Clinical trial results:
ENLIGHTEN 1: 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

Summary

EudraCT number	2021-005906-83
Trial protocol	CZ PL ES AT
Global end of trial date	16 September 2024

Results information

Result version number	v1 (current)
This version publication date	26 June 2025
First version publication date	26 June 2025

Trial information

Trial identification

Sponsor protocol code	LYR-210-2021-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05219968
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Lyra Therapeutics, Inc.
Sponsor organisation address	480 Arsenal Way, Watertown, United States, MA 02472
Public contact	Senior Vice President, Clinical Affairs, Lyra Therapeutics, Inc., 1 617-393-4600, lyraclinical@lyratx.com
Scientific contact	Senior Vice President, Clinical Affairs, Lyra Therapeutics, Inc., 1 617-393-4600, lyraclinical@lyratx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 September 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 March 2024
Global end of trial reached?	Yes
Global end of trial date	16 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the efficacy of LYR-210, compared with a sham procedure control, in improving the 3 cardinal symptoms of chronic rhinosinusitis (CRS) in CRS participants without nasal polyps who had previously failed medical management.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and with all applicable laws and regulations of the locales and countries where the study was conducted, and in compliance with Good Clinical Practice Guidelines.

Background therapy:

All participants were provided with saline and instructions for daily intranasal saline irrigation as background treatment starting from screening through Week 52/End of Study.

Evidence for comparator: -

Actual start date of recruitment	27 January 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 51
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Czechia: 10
Country: Number of subjects enrolled	United States: 124
Worldwide total number of subjects	196
EEA total number of subjects	72

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	171
From 65 to 84 years	24
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Week 24 Treatment Period: 2:1 (LYR-210 to Sham) Randomization.
Safety Extension Period: Sham participants received LYR-210; LYR-210 participants received LYR-210 or Sham (1:1).

Pre-assignment

Screening details:

Screening and Run-In Period: 2 to 4 weeks before randomization and treatment procedure.

Period 1

Period 1 title	Week 24 Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind[1]
Roles blinded	Subject, Assessor

Blinding implementation details:

Due to the nature of the procedure, the treating Investigator/surgeon was not blinded to the treatment assignment. Efforts were made to keep the study coordinator and other study staff blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	LYR-210 up to 24 Weeks

Arm description:

Single administration of LYR-210 drug matrix (7500 µg).
LYR-210: LYR-210 drug matrix (mometasone furoate).
Background Therapy: Daily Saline Irrigation

Arm type	Experimental
Investigational medicinal product name	LYR-210
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Nasal use

Dosage and administration details:

Each LYR-210 contains a total mometasone furoate (MF) dose of 7500 µg. LYR-210 is intended to be administered bilaterally into the middle meatus by an otolaryngologist under endoscopic visualization using the provided single-use applicator. Once administered, each LYR-210 is designed to gradually deliver sustained doses of MF to the inflamed mucosal tissue over a 24-week resident time. Bilateral placement of LYR-210 is designed to deliver a total dose of 15,000 µg MF over the 24 weeks, or an average daily dose of 89 µg MF per human participant (or approximately 45 µg MF per nostril).

Arm title	Sham Procedure Control up to 24 Weeks

Arm description:

Single mock administration procedure.
Sham procedure control: Sham procedure control.
Background Therapy: Daily Saline Irrigation

Arm type	sham

No investigational medicinal product assigned in this arm

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: Due to the nature of the procedure, the treating Investigator was not blinded to the treatment assignment. Efforts were made to keep the study coordinator and other study staff blinded.

Number of subjects in period 1	LYR-210 up to 24 Weeks	Sham Procedure Control up to 24 Weeks
Started	130	66
Completed	103	63
Not completed	27	3
Consent withdrawn by subject	2	2
Physician decision	-	1
Adverse event, non-fatal	3	-
treatment administration failure/procedure not	6	-
Bilateral dislodgement	13	-
not specified	3	-

Period 2

Period 2 title	Safety Extension Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind[2]
Roles blinded	Subject, Assessor

Blinding implementation details:

Due to the nature of the procedure, the treating Investigator/surgeon was not blinded to the treatment assignment. Efforts were made to keep the study coordinator and other study staff blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	LYR-210 - LYR-210 Safety Extension

Arm description:

Repeat administration of LYR-210 at Week 24.
Participants randomized to LYR-210 during the Week 24 Treatment Period received LYR-210 in the Safety Extension following 1:1 re-randomization.
Background therapy: Saline rinse

Arm type	Experimental
Investigational medicinal product name	LYR-210
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Nasal use

Dosage and administration details:

Repeat administration of LYR-210 at Week 24.
Participants randomized to LYR-210 during the Week 24 Treatment Period received LYR-210 in the Safety Extension.
Background therapy: Saline rinse.

Arm title	LYR-210 - Sham Safety Extension

Arm description:

Crossover from LYR-210 to sham procedure control at Week 24.
Participants randomized to LYR-210 during the Week 24 Treatment Period received sham procedure control in the Safety Extension following 1:1 re-randomization.

Background therapy: Saline rinse.

Arm type	sham

No investigational medicinal product assigned in this arm

Arm title	Sham - LYR-210 Safety Extension

Arm description:

Crossover from sham procedure control to LYR-210 at Week 24.
Participants randomized to sham procedure control during the Week 24 Treatment Period received LYR-210 in the Safety Extension.
Background therapy: Saline rinse.

Arm type	Experimental
Investigational medicinal product name	LYR-210
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Nasal use

Dosage and administration details:

Crossover from sham procedure control to LYR-210 at Week 24.
Participants randomized to sham procedure control during the Week 24 Treatment Period received LYR-210 in the Safety Extension.
Background therapy: Saline rinse.

Notes:

[2] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: Due to the nature of the procedure, the treating Investigator was not blinded to the treatment assignment. Efforts were made to keep the study coordinator and other study staff blinded.

Number of subjects in period 2[3]	LYR-210 - LYR-210 Safety Extension	LYR-210 - Sham Safety Extension	Sham - LYR-210 Safety Extension
Started	42	42	52
Completed	34	39	42
Not completed	8	3	10
Consent withdrawn by subject	2	-	4
Adverse event, non-fatal	2	1	1
treatment administration failure/procedure not	-	1	4
Bilateral dislodgement	4	-	1
Lost to follow-up	-	1	-

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Following the Week 24 Treatment Period, 84 LYR-210 subjects and 52 sham subjects entered the Safety Extension Period. 40 LYR-210 subjects and 14 sham subjects did not enter the Safety Extension Period.

Baseline characteristics

Reporting groups	
Reporting group title	LYR-210 up to 24 Weeks
Reporting group description:	
Single administration of LYR-210 drug matrix (7500 µg). LYR-210: LYR-210 drug matrix (mometasone furoate). Background Therapy: Daily Saline Irrigation	
Reporting group title	Sham Procedure Control up to 24 Weeks
Reporting group description:	
Single mock administration procedure. Sham procedure control: Sham procedure control. Background Therapy: Daily Saline Irrigation	

Reporting group values	LYR-210 up to 24 Weeks	Sham Procedure Control up to 24 Weeks	Total
Number of subjects	130	66	196
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	113	58	171
From 65-84 years	16	8	24
85 years and over	1	0	1
Age continuous			
Units: years			
arithmetic mean	49.2	44.9	
standard deviation	± 13.52	± 14.42	-
Gender categorical			
Units: Subjects			
Female	56	31	87
Male	74	35	109

Subject analysis sets	
Subject analysis set title	ITT Analysis Set - LYR-210
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT Analysis Set was defined as all randomized participants who successfully received the IP (LYR-210 or control) on Day 1.	
Subject analysis set title	ITT Analysis Set - Sham control procedure
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT Analysis Set was defined as all randomized participants who successfully received the IP (LYR-210 or control) on Day 1.	

Subject analysis set title	ITT Analysis Set Without Nasal Polyps - LYR-210
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Analysis Set Without Nasal Polyps was defined as all randomized participants without nasal polyps who successfully received the IP (LYR-210 or control) on Day 1.

Subject analysis set title	ITT Analysis Set Without Nasal Polyps - Sham control procedure
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Analysis Set Without Nasal Polyps was defined as all randomized participants without nasal polyps who successfully received the IP (LYR-210 or control) on Day 1.

Reporting group values	ITT Analysis Set - LYR-210	ITT Analysis Set - Sham control procedure	ITT Analysis Set Without Nasal Polyps - LYR-210
Number of subjects	124	66	101
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	107	58	88
From 65-84 years	16	8	13
85 years and over	1	0	0
Age continuous Units: years			
arithmetic mean	50	45	50
standard deviation	± 13.65	± 14.42	± 13.49
Gender categorical Units: Subjects			
Female	53	31	45
Male	71	35	56

Reporting group values	ITT Analysis Set Without Nasal Polyps - Sham control procedure		
Number of subjects	54		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	47		
From 65-84 years	7		
85 years and over	0		

Age continuous Units: years			
arithmetic mean	45		
standard deviation	± 14.79		
Gender categorical Units: Subjects			
Female	24		
Male	30		

End points

End points reporting groups

Reporting group title	LYR-210 up to 24 Weeks
Reporting group description:	
Single administration of LYR-210 drug matrix (7500 µg). LYR-210: LYR-210 drug matrix (mometasone furoate). Background Therapy: Daily Saline Irrigation	
Reporting group title	Sham Procedure Control up to 24 Weeks
Reporting group description:	
Single mock administration procedure. Sham procedure control: Sham procedure control. Background Therapy: Daily Saline Irrigation	
Reporting group title	LYR-210 - LYR-210 Safety Extension
Reporting group description:	
Repeat administration of LYR-210 at Week 24. Participants randomized to LYR-210 during the Week 24 Treatment Period received LYR-210 in the Safety Extension following 1:1 re-randomization. Background therapy: Saline rinse	
Reporting group title	LYR-210 - Sham Safety Extension
Reporting group description:	
Crossover from LYR-210 to sham procedure control at Week 24. Participants randomized to LYR-210 during the Week 24 Treatment Period received sham procedure control in the Safety Extension following 1:1 re-randomization. Background therapy: Saline rinse.	
Reporting group title	Sham - LYR-210 Safety Extension
Reporting group description:	
Crossover from sham procedure control to LYR-210 at Week 24. Participants randomized to sham procedure control during the Week 24 Treatment Period received LYR-210 in the Safety Extension. Background therapy: Saline rinse.	
Subject analysis set title	ITT Analysis Set - LYR-210
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT Analysis Set was defined as all randomized participants who successfully received the IP (LYR-210 or control) on Day 1.	
Subject analysis set title	ITT Analysis Set - Sham control procedure
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT Analysis Set was defined as all randomized participants who successfully received the IP (LYR-210 or control) on Day 1.	
Subject analysis set title	ITT Analysis Set Without Nasal Polyps - LYR-210
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT Analysis Set Without Nasal Polyps was defined as all randomized participants without nasal polyps who successfully received the IP (LYR-210 or control) on Day 1.	
Subject analysis set title	ITT Analysis Set Without Nasal Polyps - Sham control procedure
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT Analysis Set Without Nasal Polyps was defined as all randomized participants without nasal polyps who successfully received the IP (LYR-210 or control) on Day 1.	

Primary: Change From Baseline (CFBL) in the 7-day Average Composite Score of 3 Cardinal Symptoms (3CS) in Participants Without Nasal Polyps

End point title	Change From Baseline (CFBL) in the 7-day Average Composite Score of 3 Cardinal Symptoms (3CS) in Participants Without Nasal Polyps

End point description:

The 3CS are nasal blockage/obstruction/congestion, anterior/posterior nasal discharge, and facial pain/pressure. The diary is completed daily by study participants throughout the study. Each symptom/each question is rated on a 4-point (0-3) scale where 0= none/absent symptoms, 1=mild symptoms, 2=moderate symptoms, and 3=severe symptoms. The composite score of 3CS is the sum of the three cardinal symptom scores.
The 3CS total score ranges from 0-9, with higher scores indicating worse symptoms.

End point type	Primary

End point timeframe:

Week 24

End point values	ITT Analysis Set Without Nasal Polyps - LYR-210	ITT Analysis Set Without Nasal Polyps - Sham control procedure		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	101	54		
Units: Change from Baseline in 3CS Score				
arithmetic mean (standard deviation)	-2.13 (± 2.172)	-2.06 (± 2.136)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

A negative change from baseline indicates an improvement from baseline (ie, favorable outcome).
The LS means, SEs, CIs, and p-values are from an MMRM for CFBL with the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction.
CFBL = change from baseline; CI = confidence interval; LS = least squares; MMRM = mixed model with repeated measures; SD = Standard Deviation

Comparison groups	ITT Analysis Set Without Nasal Polyps - LYR-210 v ITT Analysis Set Without Nasal Polyps - Sham control procedure
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8995
Method	Mixed models analysis

Secondary: CFBL in the 7-day Average Composite Score of 3CS in All Participants at Week 24.

End point title	CFBL in the 7-day Average Composite Score of 3CS in All Participants at Week 24.

End point description:

The 3CS are nasal blockage/obstruction/congestion, anterior/posterior nasal discharge, and facial pain/pressure. The diary is completed daily by study participants throughout the study. Each symptom/each question is rated on a 4-point (0-3) scale where 0= none/absent symptoms, 1=mild symptoms, 2=moderate symptoms, and 3=severe symptoms. The composite score of 3CS is the sum of the three cardinal symptom scores.
The 3CS total score ranges from 0-9, with higher scores indicating worse symptoms.

End point type	Secondary

End point timeframe:

Week 24

End point values	ITT Analysis Set - LYR-210	ITT Analysis Set - Sham control procedure		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	66		
Units: Change from Baseline in 3CS Score				
arithmetic mean (standard deviation)	-2.35 (± 2.278)	-1.83 (± 2.104)		

Statistical analyses

No statistical analyses for this end point

Secondary: CFBL in the 22-item Sino-Nasal Outcome Test (SNOT-22) Total Score at Week 24

End point title	CFBL in the 22-item Sino-Nasal Outcome Test (SNOT-22) Total Score at Week 24

End point description:

The SNOT-22 questionnaire is a 22-item disease-specific quality of life instrument. Each symptom is scored on a 6-point scale where 0 =no problem and 5 = problem as bad as it can be. The total SNOT-22 score is the sum of the 22 items and can range from 0 to 110 with higher scores indicating worse symptoms.

End point type	Secondary

End point timeframe:

Week 24

End point values	ITT Analysis Set - LYR-210	ITT Analysis Set - Sham control procedure		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	66		
Units: Change from Baseline in SNOT-22 score				
arithmetic mean (standard deviation)	-19.7 (± 21.67)	-15.7 (± 18.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: CFBL in the 3-D Volumetric CT Score at Week 20

End point title	CFBL in the 3-D Volumetric CT Score at Week 20

End point description:

The percent opacification of the bilateral anterior and posterior ethmoids will be assessed by 3-D volumetric CT analysis at baseline and Week 20.
A negative change from Baseline indicates improvement from Baseline.

End point type	Secondary

End point timeframe:

Week 20

End point values	ITT Analysis Set - LYR-210	ITT Analysis Set - Sham control procedure		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	66		
Units: Percent ethmoid opacification				
arithmetic mean (standard deviation)	-2.705 (± 10.9320)	-0.279 (± 9.9706)		

Statistical analyses

No statistical analyses for this end point

Secondary: Participants With Rescue Treatments for CRS Through Week 24

End point title	Participants With Rescue Treatments for CRS Through Week 24

End point description:

This endpoint is descriptively summarized per the prespecified plan. This includes participants that used systemic corticosteroid for any reason as well as participants that were recommended/underwent sinonasal surgery.

End point type	Secondary

End point timeframe:

Week 24

End point values	ITT Analysis Set - LYR-210	ITT Analysis Set - Sham control procedure		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	66		
Units: Participants				
number (not applicable)	12	7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported throughout the study, from the time the informed consent form (ICF) is signed until completion of all follow-up visits up to Week 52.

Adverse event reporting additional description:

Week 24 Treatment TEAEs: AEs that start during or after the LYR-210/Sham placement procedure but no later than 31 days after discontinuation of the first study treatment (up to 24 weeks).
Extension Period TEAEs: AEs that start on or after the second placement procedure but no later than 31 days after discontinuation of second study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	LYR-210 up to 24 Weeks

Reporting group description:

Single administration of LYR-210 drug matrix (7500 µg).
LYR-210: LYR-210 drug matrix (mometasone furoate).
Background Therapy: Daily Saline Irrigation

Reporting group title	Sham Procedure Control up to 24 Weeks

Reporting group description:

Single mock administration procedure.
Sham procedure control: Sham procedure control.
Background Therapy: Daily Saline Irrigation

Reporting group title	LYR-210 - LYR-210 Extension

Reporting group description:

Repeat administration of LYR-210 at Week 24.
Background Therapy: Daily Saline Irrigation

Reporting group title	LYR-210 - Sham Extension

Reporting group description:

Crossover from LYR210 to sham procedure control at Week 24.
Background Therapy: Daily Saline Irrigation

Reporting group title	Sham - LYR-210 Extension

Reporting group description:

Crossover from sham procedure control to LYR-210 at Week 24.
Background Therapy: Daily Saline Irrigation

Serious adverse events	LYR-210 up to 24 Weeks	Sham Procedure Control up to 24 Weeks	LYR-210 - LYR-210 Extension
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 124 (3.23%)	4 / 66 (6.06%)	2 / 42 (4.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal Cancer			

subjects affected / exposed	0 / 124 (0.00%)	0 / 66 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Cervical Vertebral Fracture			
subjects affected / exposed	0 / 124 (0.00%)	1 / 66 (1.52%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 124 (0.00%)	0 / 66 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax traumatic			
subjects affected / exposed	0 / 124 (0.00%)	1 / 66 (1.52%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib Fracture			
subjects affected / exposed	0 / 124 (0.00%)	2 / 66 (3.03%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 124 (0.00%)	0 / 66 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Disease			
subjects affected / exposed	1 / 124 (0.81%)	0 / 66 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Loss of Consciousness			
subjects affected / exposed	1 / 124 (0.81%)	0 / 66 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Migraine			
subjects affected / exposed	0 / 124 (0.00%)	0 / 66 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 124 (0.00%)	0 / 66 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 66 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 124 (0.81%)	0 / 66 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 66 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 124 (0.00%)	0 / 66 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eosinophilic pneumonia			
subjects affected / exposed	0 / 124 (0.00%)	0 / 66 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			

subjects affected / exposed	1 / 124 (0.81%)	0 / 66 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal Stenosis			
subjects affected / exposed	0 / 124 (0.00%)	1 / 66 (1.52%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 124 (0.00%)	0 / 66 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 124 (0.00%)	0 / 66 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 124 (0.00%)	0 / 66 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic Abscess			
subjects affected / exposed	1 / 124 (0.81%)	0 / 66 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical Device Site Joint Infection			
subjects affected / exposed	0 / 124 (0.00%)	1 / 66 (1.52%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	LYR-210 - Sham Extension	Sham - LYR-210 Extension	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 41 (7.32%)	3 / 48 (6.25%)	
number of deaths (all causes)	0	0	

number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal Cancer			
subjects affected / exposed	0 / 41 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical Vertebral Fracture			
subjects affected / exposed	0 / 41 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 41 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	0 / 41 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib Fracture			
subjects affected / exposed	0 / 41 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Disease			
subjects affected / exposed	0 / 41 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Loss of Consciousness			
subjects affected / exposed	0 / 41 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 41 (2.44%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 41 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 41 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 41 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophilic pneumonia			

subjects affected / exposed	0 / 41 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	0 / 41 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal Stenosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 41 (2.44%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic Abscess			
subjects affected / exposed	0 / 41 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical Device Site Joint Infection			
subjects affected / exposed	0 / 41 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	LYR-210 up to 24 Weeks	Sham Procedure Control up to 24 Weeks	LYR-210 - LYR-210 Extension
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 124 (62.90%)	26 / 66 (39.39%)	21 / 42 (50.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 124 (5.65%)	1 / 66 (1.52%)	1 / 42 (2.38%)
occurrences (all)	9	1	1
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	23 / 124 (18.55%)	7 / 66 (10.61%)	6 / 42 (14.29%)
occurrences (all)	29	8	8
Nasal Odour			
subjects affected / exposed	23 / 124 (18.55%)	0 / 66 (0.00%)	6 / 42 (14.29%)
occurrences (all)	27	0	7
Infections and infestations			
Acute Sinusitis			
subjects affected / exposed	14 / 124 (11.29%)	0 / 66 (0.00%)	2 / 42 (4.76%)
occurrences (all)	15	0	2
COVID-19			
subjects affected / exposed	10 / 124 (8.06%)	4 / 66 (6.06%)	3 / 42 (7.14%)
occurrences (all)	10	4	3
Chronis Sinusitis			
subjects affected / exposed	14 / 124 (11.29%)	3 / 66 (4.55%)	6 / 42 (14.29%)
occurrences (all)	19	4	7
Nasopharyngitis			
subjects affected / exposed	10 / 124 (8.06%)	6 / 66 (9.09%)	4 / 42 (9.52%)
occurrences (all)	11	6	4
Sinusitis			
subjects affected / exposed	13 / 124 (10.48%)	3 / 66 (4.55%)	4 / 42 (9.52%)
occurrences (all)	14	4	4

Upper Respiratory Tract Infection			
subjects affected / exposed	10 / 124 (8.06%)	10 / 66 (15.15%)	1 / 42 (2.38%)
occurrences (all)	11	13	1

Non-serious adverse events	LYR-210 - Sham Extension	Sham - LYR-210 Extension	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 41 (21.95%)	19 / 48 (39.58%)	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 41 (4.88%)	2 / 48 (4.17%)	
occurrences (all)	2	2	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 41 (4.88%)	4 / 48 (8.33%)	
occurrences (all)	2	6	
Nasal Odour			
subjects affected / exposed	0 / 41 (0.00%)	8 / 48 (16.67%)	
occurrences (all)	0	10	
Infections and infestations			
Acute Sinusitis			
subjects affected / exposed	0 / 41 (0.00%)	4 / 48 (8.33%)	
occurrences (all)	0	4	
COVID-19			
subjects affected / exposed	2 / 41 (4.88%)	1 / 48 (2.08%)	
occurrences (all)	2	1	
Chronis Sinusitis			
subjects affected / exposed	4 / 41 (9.76%)	4 / 48 (8.33%)	
occurrences (all)	5	5	
Nasopharyngitis			
subjects affected / exposed	1 / 41 (2.44%)	2 / 48 (4.17%)	
occurrences (all)	1	2	
Sinusitis			
subjects affected / exposed	2 / 41 (4.88%)	3 / 48 (6.25%)	
occurrences (all)	3	3	
Upper Respiratory Tract Infection			

subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1	1 / 48 (2.08%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2022	Changes to primary and secondary objectives. Information regarding primary and secondary endpoints updated. Updated safety endpoints. Added study design rationale section. Updated inclusion and exclusion criteria. Clarifications to prohibited medications. Section Methods and Procedures updated. Section Study assessments, endpoints and activities updated. Removed the requirement for all removed drug matrices to be returned to the Sponsor. Clarified AE meaning. Recalculated sample size. Updated statistical considerations section. Schedule of Assessments updated. Questionnaires updated.
20 July 2022	Spain specific protocol amendment. Clarified that nonsedating antihistamines included second, third, and fourth generation antihistamines. Removed "Interim Analysis" section from the Protocol. Edited wording to adjust with Clinical Trials Facilitation and Coordination Group guidelines for male contraception.
25 July 2022	Czech Republic specific protocol amendment. Added "effective treatment will not be withheld from study participants solely for entering the study." Added a bullet point that allowed for beta-agonists such as LABA and SABA in COPD and asthma patients. Added asthma to the list of patients that are allowed to use inhaled anticholinergic medication. Revised the statement regarding the run-in period to "if a patient requires rescue medication, he/she will not be enrolled into the study." Added "Discontinuation of Study Participants" section that addressed the withdrawal of patients from the study. Removed "Interim Analysis" section from the Protocol.
09 March 2023	Updated inclusion and exclusion criteria. Updated permitted and prohibited medications. Updated Methods and procedures section. Added information on safety extension treatment. Added "Discontinuation of Study Participants" section. Updated Study assessments, endpoints, and activities section. Clarified protocol deviations. Removed "Interim Analysis" section from the Protocol. Updated Schedule of Assessments. Clarified nasal polyp grading. Contraception and pregnancy information clarified for US and EU. Edited male contraception information to adjust with Clinical Trials Facilitation and Coordination Group guidelines for male contraception.

31 October 2023	Changes in the body of the document were updated in the synopsis. A subsection was added to clarify the first 24-week treatment analysis and database lock. Updated Table 1 (Attributes of the Primary Estimand) to mention that data post-rescue would be imputed with the participants' worst observed score if rescue treatment was required. Removed the CFBL in the 3 individual components of the 3CS score endpoints. Added rescue treatment requirement through Week 24 endpoint. The statistical testing will be conducted from pooled studies. Clarified that the key secondary and secondary endpoints were to be analyzed for all participants. Added "descriptive summary of efficacy data from the safety extension portion" as an endpoint (#23). Updated the analysis method to MMRM. Added "interim analysis" section to the Protocol. No interim analysis was planned. Updated footnote for follow-up CT. Updated footnote for ocular exam to allow for exams to be performed outside of the visit window in case of scheduling issues.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported