NOVARTIS

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

LYS006

CLYS006X2201
ClinicalTrials.gov Identifier: NCT03497897

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

Statistical Analysis Plan (SAP)

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List of tables & figures

1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CLYS006X2201".***

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol for the final analysis, as well as the outputs planned for the interim analyses.

1.2 Study reference documentation

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1.3 Study objectives

1.3.1 Primary objective(s)

Primary objective(s)	Endpoints related to primary objective(s)
• To assess the efficacy of LYS006 versus placebo on facial inflammatory lesion counts in patients with moderate to severe inflammatory acne	• Baseline-adjusted total inflammatory facial lesion count at Week 12

1.3.2 Secondary objective(s)

Secondary objective(s)	Endpoints related to secondary objective(s)
• To assess the safety and tolerability of LYS006 in patients with moderate to severe inflammatory acne	• Number and severity of AEs

1.3.3 Exploratory objective(s)

Exploratory objective(s)	Endpoints related to exploratory objective(s)

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Exploratory objective(s)	Endpoints related to exploratory objective(s)

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Exploratory objective(s)	Endpoints related to exploratory objective(s)
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1.4 Study design and treatment

This is a randomized, placebo-controlled, subject and investigator blinded, multicenter, non-confirmatory, parallel-group, proof-of-concept study in adult patients with moderate to severe facial inflammatory acne. After an initial screening period (up to 4 weeks), the study will be conducted over a treatment period of 12 weeks to evaluate the clinical efficacy of LYS006 versus placebo. Fifty-six (56) patients will be randomized in a 3:1:3 ratio to one of the following treatment groups:

- Group 1: LYS006 capsules, high dose CCI N=24
- Group 2: LYS006 capsules, low dose CCI N=8
- Group 3: LYS006 placebo CCI , N=24

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Exposure to placebo will be limited to a maximum of 12 weeks.

After treatment period completion, all patients will enter a post-treatment safety follow-up period of 4 weeks without study drug administration.

The maximum duration of study participation will be 20 weeks.

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2 First interpretable results (FIR)

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3 Interim analyses

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4 Statistical methods: Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received. This implies that for subjects for whom the actual treatment received does not match the randomized treatment, the treatment actually received will be used for the analysis.

The Safety analysis set will include all subjects that received at least one dose of study drug.

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The PD analysis set will include all subjects with available PD data, who received any study drug and with no protocol deviations with relevant impact on PD data.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from all *(safety)* analysis in case of these protocol deviations:		Exclude subject completely from all ***(safety)*** analysis sets
INCL01	Deviation from inclusion criterion 1 (Written informed consent must be obtained before any assessment is performed)	Yes

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Subjects are excluded from PD analysis in case of these protocol deviations:		Exclude subject from PD analysis set
INCL01	Deviation from inclusion criterion 1 (Written informed consent must be obtained before any assessment is performed)	Yes

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If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

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6 Statistical methods for Efficacy/Pharmacodynamic (PD) parameters

All subjects within the PD analysis set will be included in the PD data analysis.

6.1 Primary objectives

The primary aim of this study is to assess the efficacy of LYS006 versus placebo on inflammatory facial lesion counts in patients with moderate to severe inflammatory acne.

The primary analyses will be based on on-treatment data. Data recorded after a patient discontinues study treatment will not be 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.

6.1.1 Variables

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

Baseline is defined as the Baseline (Visit 2) assessment.

6.1.2 Descriptive analyses

Total inflammatory facial lesion count will be listed by treatment group, subject and visit/time, and descriptive statistics will be provided, for raw, absolute change from baseline and percentage change from baseline, by treatment group and visit/time. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median,

minimum, maximum; geometric mean and its CV will only be provided for the raw values. A geometric mean will not be reported if the dataset includes zero values.

Graphical methods will be employed to show mean and individual (Spaghetti) plots over time.

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Note: Any plots that are reported separately by treatment (i.e., plots with one graph per page for each treatment), will use the same y-axis scale for each treatment.

6.1.3 Statistical model, assumptions and hypotheses

Data up to Week 12 will be 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 will also be included in this primary model at the time of IA and later analyses, but will mainly be summarized as described in the descriptive analyses section above.

The natural log transformed inflammatory facial lesion count is expected to be approximately normally distributed. It will be analyzed using a Bayesian mixed effect model for repeated measures (MMRM) using Proc MCMC in SAS software (Chen 2011). Baseline adjustment will be implemented by including the log transformed baseline inflammatory facial lesion count in the model as a continuous covariate. The model will also include treatment group, visit, treatment group by visit interaction, log transformed baseline inflammatory facial lesion count

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as fixed effects. Non-informative priors will be utilized for the fixed effects and for the covariance coming from a normal distribution and an inverse Wishart distribution, respectively. An unstructured covariance will be assumed; other covariance structures will be investigated if there is a convergence issue. The log transformed baseline inflammatory facial lesion count will be centered and standardized prior to being included in the model.

Bayesian posterior probabilities will be used to assess the following proof-of-concept (PoC) criteria as a guidance for decision making (Fisch et al 2015), though other criteria may be taken into account:

Efficacy criteria (only for primary objective) at IA and at the final analysis:

- If there is at least 90% probability that the treatment effect of LYS006 at 12 weeks is better than placebo, i.e., Prob (y_LYS006 - y_placebo < 0) > 90%, and
- If there is at least 50% probability that the treatment effect at 12 weeks is at least 25% in favor of LYS006, i.e., Prob (y_LYS006 - y_placebo < - 0.288) > 50%.

Where y is the log transformed facial inflammatory lesion count.

The posterior estimates of the treatment effect and the treatment difference (along with its 90% credible interval) at each post baseline visit (with Week 12 being of primary interest) will be provided. The results of the treatment effects will be presented as geometric means by back-transforming the estimates from the log-scale. The results of the treatment comparison to

placebo will be reported in terms of ratio of the geometric means by back-transforming the estimates from the log-scale.

6.1.3.1 Model checking procedures

All patients with available data after baseline and until Week 12 will be included in the interim and in the primary analyses. If study drug is permanently discontinued before Week 12, data collected after permanent discontinuation will not be considered for the purpose of the primary analyses. The primary variable analysis model is known to give unbiased results under the assumption that missing data are at random (MAR), i.e. given observed data the missingness does not depend on unobserved data. In the event that many patients discontinue treatment, alternative estimands considering the effect of LYS006 versus placebo may also be investigated.

6.1.3.2 Graphical presentation of results

Model-based geometric mean treatment estimates (+/- SE) as well as model-based geometric mean treatment ratio estimates (+/- SE) will be plotted over time and by treatment. The baseline value will also be presented in the model-based geometric mean treatment estimates (+/- SE) graphs for better visualization purposes. The baseline value that will be displayed is the averaged baseline value across treatments.

6.1.4 Sensitivity analyses

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6.1.5 Supportive analyses

In order to have better understanding of the treatment effect, the absolute change from baseline and the percentage change from baseline in total inflammatory facial lesion count will also be explored using a Bayesian mixed effect model for repeated measures (MMRM) using Proc MCMC in SAS software (Chen 2011). Baseline inflammatory facial lesion count will be included in the model as a continuous covariate. The model will also include treatment group, visit, treatment group by visit interaction, baseline inflammatory facial lesion count Commercially Confidential Information as fixed effects. Non-informative priors will be utilized for the fixed effects and for the covariance coming from a normal distribution and an inverse Wishart distribution, respectively. An unstructured covariance will be assumed; other covariance structures will be investigated if there is a convergence issue. The baseline inflammatory facial lesion count will be centered and standardized prior to being included in the model.

The posterior estimates of the treatment effect and the treatment difference (along with its 90% credible interval) at each post baseline visit (with Week 12 being of primary interest) will be provided. The results of the treatment effects will be presented as arithmetic means and the results of the treatment comparison to placebo will be reported in terms of difference of the arithmetic means.

The Bayesian posterior probability for statistical significance, i.e., the probability that the treatment effect of LYS006 is better than placebo, Prob (LYS006 - placebo < 0), will be obtained.

As an additional supportive analysis, the same Bayesian MMRM as for the primary analysis will be fitted and appropriate contrasts will be estimated in order to compare LYS006 high dose group versus placebo group on the average treatment effect combining week 8 and week 12 data.

6.1.5.1 Model checking procedures

All patients with available data after baseline and until Week 12 will be included in the interim and in the above supportive analyses. If study drug is permanently discontinued before Week 12, data collected after permanent discontinuation will not be considered for the purpose of the above supportive analyses.

6.1.5.2 Graphical presentation of results

Model-based arithmetic mean treatment estimates (+/- SE) as well as model-based arithmetic mean treatment difference estimates (+/- SE) will be plotted over time and by treatment. Baseline will also be presented as 0 in these model-based plots for better visualization of the absolute and percent changes from baseline over time.

Posterior density plots for the treatment effect will also be obtained.

As additional supportive analyses, other factors such as gender, race, center, assessor and approach of the assessment (digital or clinic) may also be considered in the primary analysis model and the above supportive analysis models either as a fixed effect or as a sub-group analyses variable to investigate for potential heterogeneity. If heterogeneity is observed, then this method may be applied to other investigated PD endpoints.

Further, supportive analyses may be performed adding other covariates in the models such as baseline IGA and other baseline characteristics.

6.2 Exploratory objectives

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6.2.1 Variables

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6.2.2 Descriptive analyses

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6.2.3 Statistical model, assumptions and hypotheses

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6.2.4 Graphical presentation of results

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7 Statistical methods for safety and tolerability data

All subjects within the Safety analysis set will be included in the safety data analysis.

7.1 Variables

The safety and tolerability variables are the number and severity of AEs/SAEs, vital signs (body temperature, height, weight, blood pressure and pulse rate), ECG intervals (PR interval, QRS duration, heart rate, RR, QT and QTcF), laboratory measurements (hematology, clinical chemistry, urinalysis), as well as subject demographics, baseline characteristics, and treatment information.

7.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group. Subject demographics will include age, sex, race, ethnicity, country, height, weight and BMI. Baseline disease characteristics include but are not limited to: facial inflammatory lesion counts (papules, pustules, nodules),

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Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

Protocol deviations

In addition to the pre-defined standard protocol deviation terms, Novartis has defined 6 new protocol deviations and the corresponding relationship (health status related vs. site lockdown, subject concerns, etc.) to the COVID-19 pandemic in line with "Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency" (January 2021) from FDA and "Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic" (February 2021) from EMA as listed below.

- Missing visits
- Changes in procedures and assessments
- Planned visits not done at sites
- Changes in drug supply method
- Treatment not given
- Subject discontinuation due to COVID-19 situation

A summary table for the pandemic related/not pandemic related protocol deviations by category and relationship (and in total) will be provided by treatment group for all subjects randomized. For those related to the pandemic, "all COVID-19 pandemic related" protocol deviations will be summarized together and by specific type of reason (site issue, subject's infection, etc.). The percentages will be calculated out of total randomized patients, since the intent is to show how much the pandemic related deviations impacted the study as a whole.

All protocol deviations will be listed. A separate listing will be provided for COVID-19 related protocol deviations.

Treatment

Data for study drug administration and concomitant therapies will be listed by treatment group and subject.

Duration of exposure to study drug in days, as well as actual total doses, actual dose intensities (total amount of drug administered per unit of time), and relative dose intensities (ratio of actual dose intensity to planned dose intensity) will be summarized using descriptive statistics by treatment group for the safety analysis set.

Compliance to the study treatment will be assessed by the frequency of dose interruptions and percent of days with received planned dose by treatment group for the safety analysis set.

Compliance to the study treatment in the percent of capsules taken will be summarized by visit and overall, and also listed.

Reason for dose interruption will be listed by subject and summarized.

Concomitant therapies prior to and after the start of study treatment will be listed and summarized by treatment group for the safety analysis set.

Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment group and visit/time.

ECG evaluations

All ECG data will be listed by treatment group, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment group and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing will be provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by treatment group and visit/time.

The laboratory data will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- Shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- Listing of all laboratory data with values flagged to show the classifications relative to the laboratory normal ranges.

Adverse events

All information obtained on adverse events will be displayed by treatment group and subject.

Summary tables for AEs will include only AEs that started or worsened after first dose, the ***treatment-emergent*** AEs (TEAEs). However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged. Listings of all AEs will be provided.

The incidence of TEAEs (new or worsening after first dose) will be summarized by system organ class (SOC) and/or preferred term (PT), maximum severity and by treatment.

Deaths reportable as SAEs and non-fatal SAEs will be listed by subject and tabulated by type of AE and treatment.

SAEs, non-serious AEs, AEs leading to study drug discontinuation, drug-related AEs CCI events will be tabulated.

A subject with multiple AEs within a body system is only counted once towards the total of this body system and treatment.

Adverse event reporting for Clinical Trial Safety Disclosure (CTSD)

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables, 1) on treatment-emergent adverse events which are not serious adverse events with an incidence greater than X% and 2) on treatment-emergent serious adverse events and SAE suspected to be related to study treatment, will be provided by SOC and PT on the safety analysis set population. These tables will be produced by Novartis. The value of the cutoff value X will be decided with the team when disclosure tables are prepared.

The summary will be done by treatment i.e. active (LYS006) or Placebo, regardless of the dose level.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1-day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1-day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non-SAE has to be checked in a block e.g., among AE's in a ≤ 1-day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

Other safety evaluations

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All other safety evaluations (e.g. pregnancy test results for women) will be listed by treatment group, subject and visit/time.

7.3 Graphical presentation of results

Boxplots to visualize trends in longitudinal safety data (vital signs, ECG evaluations and lab parameters) will be created. Mean and overlaying individual figures will be presented for selected parameters from vital signs, ECG evaluations and lab parameters.

Note: Any plots that are reported separately by treatment (i.e., plots with one graph per page for each parameter and treatment), will use the same y-axis scale for each treatment of a given parameter.

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9 Statistical methods for biomarker data

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9.2 Descriptive analyses

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9.3 Graphical presentation of results

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10 Reference list

1. Chen F (2011) The RANDOM statement and more: moving on with PROC MCMC. SAS Global Forum Proceedings, p. 334-2011.
2. Fisch R, Jones I, Jones J, et al (2015) Bayesian Design of Proof-of-Concept Trials. Therapeutic Innovation & Regulatory Science; 49. p. 155-162.
3. Fleischer AB, Dinehart S, Stough D, Plott RT. Safety and efficacy of a new extended-release formulation of minocycline. Solodyn Phase, 2. Study Group, and Solodyn Phase, 3. Study Group. Cutis 2006;78(4 Suppl):21-31.
4. Gold LS, Cruz A, Eichenfield L, et al (2010) Effective and safe combination therapy for severe acne vulgaris: a randomized, vehicle-controlled, double-blind study of adapalene 0.1%-benzoyl peroxide 2.5% fixed-dose combination gel with doxycycline hyclate 100 mg. Cutis p. 94-104.
5. Gsponer, T., Gerber, F., Bornkamp, B., Ohlssen, D., Vandemeulebroecke, M. and Schmidli, H. (2014), A practical guide to Bayesian group sequential designs. Pharmaceut. Statist., 13: 71-80. doi: 10.1002/pst.1593
6. Lee JW, Yoo KH, Park KY, et al (2011) Effectiveness of conventional, low-dose and intermittent oral isotretinoin in the treatment of acne: a randomized, controlled comparative study. Br. J. Dermatol., 164: 1369-75.
7. Leyden J, Bergfeld W, Drake L, et al (2004) A systemic type I 5 alpha-reductase inhibitor is ineffective in the treatment of acne vulgaris. J. Am. Acad. Dermatol., 50(3): 443-7.
8. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment Guidance for Industry
9. European Medicines Agency (2021). Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic
10. Food and Drug Administration (2021). Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards