NOVARTIS

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

LYS006

LYS006X2202 / NCT04074590

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

Statistical Analysis Plan (SAP)

Author(s): Personal Protected Data

Document type: SAP Documentation – NIBR

Document status: Amendment 4 / Final

Release date: 06-Mar-2023

Number of pages: 36

Commercially Confidential Information (CCI)

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Table of contents

Commercially Confidential Information

List of tables

Commercially Confidential Information

Commercially Confidential Information

List of 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 ***"CLYS006X2202".***

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

Commercially Confidential Information

1.3 Study objectives

1.3.1 Primary Objective

Primary objective	Endpoint related to primary objective
• To assess the induction of clinical remission by LYS006 in patients with mild to moderate ulcerative colitis (UC) compared to placebo	• Clinical remission rate at Week 8 using the full Mayo score

1.3.2 Secondary Objective

Secondary objective	Endpoints related to secondary objective
• To assess safety and tolerability of LYS006 in patients with mild to moderate ulcerative colitis compared to placebo	• Number and severity of adverse events/ number of subjects with adverse events • Safety and tolerability based on general safety measurements (safety laboratory measurements, vital signs and ECG parameters)

Commercially Confidential Information

Commercially Confidential Information

1.4 Study design and treatment

This is a randomized, placebo-control, subject and investigator blinded, multicenter, parallel group study in patients with mild to moderate ulcerative colitis (UC).

Approximately 45 patients will be randomized in a 2:1 ratio to one of the following groups:

- Group 1: LYS006 capsules (20 mg BID)
- Group 2: matching placebo (BID)

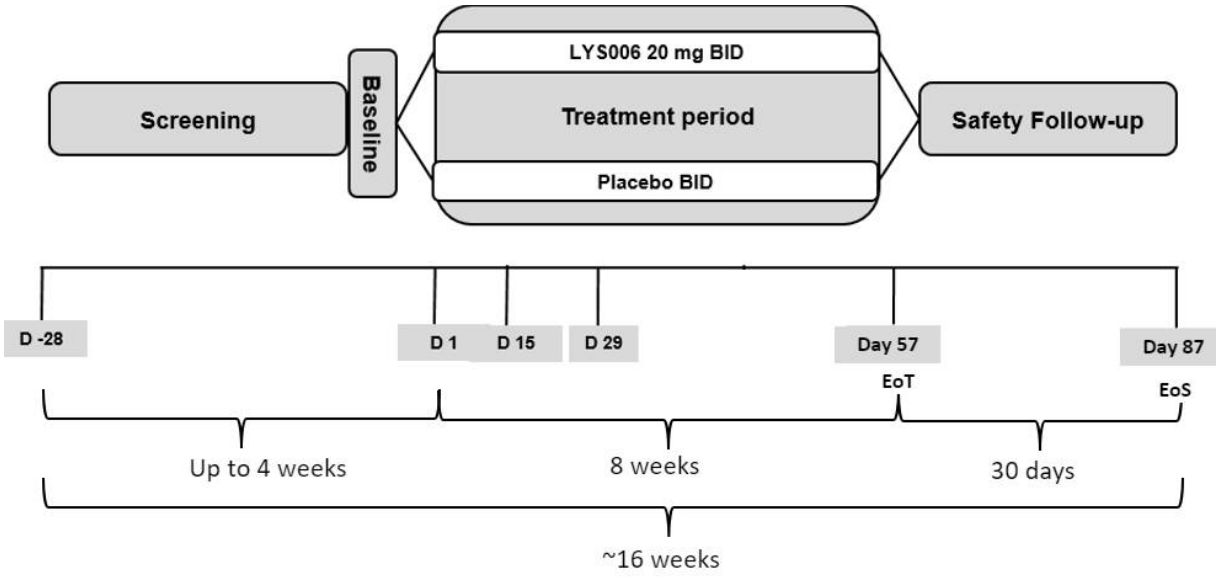
Figure 1-1 depicts the design of the study, starting from a screening epoch of up to 4 weeks (minimum screening duration of 7 days to enable collection of stool frequency and rectal bleeding subscores), a treatment period of 8 weeks and a follow-up period of 30 days post last administration of study treatment, before the End of Study (EoS) visit. The total duration for each subject in the study will be up to 16 weeks.

For the entire duration of the treatment period (8 weeks), subjects will receive twice-daily doses of LYS006 or placebo. Each subject will take 4 capsules to make up to a dose of 20 mg twice a day.

Baseline visit will be Day 1. Baseline and drug administration can be done the same day if all eligibility criteria are met.

Commercially Confidential Information

Figure 1-1 Study design



2 First interpretable results (FIR)

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

3 Interim analyses

Commercially Confidential Information

4 Statistical methods: Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The safety analysis set will include all subjects that received any study drug.

Commercially Confidential Information

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

The data collected from the subjects Commercially Confidential Information will be pooled for all the analyses listed in this document.

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

Category Deviation code	Text description of deviation	Data exclusion
Commercially Confidential Information		
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
TRT04	Wrong dose of study drug	Yes
OTH12PA2	Change in Standard of Care treatment	Yes
Commercially Confidential Information		

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

Commercially Confidential Information

6 Statistical methods for Pharmacodynamic (PD) parameters

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

6.1 Primary objective

The primary aim of this study is to assess the induction of clinical remission by LYS006 compared to placebo in patients with mild to moderate UC using the total Mayo score.

6.1.1 Variables

The primary PD variable of this study is the clinical remission rate at the EoT visit CCI , i.e. the proportion of patients who reach the status of clinical remission at the EoT visit.

Clinical remission is based on total Mayo score, defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding one point. The total Mayo score is the sum of four subscores, ranging from 0 to 12: stool frequency (recorded on a daily basis by a diary card), rectal bleeding (recorded on a daily basis by a diary card), endoscopic findings and Physician's

Global Assessment (PhGA). Each subscore grading ranges from 0 to 3, from free of disease to severe disease.

The stool frequency subscore should be calculated from the most recent three consecutive days within the week prior to the day of endoscopy bowel preparation. If three consecutive days are not available, the most recent non-consecutive 3 days within the week prior to the day of endoscopy bowel preparation should be used. The stool frequency subscore is the average of the 3 daily stool frequency subscores. The rectal bleeding subscore will be calculated in the same manner as stool frequency subscore.

Commercially Confidential Information

6.1.2 Descriptive analyses

The raw total Mayo scores and subscores will be listed by treatment group, subject and visit/time. Descriptive statistics of both the raw and change from baseline at 2-week and 8-week visit will be provided by treatment group when relevant.

6.1.2.1 Graphical presentation of results

Scatter plots to visualize trends over time in total Mayo score, CCI and individual endoscopic, stool frequency, rectal bleeding and PhGA subscores will be created by treatment group.

6.1.3 Statistical model, assumptions and hypotheses

The binary endpoint of clinical remission rate (Yes/No) will be modelled with binomial distribution and analyzed via Bayesian approach with baseline total Mayo score and treatment group as explanatory variables, to compare the remission rates between the LYS006 and placebo groups.

Prior distributions:

- LYS006 group: Clinical remission rate_LYS006 ~ Beta (1/3, 1/3)
- Placebo group: Clinical remission rate_Placebo ~ Beta (18.9, 167.4), Beta (3.2, 24.2), Beta (1.0, 3.3) and Beta (1,1)

The clinical remission rate for the LYS006 group will be given a neutral prior (Kerman 2011), Beta (1/3, 1/3). The clinical remission rate for the placebo group will be given an informative prior derived via the meta-analytic predictive (MAP) approach (Neuenschwander et al. 2010 and Schmidli et al. 2014). This prior is based on the control groups from a number of historical UC trials (Rutgeerts et al. 2005, Reinisch et al. 2011, Sandborn et al. 2012 and Ito et al. 2010) and the selection of historical UC studies was based on patient population and the endpoint. The MAP prior for the placebo remission rate will be a mixture of the following four beta-distributions, Beta (18.9, 167.4), Beta (3.2, 24.2), Beta (1.0, 3.3) and Beta (1, 1), with the mixture weights being 0.43, 0.34, 0.03 and 0.2 respectively. The last non-informative component is added to robustify the outcome in case of any difference between within-study placebo group and those from the historical studies.

With the specified priors and the observed remission rates from this study, the posterior distributions for clinical remission rates in LYS006 and placebo groups will be computed. The posterior probabilities as defined in the dual efficacy criteria below will be provided, along with the posterior remission rates by group and the treatment difference with 90% credible intervals.

The dual efficacy criteria are defined as ("diff" refers to the difference of true remission rates in LYS006 and placebo):

(1) EoT clinical remission rate better than placebo with high confidence (90%), i.e., Prob (diff > 0) > 90%, and

(2) Average magnitude of effect on EoT clinical remission rate > 15% over placebo, i.e., Prob (diff > 15%) > 50%.

6.1.3.1 Model checking procedures

Subjects who discontinued from the study for reasons other than COVID-19 before the EoT visit, or have received rescue or prohibited medication for the treatment of UC during the treatment period will be considered failed to achieve clinical remission. Any CCI data for a subject that were recorded at or after the start of a rescue or prohibited medication should be removed from the CCI statistical analyses.

Any missing subscore Commercially Confidential Information will lead to a non-evaluable clinical remission status and the subject will also be considered failed to achieve clinical remission. Reasons for missing Mayo scores or subscores need to be collected to understand the impact of such analysis approach. Imputation methods such as tipping point analysis may be explored.

Discontinuation prior to EoT, or subjects for which central reading of EoT endoscopy was not available due to local COVID-19 related restrictions will be considered as missing data.

Commercially Confidential Information

The homogeneity of the total Mayo scores between subjects CCI will be explored visually by each visit.

6.2 Secondary objectives

Not Applicable.

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

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 Adverse events (AEs)/Serious adverse events (SAEs), physical examinations, 12-lead ECG intervals (PR interval, QRS duration, heart rate, RR interval, QT interval and QTcF), vital signs (body temperature, height, weight, blood pressure and pulse rate), standard clinical laboratory evaluations (hematology, biochemistry and urinalysis), study-specific safety laboratory

evaluations Commercially Confidential Information as well as subject demographics, baseline characteristics, and treatment information.

7.2 Descriptive analyses

Subject demographics and other baseline characteristics

Demographics and baseline characteristics variables are defined in Section 2. All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided overall and by treatment group. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum and maximum will be presented.

Relevant medical histories, current medical conditions at baseline, results of laboratory screens 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, to show how 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 changes in dosage will be listed by treatment group and subject, including but not limited to:

- Dates of first and last exposure
- Any changes in dosage or missed doses (Y/N)?
- If changes in dosage or missed doses = Yes:

- Doses prescribed and administered (in mg)
- Total daily dose (in mg)
- Frequency of dosing
- Start and end dates of dose change
- Type of dose change
- Reason for dose change

Compliance to the study treatment data (% of missing doses and % of capsules taken with respect to the total number of expected doses/capsules during the treatment period) will not be analyzed or reported, the study drug accountability data not being captured in the CRF.

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

Vital signs

A listing will be provided presenting all vital signs measurements in a subject with any abnormal values (based on reference ranges). This listing will be sorted by treatment group, subject and visit/time. If there is any abnormality of a vital sign for a subject, all measurements of this vital sign for the subject will be presented in this listing. Abnormalities will be flagged using the following reference ranges:

Vital Sign Parameter	**Reference Range**
Systolic Blood Pressure	90-140 mmHg
Diastolic Blood Pressure	50-90 mmHg
Pulse Rate	40-90 bpm
Body Temperature	35.0-37.5 C

Baseline will be defined as the last available pre-dose measurement.

Summary statistics (absolute values) will be provided by treatment group and visit/time. Measurements obtained at Screening and EoS will be included in the tabulations for the overall safety population only.

Clinical laboratory evaluations

A listing with laboratory parameters and their corresponding lab test codes (if applicable) and units will be provided for each lab category (hematology, biochemistry, and urinalysis).

A listing will be provided presenting all laboratory parameters in a subject with any out of range values. This listing will be sorted by treatment group, subject and visit/time for each lab category. If there is any abnormality of a parameter for a subject, all measurements of this parameter for the subject will be presented in this listing. Out of range values will be flagged as recorded in the database, e.g. for numerical results as “L” (for values lower than the lower limit of the reference range) and “H” (for values higher than the upper limit of the reference range).

Baseline will be defined as the last available pre-dose measurement.

Summary statistics (absolute values) of hematology and biochemistry tests will be provided by treatment group and visit/time. Measurements obtained at Screening and EoS will be included in the tabulations for the overall safety population only.

In particular, the following by-treatment summaries will be generated:

- Shift tables using the low/normal/high classification based on laboratory normal ranges to compare baseline to the worst on-treatment value (separately for hematology, biochemistry and urinary laboratory tests)

Commercially Confidential Information

ECG evaluations

A listing will be provided presenting all ECG data in a subject with any abnormal values (based on the PI's interpretation). This listing will be sorted by treatment group, subject and visit/time. If there is any abnormality (marked as abnormal by the PI) of an ECG parameter for a subject, all measurements of this parameter for the subject will be presented in this listing. Abnormalities, based on the PI's interpretation, will be flagged. Clinically notable values will also be flagged in the listing using the following criteria:

ECG Parameter	**Clinically Notable Criteria**
PR	PR > 200 msec
QRS	QRS complex > 120 msec
QTcF	Males: QTcF > 450 msec Females: QTcF > 460 msec

Baseline will be defined as the last available pre-dose measurement.

Summary statistics (absolute values) will be provided by treatment group and visit/time. Measurements obtained at Screening and EoS will be included in the tabulations for the overall safety population only.

A categorical summary of QT/QTcF interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute QT/QTcF intervals or changes from baseline, at any time post-baseline, will be presented by treatment group. Specifically, frequency counts and percentages will be provided for each category of interest. The QT/QTcF categories of interest will be as follows:

Observed Value (msec)	Change from Baseline (msec)
Males: ≤ 450 > 450 - 480 > 480 - 500 >500 Females: ≤ 460 > 460 - 480 > 480 - 500 > 500	≤ 30 > 30 - 60 > 60

Adverse events

All AEs occurring during this clinical trial will be coded using MedDRA. All information obtained on AEs 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.

The number and percentage of subjects with TEAEs will be tabulated by system organ class (SOC) and preferred term (PT) with a breakdown by treatment and also by SOC, PT and maximum severity with a breakdown by treatment. Summaries will also be provided for the number of AEs by treatment.

Separate summaries will be provided for study medication related AEs, deaths, SAEs, and other significant AEs leading to discontinuation.

The number and percentage of subjects with events of special interest CCI will be summarized by treatment.

A subject with multiple AEs within a SOC/PT and treatment is only counted once towards the total of this SOC/PT and treatment.

Subject listings of all AEs will be provided. Deaths and other serious or clinically significant non-fatal AEs will be listed separately.

Adverse event reporting for Clinical Trial Safety Disclosure (CTSD)

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables, 1) on TEAEs which are not SAEs with an incidence greater than X% and 2) on treatment-emergent SAEs and SAEs suspected to be related to study treatment will be provided by SOC and PT on the safety analysis set. 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 overall and 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

Commercially Confidential Information

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

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

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

9 Reference list

Commercially Confidential Information

4. Guyatt G, et al (1989) A new measure of Health Status for Clinical Trials in inflammatory bowel disease. Gastroenterology; 96:804-10.
5. Kerman J (2011) Neutral noninformative and informative conjugate beta and gamma prior distributions. Electronic Journal of Statistics; 5:1450-70.
6. Neuenschwander B, Capkun-Niggli G, Branson M, et al (2010) Summarizing historical information on controls in clinical trials. Clin Trials; 7:5-18.
7. Schmidli H, Gsteiger S, Roychoudhury S, et al (2014) Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics; 70(4):1023-32.
8. Rutgeerts P, Sandborn WJ, Feagan BG, et al (2005) Infliximab for induction and maintenance therapy for ulcerative colitis. N. Engl. J. Med; 353(23):2462-76.
9. Reinisch W, Sandborn WJ, Hommes DW, et al (2011) Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut; 60(6):780-7.
10. Sandborn WJ, van Assche G, Reinisch W, et al (2012) Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology; 142(2):257-65.e1-3.
11. Ito H, Iida M, Matsumoto T, et al (2010) Direct comparison of two different mesalamine formulations for the maintenance of remission in patients with ulcerative colitis: a double-blind, randomized study. Inflamm. Bowel Dis; 16(9):1567-74.
12. Regor JC, McDonald JW, Klar N, et al (1997) An evaluation of utility measurement in Crohn's disease. Inflamm Bowel Dis; 3:265–76.

Commercially Confidential Information

10 Appendix

10.1 Imputation rules for AE and ConMed dates

Table 10-1 Imputation of start dates (AE, CM)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing start dates
day, month	• If available year = year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY o Else set start date = study treatment start date. • If available year > year of study treatment start date then 01JanYYYY • If available year < year of study treatment start date then 01JulYYYY
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY If available month and year < month and year of study treatment start date then 15MONYYYY

Table 10-2 Imputation of end dates (AE, CM)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing end dates
day, month	• No imputation will be done for partial end dates
day	• No imputation will be done for partial end dates

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.