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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Not Applicable

Trial Indication(s)

Ulcerative colitis

Protocol Number

CLYS006X2202

Protocol Title

A randomized, multi-center, subject and investigator-blinded, placebo-controlled, parallel-group study to assess the efficacy safety and tolerability of LYS006 in patients with mild to moderate ulcerative colitis

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase 2

Study Start/End Dates

Study Start Date: February 03, 2020 (Actual)
Primary Completion Date: November 07, 2022 (Actual)
Study Completion Date: November 07, 2022 (Actual)

Reason for Termination (If applicable)

Sponsor decision due to strategic considerations

Study Design/Methodology

This was a randomized, placebo-controlled, patient and investigator blinded, multicenter, non-confirmatory, parallel group, proof of concept study in patients with mild to moderate ulcerative colitis. This study consisted of a screening period of up to 4 weeks (minimum one week), an 8-week treatment period followed by a 30-day post treatment period safety follow up. The total duration for each patient in the study was up to 16 weeks.

At the beginning of the treatment period, patients were randomized to either 20 mg LYS006 twice a day (BID) or matching placebo (BID) in a randomization ratio of 2:1. The treatment period was reduced from 12 to 8 weeks in protocol amendment 1. This was based on the clinical consensus to assess efficacy (clinical remission rate) in ulcerative colitis patients at Week 8.

Centers

9 centers in 6 countries: Czech Republic(2), Germany(1), Poland(3), Bulgaria(1), Russia(1), Slovakia (Slovak Republic)(1)

Objectives:

The primary objective of the trial was to assess the induction of clinical remission by LYS006 in patients with mild to moderate ulcerative colitis compared to placebo.

The secondary objective of the trial was to assess safety and tolerability of LYS006 in patients with mild to moderate ulcerative colitis compared to placebo.

Test Product (s), Dose(s), and Mode(s) of Administration

Participants received oral dose twice daily of LYS006 20 mg or matching placebo. Participants took 4 capsules of 5 mg at each dose to make up to 20 mg.

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Statistical Methods

The primary endpoint of this study was the clinical remission rate at the EoT visit (Week 12 for original protocol and Week 8 for subsequent protocol amendments) using the total Mayo score, i.e., the proportion of patients who reached a total Mayo score of 2 points or lower, with no individual subscore exceeding one point, at the EoT visit.

The binary endpoint of clinical remission rate at the EoT visit was modelled with binomial distribution and analyzed via the Bayesian approach with baseline total Mayo score and treatment group as explanatory variables, to compare the clinical remission rates between the LYS006 and placebo groups. The clinical remission rate for the LYS006 group was given a neutral prior, and the clinical remission rate for the placebo group was given an informative prior derived via the meta-analytic predictive (MAP) approach (i.e., historical placebo data was used to supplement the placebo arm data).

The incidence of treatment-emergent AEs (TEAEs) (new or worsening after first dose) was summarized by system organ class (SOC) and/or preferred term (PT), maximum severity and by treatment. Serious AEs (if any), non-serious AEs, AEs leading to study drug discontinuation, drug-related AEs as well as new renal and hepatic/pancreatic events were tabulated by treatment.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

- Male and female subjects 18-75 years of age with an established diagnosis of ulcerative colitis at least 3 months prior to screening are eligible for the study.
- Patients must have active disease with a full Mayo Score between 5 and 10 (inclusive) with an endoscopy score of 2 or 3; rectal bleeding and stool frequency scores 1 to 3 and a physician's global assessment of 1 or 2.
- Patients must have responded inadequately to conventional therapy with oral 5-ASA prior to screening.

Key Exclusion Criteria:

- Has previous diagnosis with Crohn's disease, indeterminate colitis, microscopic colitis or acute diverticulitis based on medical history.
- History of toxic megacolon, abdominal abscess, symptomatic colonic stricture, or stoma; history or is at risk of colectomy.
- Treatment with biologics within 3 months or 5 half-lives (whichever is longer) prior to screening endoscopy, non-biologics advanced

therapies within 4 weeks prior to screening endoscopy, systemic immunosuppressant or immunomodulator within 6 week, topical treatment with 5-ASA or steroids within 2 weeks prior to screening endoscopy

Participant Flow Table

Overall Study

	LYS006 20mg	Placebo	Total
Arm/Group Description	LYS006 20mg oral dose, twice daily	Placebo oral dose, twice daily	
Started	16	7	23
Completed	12	7	19
Not Completed	4	0	4
Adverse Event	1	0	1
Physician Decision	1	0	1
Withdrawal by Subject	2	0	2

Baseline Characteristics

	LYS006 20mg	Placebo	Total
Arm/Group Description	LYS006 20mg oral dose, twice daily	Placebo oral dose, twice daily	
Number of Participants [units: participants]	16	7	23
Baseline Analysis Population Description			
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation			

	38.3±12.20	45.7±12.37	40.6±12.46
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Female	8	5	13
Male	8	2	10
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
White	16	7	23

Primary Outcome Result(s)

Clinical remission rate at the End of the study treatment

Description	The Mayo score is an instrument designed to measure activity of ulcerative colitis. The Mayo score comprises of four sub scores: stool frequency, rectal bleeding, endoscopic findings and the Physician's Global Assessment (PhGA). Each sub score is graded from 0 to 3 with higher scores indicating more severe disease. The full Mayo score is the sum of four sub scores, ranging from 0 to 12. Clinical remission is defined as a full Mayo score of 2 points or lower, with no individual subscore exceeding one point. The clinical remission rate is expressed as percentage of participants. The binary endpoint of clinical remission rate (Yes/No) at the EoT visit was modelled with binomial distribution and analyzed via the Bayesian approach with baseline total Mayo score and treatment group as explanatory variables, to compare the remission rates between the LYS006 and placebo groups.
Time Frame	Week 8
Analysis Population Description	The PD analysis set included all participants who received any study drug and had no protocol deviations with relevant impact on PD data.

	LYS006 20mg	Placebo
Arm/Group Description	LYS006 20mg oral dose, twice daily	Placebo oral dose, twice daily
Number of Participants Analyzed [units: participants]	14	7
Clinical remission rate at the End of the study treatment (units: Percentage of participants)	**Number** **(90% Confidence Interval)**	**Number** **(90% Confidence Interval)**
	8.95 (0.87 to 23.31)	12.24 (5.67 to 24.12)

Statistical Analysis

Groups	LYS006 20mg, Placebo	
Type of Statistical Test	Other	
Non-Inferiority/Equivalence Test	A Bayesian analysis of clinical remission rate (based on total Mayo score) with binomial distribution, was modelled with baseline total Mayo score and treatment group as explanatory variables, to compare the remission rates between LYS006 and placebo groups.	
P Value	0.314	Posterior probability that clinical remission rate is better than placebo: Prob (diff>0)
Method	Other Bayesian analysis	
Other Posterior estimate treatment difference	-3.29	90% credible intervals are reported on the treatment difference
90 % Confidence Interval 2-Sided	-18.02 to 13.23	

Statistical Analysis

Groups	LYS006 20mg, Placebo	
Type of Statistical Test	Other	
Non-Inferiority/Equivalence Test	A Bayesian analysis of clinical remission rate (based on total Mayo score) with binomial distribution, was modelled with baseline total Mayo score and treatment group as explanatory variables, to compare the remission rates between LYS006 and placebo groups.	
P Value	0.037	Posterior probability that clinical remission rate >15% over placebo: Prob (diff>0.15)
Method	Other Bayesian analysis	
Other Posterior estimate treatment difference	-3.29	90% credible intervals are reported on the treatment difference
90 % Confidence Interval 2-Sided	-18.02 to 13.23	

Secondary Outcome Result(s)

Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs)

Description	Number of participants with treatment emergent AEs, AEs led to study treatment discontinuation, SAEs and SAEs led to study treatment discontinuation.
Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of approximately 115 days for participants treated for 12 weeks and up to a maximum duration of approximately 87 days for participants treated for 8 weeks.

Analysis Population Description	The safety analysis set included all participants that received any study drug.

	LYS006 20mg	Placebo
Arm/Group Description	LYS006 20mg oral dose, twice daily	Placebo oral dose, twice daily
Number of Participants Analyzed [units: participants]	16	7
Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs) (units: participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
At least one AE	7 (43.75%)	5 (71.43%)
At least one SAE	0 (%)	0 (%)
AE leading to discontinuation	2 (12.5%)	0 (%)
SAE leading to discontinuation	0 (%)	0 (%)

Safety Results

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of approximately 115 days for participants treated for 12 weeks and up to a maximum duration of approximately 87 days for participants treated for 8 weeks.
Source Vocabulary for Table Default	MedDRA (25.1)

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Collection Approach for Table Default Systematic Assessment

All-Cause Mortality

	LYS006 20 mg N = 16	Placebo N = 7	Total N = 23
Arm/Group Description	LYS006 20 mg oral dose, twice daily	Placebo oral dose, twice daily	Total
Total Number Affected	0	0	0
Total Number At Risk	16	7	23

Serious Adverse Events

No Serious Adverse Events were observed in the study

Other (Not Including Serious) Adverse Events

Frequent Event Reporting Threshold 0%

	LYS006 20 mg N = 16	Placebo N = 7	Total N = 23
Arm/Group Description	LYS006 20 mg oral dose, twice daily	Placebo oral dose, twice daily	Total
Total # Affected by any Other Adverse Event	7	5	12

Total # at Risk by any Other Adverse Event	16	7	23
Cardiac disorders			
Atrioventricular block first degree	0 (0.00%)	1 (14.29%)	1 (4.35%)
Gastrointestinal disorders			
Colitis ulcerative	3 (18.75%)	1 (14.29%)	4 (17.39%)
Vomiting	1 (6.25%)	0 (0.00%)	1 (4.35%)
General disorders and administration site conditions			
Pyrexia	1 (6.25%)	0 (0.00%)	1 (4.35%)
Hepatobiliary disorders			
Drug-induced liver injury	0 (0.00%)	1 (14.29%)	1 (4.35%)
Infections and infestations			
Nasopharyngitis	0 (0.00%)	1 (14.29%)	1 (4.35%)
Upper respiratory tract infection	1 (6.25%)	0 (0.00%)	1 (4.35%)
Investigations			
Faecal calprotectin increased	0 (0.00%)	1 (14.29%)	1 (4.35%)
Urine protein/creatinine ratio increased	0 (0.00%)	1 (14.29%)	1 (4.35%)
Musculoskeletal and connective tissue disorders			
Pain in extremity	1 (6.25%)	0 (0.00%)	1 (4.35%)
Nervous system disorders			
Headache	1 (6.25%)	0 (0.00%)	1 (4.35%)

Conclusion:

The primary efficacy endpoint was not achieved in this study at the time of early termination. There was no statistically significant difference in the clinical remission rate based on the total Mayo score (covering the 4 components of stool frequency, rectal bleeding, endoscopic findings and PhGA) between LYS006 20 mg BID and placebo at end of treatment (EoT). Clinical remission at EoT was achieved in 1 out of 14 patients (7.1%) and 1 out of 7 patients (14.3%) in the LYS006 and Placebo treatment groups, respectively.

LYS006 was generally well tolerated in patients with mild to moderate ulcerative colitis with an acceptable safety profile and no new safety signals identified.

Date of Clinical Trial Report

21-August-2023