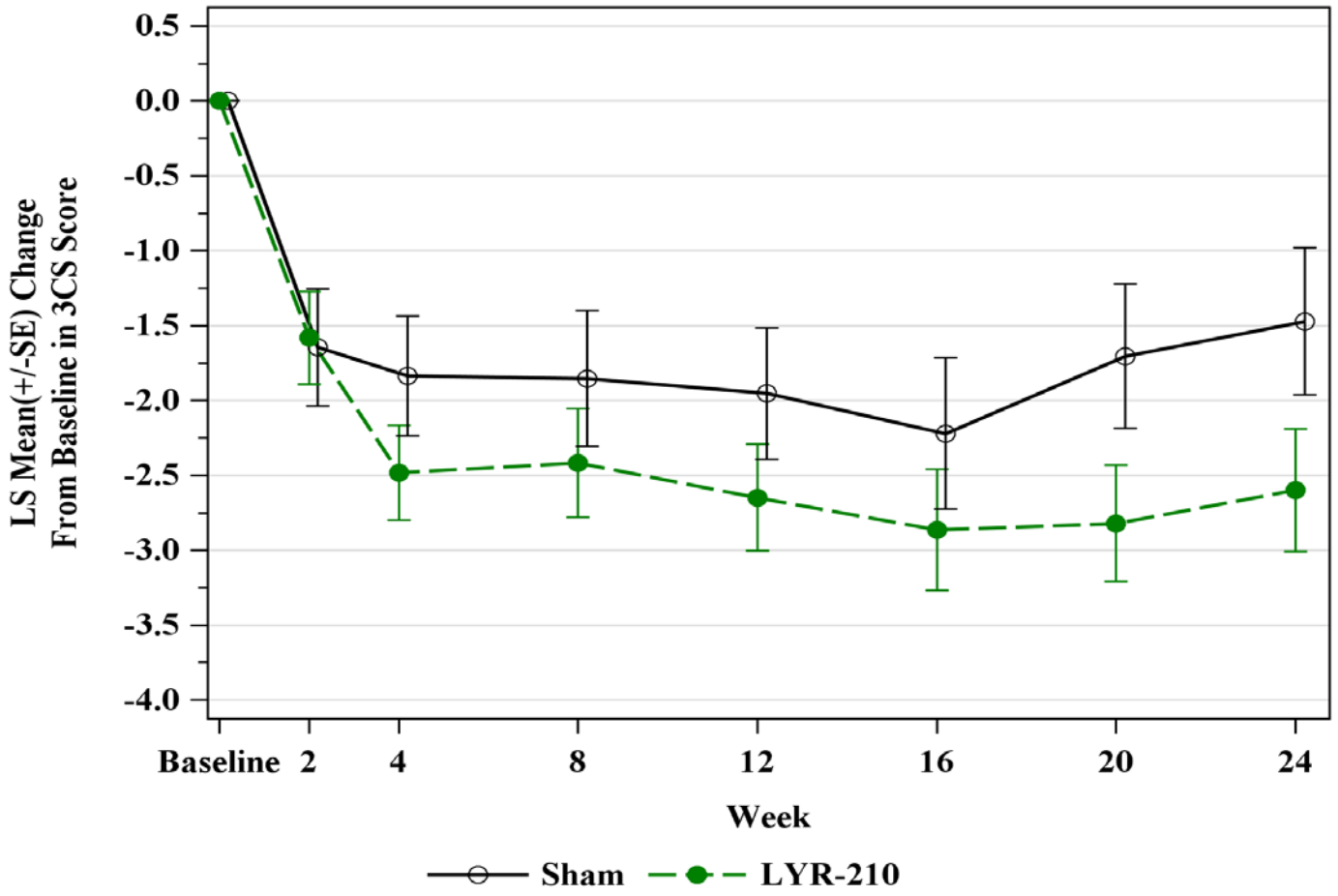
Numerical improvement in % ethmoid opacification by CT

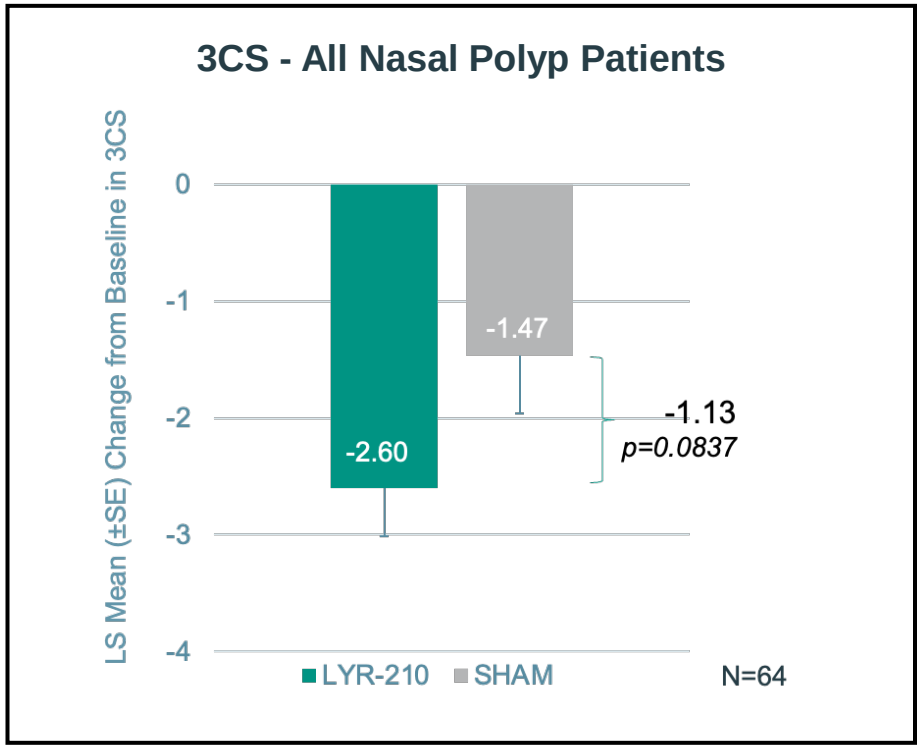


(1) Key secondary endpoint population is the intent-to-treat (ITT) analysis set (patients with or without Nasal Polyps).

ENLIGHTEN 1 and 2 Pooled CRS with Nasal Polyps:
Change from Baseline in 3CS Score at Week 24

Consistent, positive trend starting in Week 4 and further improvement at Weeks 20 and 24 with small sample size (n=64)

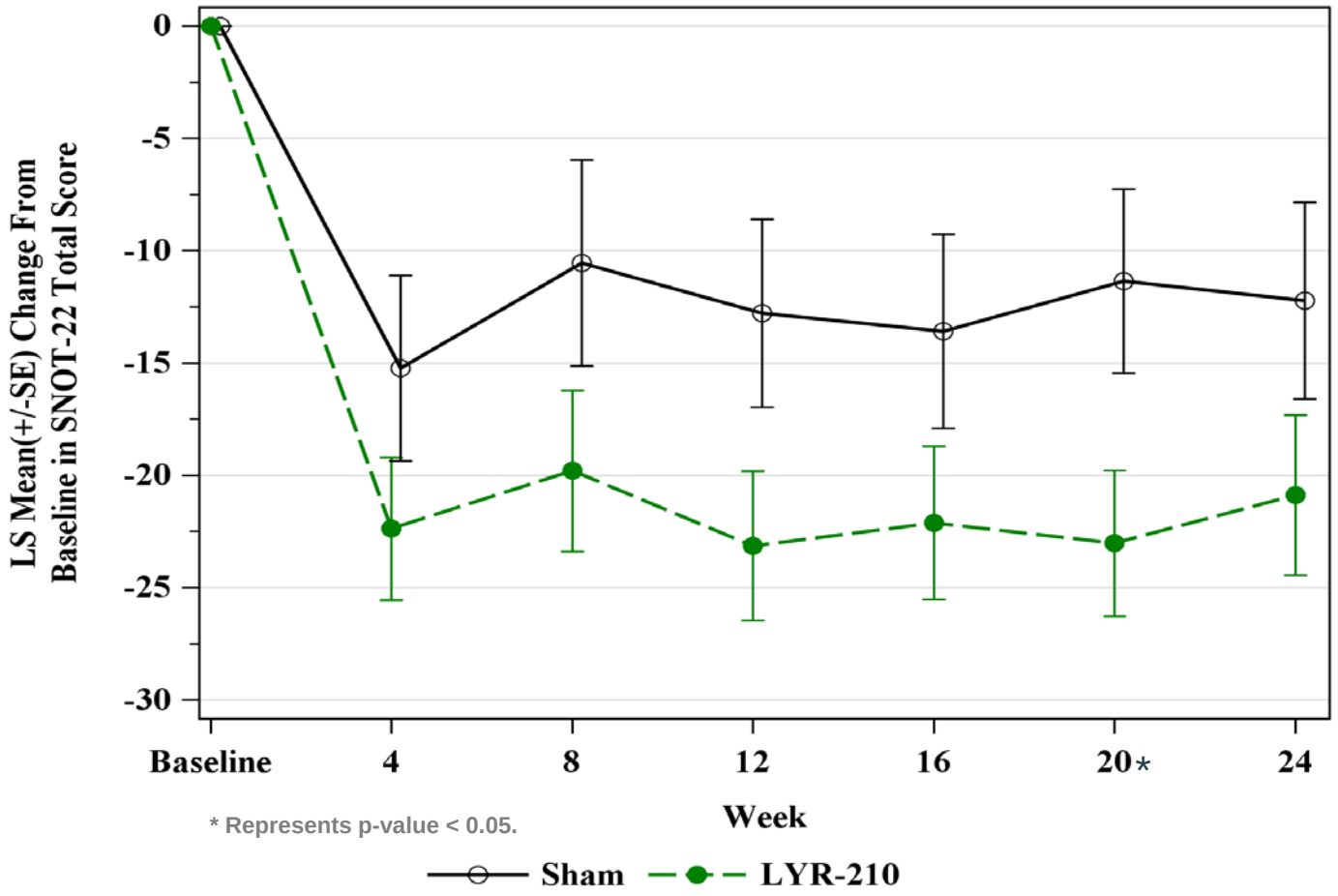


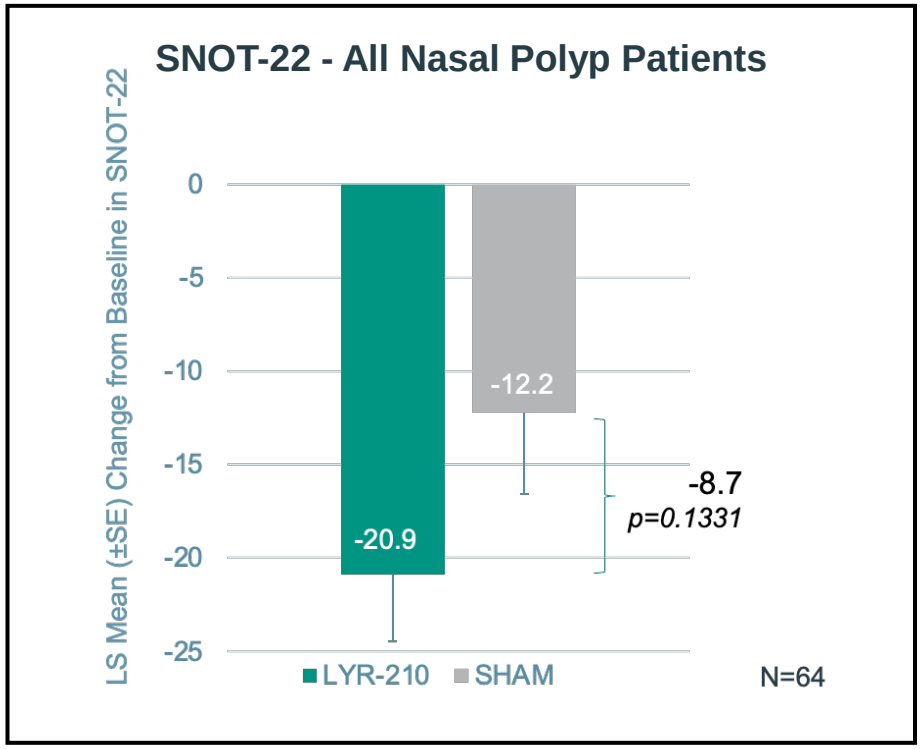


Analysis population is the pooled intent-to-treat (ITT) analysis set with nasal polyps.

ENLIGHTEN 1 and 2 Pooled CRS with Nasal Polyps:
Change from Baseline in SNOT-22 Score at Week 24

Consistent, positive trend in SNOT-22 score starting in Week 4 and throughout Week 24

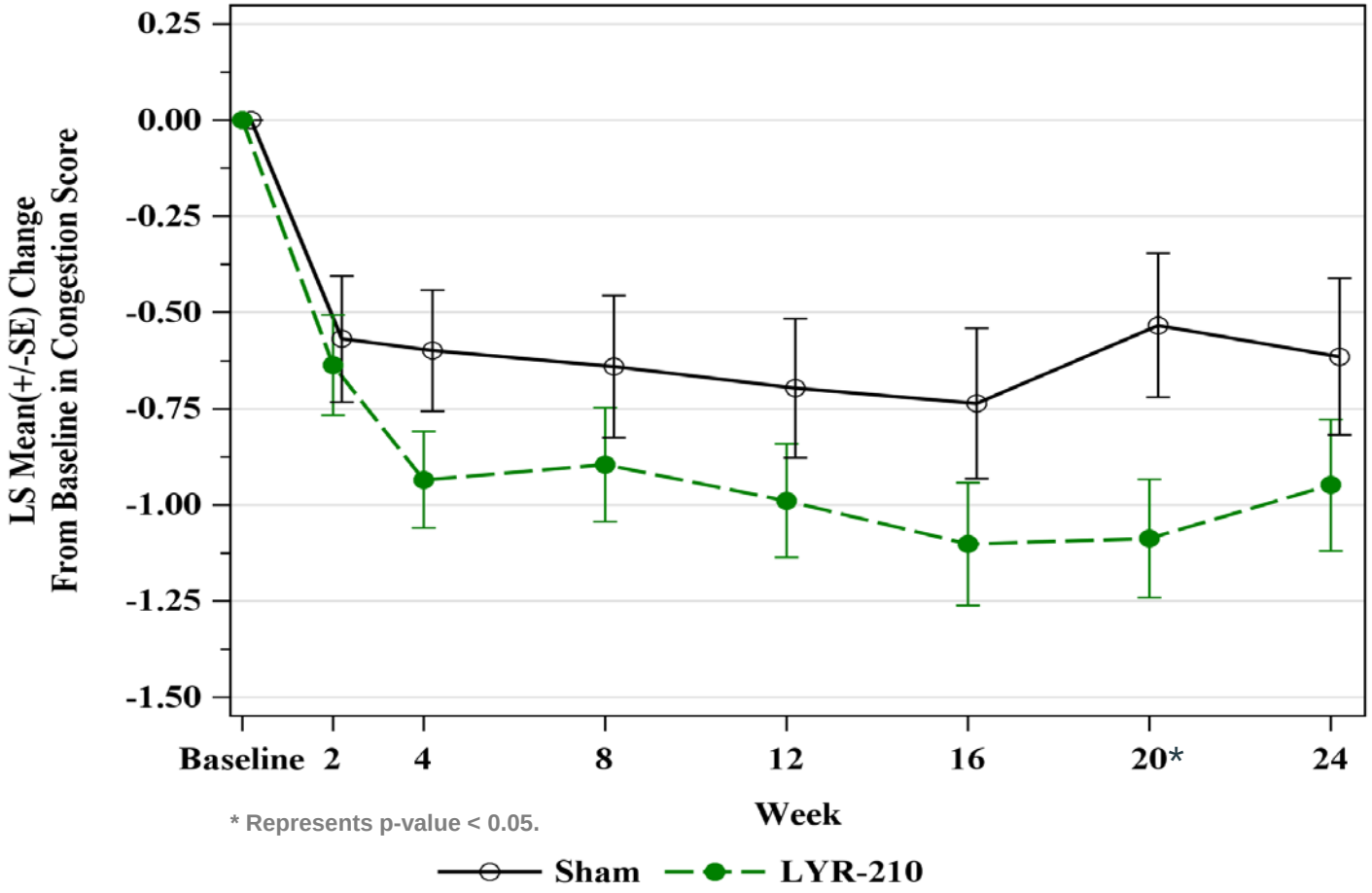


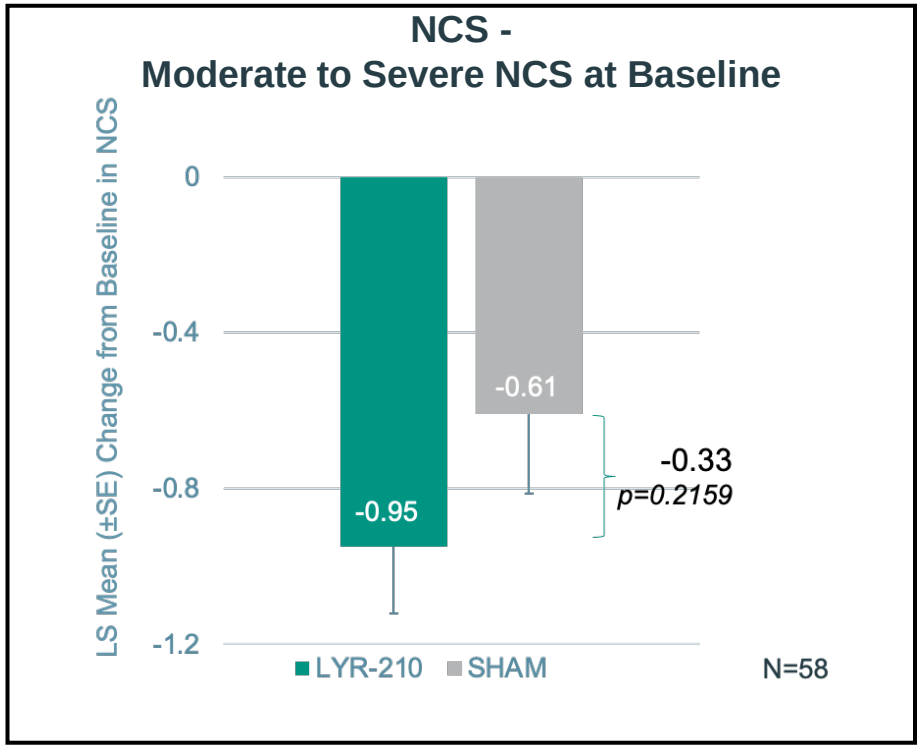


Analysis population is the pooled intent-to-treat (ITT) analysis set with nasal polyps.

ENLIGHTEN 1 and 2 Pooled CRS with Nasal Polyps:
CFBL in Nasal Congestion Score (NCS) at Week 24 (for Subjects with Baseline NCS ≥2)

Consistent, positive trend of improvement in nasal congestion score starting in Week 4 and throughout Week 24





Analysis population is the pooled intent-to-treat (ITT) analysis set with nasal polyps.

Summary of ENLIGHTEN 2 Results

- **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**
  - Demonstrated statistically significant results in 3CS at Week 24
    - Improvement in 3CS observed as early as Week 12 and sustained to Week 24
  - Demonstrated statistically significant results in SNOT-22 at Week 24
    - Improvement in SNOT-22 observed as early as Week 4 and sustained through Week 24
    - Clinically meaningful improvement, with almost twice the minimal clinically important difference observed at Week 24 (-22.4 points)
- **Numerical improvement in key secondary endpoint of change in % ethmoid opacification (CT)**
- **Well tolerated with no treatment-related serious adverse events reported in the study**
- **In the pooled ENLIGHTEN 1 and ENLIGHTEN 2 patients with grade 1 nasal polyps, consistent, positive trend in symptomatic endpoints starting in Week 4 and throughout Week 24**

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
- Est. 2H 2025: FDA meeting to align on strategy for CRS without Nasal Polyps
- Est. 1H 2026: Initiate Phase 3 Trial in CRS with Nasal Polyps(1)

(1) Subject to additional financing.

LYRA THERAPEUTICS