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Sponsor

Novartis

Generic Drug Name

LYS006

Trial Indication(s)

Inflammatory acne

Protocol Number

CLYS006X2201

Protocol Title

A randomized, subject and investigator blinded, placebo controlled, multi-center study in parallel groups to assess the efficacy and safety of LYS006 in patients with moderate to severe inflammatory acne

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: September 10, 2018 (Actual)
Primary Completion Date: February 24, 2022 (Actual)
Study Completion Date: March 09, 2022 (Actual)

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Study Design/Methodology

This was a randomized, placebo-controlled, subject- and investigator-blinded, multicenter, nonconfirmatory, parallel group, and proof-of-concept study in adult patients with moderate to severe inflammatory acne. After an initial screening period (up to 4 weeks), subjects were treated with LYS006 or matching placebo for 12 consecutive weeks to assess preliminary clinical efficacy, safety, and tolerability in the targeted subject population. At the beginning of the treatment period, subjects were randomized to one of three treatment groups, i.e., LYS006 20 mg twice daily (BID), LYS006 2 mg BID or matching placebo in a 3:1:3 ratio. After treatment period completion, all subjects entered a post-treatment safety follow-up period of 4 weeks without study drug administration. The maximum duration of study participation was 20 weeks. Study completion was defined as when the last subject completed his/her study completion visit, and any repeat assessments associated with this visit were documented and followed-up appropriately by the investigator, or in the event of an early study termination decision, the date of that decision.

Centers

18 centers in 6 countries: United States(8), Germany(4), Hungary(2), Netherlands(1), Czech Republic(1), France(2)

Objectives:

Primary objective

To assess the efficacy of LYS006 versus placebo on facial inflammatory lesion counts in subjects with moderate to severe inflammatory acne.

Secondary objective

To assess the safety and tolerability of LYS006 in subjects with moderate to severe inflammatory acne.

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

- LYS006, 2 or 20 mg BID, oral administration for 12 weeks, hard gelatin capsules

- Matching placebo

Statistical Methods

The primary variable was the natural log transformed total inflammatory facial lesion counts (sum of papules, pustules, and nodules) at Week 12.

The primary analyses were based on on-treatment data. Data recorded after a subject discontinued study treatment were not included in the primary analyses. This corresponds to the aim of this proof of concept of assessing the effect of LYS006 when taken as planned versus placebo used alone.

Data up to Week 12 were included in a Bayesian mixed effect model for repeated measures (MMRM) for the comparison of LYS006 high dose group versus placebo group at 12 weeks, which is of primary interest. Data from the LYS006 low dose group were also included in this primary model but were mainly summarized with descriptive statistics.

The incidence of treatment-emergent AEs (TEAEs) (new or worsening after first dose) was summarized by system organ class (SOC) and preferred term (PT).

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Male and female subjects aged 18 to 45 years of age inclusive, and otherwise in good health as determined by medical history, physical examination, vital signs, ECGs and laboratory tests at screening.
- Body weight between 50 and 120 kg, both inclusive, at screening.
- Patients with papulo-pustular acne vulgaris (inflammatory acne) presenting with 20 to 100 facial inflammatory lesions (papules, pustules and nodules) at baseline, no more than 2 facial inflammatory nodules or cysts at screening and baseline, and a minimun number of 10 non-inflammatory facial lesions (open and closed comedones).
- Patients who are candidates for systemic treatment and for whom in the opinion of the investigator, an appropriate previous treatment with topical anti-acne medication failed, or was not well tolerated, or is not indicated (e.g., due to large body surface area affected, e.g., on the back)
- Patients with Grade 3 (moderate) or Grade 4 (severe) IGA score assessed by the investigator at screening and baseline.

Exclusion criteria:
- Appropriate wash out periods are required for investigational drugs, any oral/systemic treatment for acne, systemic or lesional injected (for acne) corticosteroids or systemic immunomodulators, any systemic hormonal treatments, previous treatment with biologics, oral retinoids (in particular isotretinoin) and any topical anti-acne treatment.
- Previous surgical, physical (such as ThermaClear™), light (including blue or UV light, photodynamic therapy or laser therapy within 4 weeks prior to baseline
- Use of facial medium depth chemical peels (excluding home regimens) within 3 months prior to baseline.
- Any other forms of acne
- Any severe, progressive or uncontrolled medical or psychiatric condition or other factors at randomization that in the judgment of the investigator prevents the patient from participating in the study.
- Active systemic infections (other than common cold) during the 2 weeks prior to baseline.
- History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result at screening.
- Chronic infection with Hepatitis B or Hepatitis C virus.
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive Human chorionic gonadotropin (HCG) laboratory test.
- Sexually active males or women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of study treatment.

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Participant Flow Table

Overall Study

	LYS006 20 mg BID	LYS006 2 mg BID	Placebo BID	Total
Arm/Group Description	LYS006, 20 mg, orally, twice daily (BID), for 12 weeks	LYS006, 2 mg, orally, BID, for 12 weeks	Matching placebo, orally, BID, for 12 weeks	
Started	26	11	29	66
Completed Treatment Period	23	9	24	56
Pharmacodynamic (PD) Analysis Set	24	11	28	63
Completed	20	9	23	52
Not Completed	6	2	6	14
Adverse Event	1	1	1	3
Lost to Follow-up	2	0	2	4
Physician Decision	1	0	0	1
Subject/Guardian Decision	2	1	3	6

Completed represents number of participants who completed the study.
Not Completed represents number of participants who did not complete the study.

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Baseline Characteristics

	LYS006 20 mg BID	LYS006 2 mg BID	Placebo BID	Total
Arm/Group Description	LYS006, 20 mg, orally, twice daily (BID), for 12 weeks	LYS006, 2 mg, orally, BID, for 12 weeks	Matching placebo, orally, BID, for 12 weeks	
Number of Participants [units: participants]	26	11	29	66
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation				
	23.2±6.89	24.5±6.23	25.0±5.40	24.2±6.13
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
Female	16	8	22	46
Male	10	3	7	20
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants				
Asian	1	1	1	3
Black or African American	2	1	6	9
Other	2	1	6	9
White	21	8	16	45

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Primary Outcome Result(s)

Total inflammatory lesion count

Description: Inflammatory facial lesion count included papules, pustules, and nodules. The natural log transformed inflammatory facial lesion count up to Week 12 was analyzed using a Bayesian mixed effect model for repeated measurements (MMRM). Values estimated from the model at Week 12 are presented in the table. Posterior geometric mean and 90% credible intervals in each group are presented.

Time Frame: Week 12

	LYS006 20 mg BID	LYS006 2 mg BID	Placebo BID
Arm/Group Description	LYS006, 20 mg, orally, twice daily (BID), for 12 weeks	LYS006, 2 mg, orally, BID, for 12 weeks	Matching placebo, orally, BID, for 12 weeks
Number of Participants Analyzed [units: participants]	21	9	23
Total inflammatory lesion count (units: lesions)	**Geometric Mean (90% Confidence Interval)**	**Geometric Mean (90% Confidence Interval)**	**Geometric Mean (90% Confidence Interval)**
	18.55 (14.16 to 24.32)	24.51 (16.35 to 36.94)	20.04 (15.42 to 26.13)

Statistical Analysis

Groups	LYS006 20 mg BID, Placebo BID	
Type of Statistical Test	Other	The effects included in the model are: log transformed baseline inflammatory facial lesion count, treatment group, visit, treatment group by visit interaction, log transformed baseline inflammatory facial lesion count by visit interaction and type of center.
Method	Other Bayesian analysis	Bayesian mixed effect model with repeated measures
Other Posterior geometric mean ratio	0.93	90% credible intervals are reported on the geometric means ratio

90 % Confidence Interval 2-Sided	0.64 to 1.34

Statistical Analysis

Groups	LYS006 20 mg BID, Placebo BID	
Type of Statistical Test	Other	The effects included in the model are: log transformed baseline inflammatory facial lesion count, treatment group, visit, treatment group by visit interaction, log transformed baseline inflammatory facial lesion count by visit interaction and type of center.
Method	Other Bayesian analysis	Bayesian mixed effect model with repeated measures
Other P(Geometric Mean Ratio<1)	0.637	Posterior probability on geometric mean ratio is reported.

Statistical Analysis

Groups	LYS006 20 mg BID, Placebo BID	
Type of Statistical Test	Other	The effects included in the model are: log transformed baseline inflammatory facial lesion count, treatment group, visit, treatment group by visit interaction, log transformed baseline inflammatory facial lesion count by visit interaction and type of center.
Method	Other Bayesian analysis	Bayesian mixed effect model with repeated measures
Other P(Geometric Mean Ratio<0.75)	0.171	Posterior probability on geometric mean ratio is reported.

Secondary Outcome Result(s)

There were no secondary outcome measures.

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 128 days
Source Vocabulary for Table Default	MedDRA (24.1)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	LYS006 20 mg BID N = 26	**LYS006 2 mg BID N = 11**	**Placebo BID N = 29**	**Total N = 66**
Arm/Group Description	LYS006, 20 mg, orally, twice daily (BID), for 12 weeks	LYS006, 2 mg, orally, BID, for 12 weeks	Matching placebo, orally, BID, for 12 weeks	Total
Total Number Affected	0	0	0	0
Total Number At Risk	26	11	29	66

Serious Adverse Events

No data identified.

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Other (Not Including Serious) Adverse Events

	LYS006 20 mg BID N = 26	LYS006 2 mg BID N = 11	Placebo BID N = 29	Total N = 66
Arm/Group Description	LYS006, 20 mg, orally, twice daily (BID), for 12 weeks	LYS006, 2 mg, orally, BID, for 12 weeks	Matching placebo, orally, BID, for 12 weeks	Total
Total # Affected by any Other Adverse Event	10	8	16	34
Total # at Risk by any Other Adverse Event	26	11	29	66
Blood and lymphatic system disorders				
Haemoglobinaemia	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Polycythaemia	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Ear and labyrinth disorders				
Tinnitus	0 (0.00%)	1 (9.09%)	0 (0.00%)	1 (1.52%)
Gastrointestinal disorders				
Abdominal pain	0 (0.00%)	2 (18.18%)	0 (0.00%)	2 (3.03%)
Abdominal pain upper	1 (3.85%)	0 (0.00%)	1 (3.45%)	2 (3.03%)
Constipation	1 (3.85%)	0 (0.00%)	1 (3.45%)	2 (3.03%)
Diarrhoea	0 (0.00%)	1 (9.09%)	0 (0.00%)	1 (1.52%)
Flatulence	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Nausea	1 (3.85%)	1 (9.09%)	1 (3.45%)	3 (4.55%)
Vomiting	0 (0.00%)	1 (9.09%)	2 (6.90%)	3 (4.55%)
General disorders and administration site conditions				
Fatigue	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (1.52%)
Influenza like illness	0 (0.00%)	1 (9.09%)	0 (0.00%)	1 (1.52%)

Oedema	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Infections and infestations				
Acarodermatitis	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Bronchitis	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (1.52%)
COVID-19	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Cystitis	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Gastrointestinal infection	0 (0.00%)	1 (9.09%)	0 (0.00%)	1 (1.52%)
Genital infection fungal	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Gingivitis	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (1.52%)
Nasopharyngitis	3 (11.54%)	3 (27.27%)	3 (10.34%)	9 (13.64%)
Otitis media	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Sinusitis	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (1.52%)
Urethritis	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Urinary tract infection	0 (0.00%)	2 (18.18%)	2 (6.90%)	4 (6.06%)
Vulvovaginal mycotic infection	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (1.52%)
Injury, poisoning and procedural complications				
Muscle strain	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (1.52%)
Procedural pain	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Skin abrasion	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Sunburn	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (1.52%)
Investigations				
Albumin urine present	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Aspartate aminotransferase increased	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Bacterial test positive	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)

Blood creatine phosphokinase increased	2 (7.69%)	1 (9.09%)	3 (10.34%)	6 (9.09%)
Blood creatinine increased	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (1.52%)
Blood urine present	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Creatinine urine increased	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Crystal urine present	2 (7.69%)	0 (0.00%)	4 (13.79%)	6 (9.09%)
Haematocrit increased	1 (3.85%)	0 (0.00%)	1 (3.45%)	2 (3.03%)
Haemoglobin increased	0 (0.00%)	0 (0.00%)	2 (6.90%)	2 (3.03%)
Lipase increased	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (1.52%)
Neutrophil count increased	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (1.52%)
Protein urine present	1 (3.85%)	0 (0.00%)	1 (3.45%)	2 (3.03%)
Urine protein/creatinine ratio increased	2 (7.69%)	1 (9.09%)	1 (3.45%)	4 (6.06%)
White blood cell count increased	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (1.52%)
White blood cells urine positive	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Nervous system disorders				
Headache	0 (0.00%)	2 (18.18%)	3 (10.34%)	5 (7.58%)
Psychiatric disorders				
Insomnia	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (1.52%)
Renal and urinary disorders				
Micturition urgency	0 (0.00%)	1 (9.09%)	0 (0.00%)	1 (1.52%)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Epistaxis	0 (0.00%)	2 (18.18%)	0 (0.00%)	2 (3.03%)
Tonsillar hypertrophy	0 (0.00%)	1 (9.09%)	0 (0.00%)	1 (1.52%)

Skin and subcutaneous tissue disorders				
Acne	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Dermatitis contact	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (1.52%)
Pruritus	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Rash	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Rash papular	1 (3.85%)	0 (0.00%)	0 (0.00%)	1 (1.52%)
Urticaria aquagenic	0 (0.00%)	0 (0.00%)	1 (3.45%)	1 (1.52%)

Conclusion:

LYS006 was well tolerated in the study with no serious adverse events and no unexpected adverse events.

No clear clinical signal in reducing inflammatory lesions by LYS006 over placebo could be detected.

Date of Clinical Trial Report

22-Nov-2022