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LYS006

Clinical Trial Protocol CLYS006X2202 / 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

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study procedures. Note: The SOM will not be a part of the Clinical Study Report.

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List of abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
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BMI	Body Mass Index
BUN	blood urea nitrogen
CK	creatinine kinase
CMO&PS	Chief Medical Office & Patient Safety
COVID-19	Coronavirus disease 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CTC	Common Toxicity Criteria
CV	coefficient of variation
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EoS	End of Study
EoT	End of Treatment
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
FDA	Food and Drug Administration
FiH	First in human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
h	hour
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology

LDH	lactate dehydrogenase
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LTA4H	Leukotriene A4 hydrolase
LTB4	Leukotriene A4
LTC4	Leukotriene C4
LXA4	Lipoxin A4
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
PD	pharmacodynamic(s)
PhGA	Physician's global assessment

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PT	prothrombin time
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QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RBC	red blood cell(s)
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCR	serum creatinine
SD	standard deviation
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SMQ	Standardized MedDRA Query
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total bilirubin
TNF	Tumor necrosis factor
UC	Ulcerative colitis
ULN	upper limit of normal
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WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last subject or at a later point in time as defined by the protocol
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug/treatment	The drug whose properties are being tested in the study
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource

Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal date

Protocol summary

Protocol number	LYS006X2202
Full 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.
Brief title	Study of efficacy, safety and tolerability of LYS006 in patients with mild to moderate ulcerative colitis
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of the study is to assess preliminary efficacy, safety and tolerability of LYS006 in patients with mild to moderate ulcerative colitis and to determine if LYS006 has an adequate clinical profile for further clinical development in this indication.
Primary Objective(s)	To assess the induction of clinical remission by LYS006 in patients with mild to moderate ulcerative colitis using the full Mayo score.
Secondary Objectives	To assess safety and tolerability of LYS006 in patients with mild to moderate ulcerative colitis
Study design	This is a randomized, placebo-controlled, subject and investigator blinded, multicenter, non-confirmatory, parallel group, proof of concept study in patients with mild to moderate ulcerative colitis. This study consists 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 maximum study duration for each such including the maximum 4-week screening period is 16 weeks. At the beginning of the treatment period, subjects will be randomized to one of the two following treatment groups in 2:1 ratio: • 20 mg LYS006 (BID) • matching placebo (BID)
Population	This study will include patients with mild to moderate ulcerative colitis who failed an appropriate, previous treatment with 5-ASA. These patients should have active disease defined as having a full Mayo Score between 5 and 10 (inclusive), with baseline endoscopic sub score of 2 or 3; rectal bleeding and stool frequency score of 1 to 3 and physician's global assessment 1 or 2. Approximately 45 subjects are planned to be enrolled.
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 with a maximum of 1 or 2. • Patients must have responded inadequately to conventional therapy with oral 5-ASA prior to screening.

Key Exclusion criteria	• Has severe UC at screening, as defined by ≥6 bloody stools per day and at least one of the following:
	  • Pulse >90 bpm
	  • Oral temperature of >37.8°C
	  • Hemoglobin of <10.5 g/dL
	  • CRP > 30 mg/L
	  • Erythrocyte sedimentation rate (ESR) >30 mm/h
	• Has previous diagnosis with Crohn's disease, indeterminate colitis, microscopic colitis or acute diverticulitis based on medical history.
	• Previous treatment with biologics (such as anti-TNFα agents) within 3 months or 5 half-lives (whichever is longer) prior to screening endoscopy
	• Previous treatment with non-biologics (such as JAK inhibitors) within 4 weeks prior to screening endoscopy
	• Any systemic immunosuppressant or immunomodulator, such as cyclosporine, methotrexate, azathioprine within 6 weeks and cyclophosphamide within 3 months, prior to screening endoscopy
	• A dose of > 10 mg/d prednisone or equivalent in the last 4 weeks prior to screening endoscopy. Oral budesonide is allowed if the dose is ≤ 9 mg/day with a stable dose administered for at least 4 weeks prior to the screening endoscopy.

Study treatment	• LYS006 20 mg BID: 8 weeks • Matching placebo BID: 8 weeks

Key Efficacy assessments	• Mayo Score based on:
	  • Stool frequency
	  • Rectal bleeding
	  • Endoscopic findings
	  • Physician's Global Assessment

Other assessments	Commercially Confidential Information
Key safety assessments	• AE, SAE monitoring • Physical examinations • Monitoring of laboratory safety • ECGs • Vital signs
Data analysis	The primary endpoint of this study is the clinical remission rate at End of treatment (EoT) CCI and Week 8 for subsequent protocol amendments), i.e. the proportion of patients reaching the status of clinical remission. This primary endpoint of clinical remission is based on full Mayo score, defined as a Mayo score ≤2 with no individual subscore >1. Patients who discontinue for reasons other than COVID-19, or receive any rescue medication before EoT will be considered as treatment failure. This binary endpoint will be analyzed with a Bayesian approach, to compare the remission rates between LYS006 and placebo group. An informative prior will be used for the remission rate for placebo (refer to Sample Size section for details) and a neutral prior (Kerman 2011), Beta (1/3, 1/3), for LYS006. The posterior probabilities as defined in the dual efficacy criteria detailed in the

	analysis of the primary endpoint section will be provided, along with the posterior remission rates by group and the treatment difference with 90% credible intervals.
Key words	Ulcerative colitis, efficacy, safety

1 Introduction

1.1 Background

Ulcerative colitis (UC) is a common chronic immune-mediated disorder that results in inflammation and ulcers in the gastrointestinal tract, and leads to symptoms such as diarrhea, abdominal pain and rectal bleeding. Although 5-ASA compounds as first line agents have been proven safe and are used extensively in UC, there is a significant proportion of patients with inadequate responses due to insufficient therapeutic response or toxicity.

During relapse, UC is characterized by acute neutrophilic inflammation accompanied by considerably enhanced mucosal levels of inflammatory lipidic mediators including Leukotriene B4 (LTB4). LTB4 is a potent neutrophil chemoattractant and chemoactivator. Functional studies have established that LTB4 accounts for the majority of the chemoattractant stimulus to continuing neutrophil infiltration found during relapse (Sharon and Stenson 1984; Cole et al 1992). 5-Lipoxygenase (5-LO, upstream to LTA4H) inhibitor Zileuton indicates clinical benefit of inhibiting LTB4 release in ulcerative colitis (Peppercorn et al 1994). LTA4H inhibition is expected to lead to better efficacy than 5-LO inhibition due to more complete pathway inhibition and simultaneous elevation of LXA4 (maintenance of resolution lipids), a mediator that has been found to be elevated during the remission period in UC patients (Vong et al 2012).

Therefore, LYS006, a potent LTA4H inhibitor that abrogates the production of LTB4 and triggers elevation of pro-resolution mediators such as LXA4, may be beneficial to subjects with ulcerative colitis.

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Additionally, LTA4H inhibition improves colitis in rats /cotton top tamarins **(**Whittle et al 2008; Penning 2001**)**. These preclinical findings suggest that using LYS006 to target neutrophilic inflammation through the leukotriene pathway may be a therapeutic option for UC, in particular for subjects with active UC who have failed first line therapy with 5-ASA and for whom no safe treatment or combination of medical treatments has proven fully efficacious and/or safe and the unmet medical need is still high.

The most relevant data on LYS006 are summarized in the sections below. For detailed information, please refer to the Investigator's Brochure (IB).

Relevant data summary

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In parallel to the proposed Phase 2 study in UC, LYS006 is being evaluated in inflammatory acne, hidradenitis suppurativa and nonalcoholic steatohepatitis (all phase 2 studies).

1.2 Purpose

The study is designed to assess clinical efficacy and safety of LYS006 in adult patients with mild to moderate ulcerative colitis.

2 Objectives and endpoints

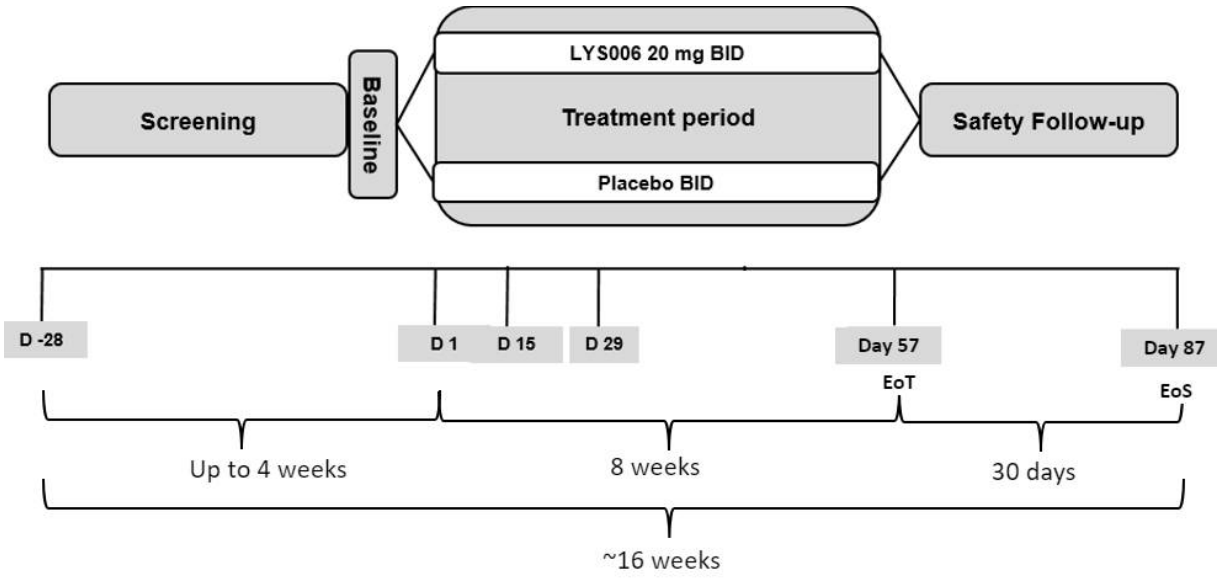
Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the induction of clinical remission by LYS006 in patients with mild to moderate ulcerative colitis compared to placebo	• Clinical remission rate at week 8 using the full Mayo score (see Section 12.4.1 for more details)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• 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 parameters, vital signs and ECG parameters)

3 Study design

This is a randomized, placebo-controlled, subject and investigator blinded, multicenter, parallel group study in patients with mild to moderate ulcerative colitis. Each individual subject will first undergo a screening period 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 visit. The total duration for each subject in the study will be up to 16 weeks. See Figure 3-1.

Figure 3-1 Study design



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

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

For the entire duration of the treatment period (8 weeks), subjects will receive twice-daily doses of LYS006 or placebo, so that the blind is maintained throughout the entire study. For further details, please refer to Section 6.

Safety assessments will include physical examination, ECGs, vital signs, standard clinical laboratory evaluations (hematology, biochemistry and urinalysis) as well as adverse event and serious adverse event monitoring.

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Screening

After signing informed consent, screening evaluations will take place from Day -28 to Day -1 (minimum screening duration of 7 days to enable collection of stool frequency and rectal bleeding subscores). During that period all safety and other assessments must be performed to evaluate eligibility. The endoscopy* is to be performed between Day -7 and Day -4 before the planned baseline visit. (Table 8-1).

*A colonoscopy is required if the patient has no documented colonoscopy within the preceding 12 months. All other subjects can have a sigmoidoscopy performed at screening.

Subjects will be provided with the paper diaries to record data on stool frequency and rectal bleeding parameters on a daily basis until the end of the study. In addition, study medication intake data will also be recorded by the subject for compliance reasons.

Subjects that fail screening, may be re-screened on one further occasion after discussion and agreement with the sponsor on a case by case basis.

Baseline

Eligible subjects will return for the Baseline visit on Day 1. Eligibility must be confirmed prior to randomization and required baseline assessments must be completed prior to dosing on Day 1.

Treatment

Subjects will be randomized to the respective treatment arm using a centralized Interactive Response Technology (IRT) system at the completion of Baseline visit, after eligibility is confirmed. Subjects will receive their morning dose of LYS006 or placebo at the site on Days 1, 29 and 57, CCI , once all pre-dose assessments have been completed. Subjects will then be provided study drug and may return home to continue their daily dosing regimen (self-administration).

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At all study visits, subjects will undergo safety and efficacy assessments, CCI as indicated in the Assessment Schedule and described in Section 8.

At all visits CCI subjects will return their used drug supply kits for compliance and accountability assessment Commercially Confidential Information

Subjects' diary data on stool frequency and rectal bleeding parameters will be checked by site personnel on visit days for efficacy assessment. Commercially Confidential Information

Subjects will be contacted by the Investigator/site staff during the study to ensure compliance/monitor safety by telephone or other means, if it is deemed appropriate or necessary by the Investigator.

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Follow up and End of Study visit (EoS)

After the last day of dosing (EoT), and all safety and efficacy assessments are completed, all subjects will enter a 30-day Post-Treatment Follow Up period without study drug administration. Subjects will then be asked to return to the site at Day 87 for the End of Study visit. At this visit, subjects will undergo final assessments as indicated in the Assessment schedule (Table 8-1). Upon completion of this visit, subjects will be discharged from the study.

4 Rationale

4.1 Rationale for study design

The study is blinded for study subjects and investigators/site staff until final database lock (except where indicated in Section 6.4) to reduce potential bias in the assessment of subjective readouts.

The chosen design follows the design recommended in the EMA Guideline (2018). As per guidelines, design of phase 2 trials should be parallel-group, subject and investigator blinded and placebo controlled.

Using placebo as treatment control is recommended by ICH E10 (Guyatt et al 1989): Choice of control group in clinical trials), to obtain information on a specific versus non-specific effects of active treatment. Elaborated further in Section 4.3.

Randomization is utilized for the allocation of subjects to either of the two treatment groups to avoid selection bias in the assignment of treatment. Random assignment of treatment will also help to achieve a balanced distribution of disease severity between the two treatment groups. A randomization ratio of 2:1 is used because of the inclusion of historical control data from similar historical UC trials (Section 12.4.2), which allows less exposure to placebo in this study without compromising the study power.

UC is a chronic inflammatory bowel disease with onset most frequently in young adulthood. Most patients with UC have a mild-to-moderate course characterized by periods of activity or remission. More than 90% of patients with UC are treated with 5-aminosalicylates (5-ASA) shortly after disease diagnosis, and most who achieve clinical remission with these medications continue them for maintenance of remission (Fumery et al 2018).

However, there is still unmet medical need and some patients will not respond adequately to 5-ASA, and may need to escalate therapy to systemic corticosteroids, or immunomodulators, or biologic therapies for induction and maintenance of remission. This population of patients not controlled with standard dose of conventional therapies and potentially requiring an escalation of therapy will be selected for investigating the efficacy of LYS006. Indeed, and as outlined in the scientific rationale for LYS006 in UC, the anti-inflammatory effect of LYS006 may induce disease control in these patients, providing an alternate option for these patients, prior escalating to immunosuppressive or biologic therapies.

Therefore, the selected population will include mild to moderate patients with full Mayo score from 5 to 10. In case LYS006 shows efficacy in such population, further investigation of LYS006 in more severe forms of UC may be considered in future studies.

In ulcerative colitis, incidence peaked in the age interval 20-30 years with a second peak in the ages 60-79 (Mak et al 2020), so including subjects between the ages of 18 to 75 is rational considering the natural tendency of disease.

4.2 Rationale for dose/regimen and duration of treatment

For this study, a dose of 20 mg BID is proposed to explore safety and efficacy in mild to moderate ulcerative colitis population. This dose is expected to be safe and provide full target inhibition CCI and therefore expected to generate a maximal clinical response.

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The 8-week treatment duration is based on the clinical consensus and current guidance documents. The EMA Guideline (2018) on the development of new medicinal products for the treatment of Ulcerative Colitis, recommends 6-12 weeks and the FDA draft guidance for industry on ulcerative colitis (FDA UC Draft Guidance 2016), refers to induction trials demonstrating efficacy after a short treatment duration such as 1 to 3 months. Assessing

efficacy at week 8 in this Proof-of-Concept study will inform further clinical development of LYS006 in ulcerative colitis.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

In this proof-of-concept study, the efficacy, safety and tolerability of LYS006 will be assessed using a subject and investigator-blinded study design as compared to placebo. The choice of placebo as treatment control is essential to obtain information on the specific versus non-specific effects of active treatment (ICH E10). Placebo as treatment control also provides the best way of evaluating the efficacy and of assessing the true safety and tolerability profiles of LYS006 in the phase II trial with the first exposure of subjects with ulcerative colitis. The short exposure of subjects with mild to moderate UC as specified in this protocol to placebo for 8 weeks, in addition to oral 5-ASA agents, is scientifically and ethically well accepted, as there is no evidence that short term restriction regarding other immunosuppressive therapy leads to longer term differences in outcomes. Furthermore, rescue medication will be available for subjects at the investigator's discretion (see Section 6.2.3).

4.4 Purpose and timing of interim analyses/design adaptations

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4.5 Risks and benefits

As the therapeutic effect of LYS006 in mild to moderate UC patients on top of first–line standard of care is currently unproven, patients may not benefit from the study treatment.

The risk to subjects in this trial will be minimized by adhering to the eligibility criteria, close clinical monitoring, and adequate post-treatment safety follow-up to capture any potential late occurring AEs.

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while for this present study, daily dosing of up to 20 mg BID is planned.

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Treatment for AEs should follow general guidelines for standard-of-care, and is at the discretion of the investigator or treating physician. There are no specific treatment recommendations for AEs that may possibly occur in in this trial.

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Due to early stage of development, there may be unknown risks of LYS006 which may be serious.

4.5.1 Blood sample volume

Approximately CCI from each subject is planned to be collected over a period of 16 weeks from Screening until EoS as part of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment schedule (Table 8-1).

A summary blood log is provided in the Site Operations Manual (SOM). Instructions for all sample collection, processing, storage and shipment information is available in the central Laboratory Manual.

See Section 8.5.3 regarding the potential use of residual samples.

5 Population

The study population will be comprised of patients with mild to moderate active UC, who are intolerant or have responded inadequately to conventional therapy with oral 5-ASA prior to screening. About 45 subjects will be enrolled in the study and randomized to LYS006 and placebo groups with an approximate ratio of 2:1. No replacement of patients is planned.

Subject selection is to be established by checking through all inclusion/exclusion criteria during screening and study baseline. A relevant record (e.g. checklist) must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a subject from enrollment into the study.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female subjects aged 18-75 years at screening
3. Patients diagnosed with UC established at least 3 months prior to screening.
4. Patients with mild to moderate UC which is defined by a total Mayo Score between 5 and 10 (inclusive), comprised of the following subscores;
    - Endoscopic subscore: 2 or 3 (determined from central reading of screening endoscopy)
    - Stool frequency subscore: 1-3

- Rectal bleeding subscore: 1-3
- Physician's global assessment subscore: 1-2.

  Please see the SOM for guidance on completion of Mayo scores

5. Disease must extend beyond 15 cm from the anal verge (assessed by screening endoscopy).
6. Patients must have responded inadequately or have intolerance to conventional therapy with oral 5-ASA prior to screening, and be willing to continue 5-ASA at a stable dose during the study treatment period. Inadequate response is defined by the following:
   - Active disease despite induction therapy with 5-ASA agents where adequate therapy is a stable oral 5-ASA dose.
   - Adequate therapy is an oral 5-ASA (mesalamine ≤4.8 g/day, sulfasalazine ≤6 g/day, balsalazide ≤7.5 g/day or olsalazine ≤3 g/day) with a stable dose administered for at least 4 weeks prior to the screening endoscopy.
   - In addition to oral 5-ASA, oral corticosteroids including oral budesonide are permitted provided the following criteria are met and the patient is willing to continue to continue the medication at a stable dose during the study treatment period
     - Oral corticosteroids are allowed if the dose is ≤ 10 mg/day with a stable dose administered for at least 4 weeks prior to the screening endoscopy.
     - Oral budesonide is allowed if the dose is ≤ 9 mg/day with a stable dose administered for at least 4 weeks prior to the screening endoscopy.
7. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Use of investigational drugs within 4 weeks or 5 half-lives of screening, whichever is longer; or longer if required by local regulations.
2. Confirmed laboratory findings at screening showing:
   - Total white blood cell count (WBC) outside the range of 3,000 – 12,000 /μL.
     - Subjects with mild leukocytosis (WBC not higher than 15,000 /μL) may be eligible, if the elevated WBC, according to the Investigator, is attributable to disease activity and/or to corticosteroid therapy and other causes such as hematological or infectious diseases can be excluded;
   - Platelets <100,000/μL;
   - Hemoglobin <9 g/dL and/or other signs of severe anemia
3. Are taking any of the prohibited medications listed in Table 6-2 and do not fulfill the washout period.

5. Has severe UC during the screening period, as defined by ≥6 bloody stools per day **AND** at least one of the following:
   - Pulse >90 bpm
   - Oral temperature of >37.8°C
   - Hemoglobin of <10.5 g/dL (applicable in assessment of severe UC in the event of ≥6 bloody stools per day)
   - CRP >30 mg/L
   - Erythrocyte sedimentation rate (ESR) >30 mm/h
6. Has previous diagnosis with Crohn's disease, indeterminate colitis, microscopic colitis or acute diverticulitis based on medical history.
7. 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.
8. History of hypersensitivity or allergy to the investigational compound and inhibitors of LTA4H or LTB4 being used in this study.
9. Active systemic infections (other than common cold) during the 2 weeks prior to randomization. Evidence of *Clostridium difficile* infection within 8 weeks or other intestinal pathogen infection within 4 weeks prior to the first dose of study drug.
10. History of toxic megacolon, abdominal abscess, symptomatic colonic stricture, or stoma; history or is at risk of colectomy.
11. History or presence of impaired renal function indicated by clinically significantly abnormal creatinine or BUN and/or urea values, or abnormal urinary constituents (e.g. albuminuria) at screening;

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15. History or symptoms of malignancy of any organ system, treated or untreated, within the 5 years prior to screening, regardless of whether there is evidence of local recurrence or metastases. Patients with a history of basal cell carcinomas and/or up to 3 squamous cell carcinomas of the skin are allowed if successful treatment has been performed, with no signs of recurrence. Actinic keratoses present at screening should be managed according to standard of care before randomization.
16. Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV) at screening. A positive HBV surface antigen (HBsAg) test, or if standard local practice, a positive HBV core antigen test, excludes a subject. Patients with a positive HCV antibody test should have HCV RNA levels measured. Patients with positive (detectable) HCV RNA should be excluded.
17. History of auto-immune or immunodeficiency diseases, or a positive human immunodeficiency virus (HIV) test result (ELISA and Western blot) test result at screening.

18. 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 hCG laboratory test at screening.
19. 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. Basic contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (i.e., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject
    - Barrier methods of contraception: Condom or Occlusive cap. ***Not applicable to Czech Republic.***
    - Use of oral, injected or implanted hormonal methods of contraception (see also table of prohibited treatment for guidance) or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

    In case of use of oral contraception women should have been treated with the same pill and dose for a minimum of 3 months before taking study treatment.

    Women are considered post-menopausal and not of child bearing potential if they have had
    - 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or
    - have had surgical bilateral oophorectomy (with or without hysterectomy) or
    - tubal ligation at least six weeks ago.

    In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
20. History of drug abuse or harmful alcohol use within the 12 months prior to dosing, or evidence of such abuse. Harmful alcohol use is defined as a history of, or current alcohol misuse/abuse, defined as “Five or more drinks on the same occasion on each of 5 or more days in the past 30 days."
21. Donation of 400 ml or more of blood within 8 weeks prior to baseline, or longer if required by local regulation.
22. Inability or unwillingness to undergo repeated venipunctures (e.g., due to poor tolerability or lack of access to veins).
23. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study. The investigator should make this determination, at

screening, in consideration of the patient's medical history and/or clinical or laboratory evidence of any of the following:

- Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy or bowel resection;
- Pancreatic injury or pancreatitis;
- Liver disease or liver injury as indicated by abnormal liver function tests as defined by the following 3 criteria at screening.
  - ALT must be within the normal range;
  - Serum bilirubin must not exceed 1.5 x ULN;
  - GGT, AST and alkaline phosphatase must not exceed 2 x ULN.

24. A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening (central read) or baseline (local read):
    - PR > 200 msec
    - QRS complex > 120 msec
    - QTcF > 450 msec (males)
    - QTcF > 460 msec (females)
25. Patients with clinically relevant primary sclerosing cholangitis
26. Patients who previously received more than one class of biologic therapy for UC (i.e. anti-TNF blockers).
27. History or current evidence of colonic dysplasia or adenomatous colonic polyps.

6 Treatment

6.1 Study treatment

LYS006 and its matching placebo will be taken orally by the subject (4 capsules each) twice daily, in the morning and in the evening.

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On visit days, the CCI administration shall occur at the clinical site.

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Study drug administration on other days will occur on an outpatient basis.

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Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing, and taking study treatment are outlined in the SOM.

6.1.1 Investigational and control drugs

The Investigational drug, LYS006 5 mg IR (immediate release) capsules and matching placebo will be prepared and supplied by Novartis to Investigator's site as double blind patient kits. Each subject will take 4 capsules to make up to a dose of 20 mg twice a day. Drug will be administered orally in accordance with the specified study procedures in Section 6.1

Table 6-1 Investigational and control drug

Investigational Drug	Pharmaceutical Dosage Form	Unit Dose	Route of Administration	Supply Type	Sponsor
LYS006	Hard Gelatin Capsule	5 mg	Oral	Double Blind patient kits	Novartis
Placebo	Hard Gelatin Capsule	0 mg	Oral	Double Blind patient kits	Novartis

6.1.2 Additional study treatments

No additional Novartis drug supplies beyond investigational drug and control drug on top of standard of care are included in this trial.

6.1.3 Treatment arms/group

Subjects will be assigned to one of the following 2 treatment groups in a randomization ratio of 2:1, for a total of 8 weeks:

- Group 1: LYS006 20 mg BID
- Group 2: matching placebo BID

Subjects will take 4 capsules of 5 mg at each dose to make up to 20 mg. There will be a morning and evening dose (4 capsules each) for all subjects.

All subjects will receive their respective supply of LYS006 or placebo capsules every 4 weeks during their scheduled visits to the site.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The investigator must instruct the subject to notify the study site about any new medications he/she takes after the subject is enrolled into the study.

All prescription medications, over-the-counter drugs, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Subjects are required to continue to take standard of care treatment (5-ASAs and if relevant oral corticosteroids (max 10 mg per day prednisone or equivalent) or oral budesonide (≤ 9 mg/day)) at a stable dose for four weeks prior to the screening endoscopy until the End of Treatment period.

Subjects on concomitant chronic treatment for hypertension, diabetes and/or other for chronic illness that may not confound the interpretation of study results or put the subject in risk are allowed to continue on their regular treatment regimen but it should be documented in the source document. The investigator must discuss the concomitant medications with the Sponsor on a case by case basis where there is a potential for these medications to alter the efficacy measurements, interfere with the study medication, or interpretation of results.

Hormonal contraception is allowed during the study, and is mandatory if it is the only method of contraception (please refer to inclusion/exclusion criteria).

Administration of paracetamol (acetaminophen) is acceptable, but must be documented.

6.2.2 Prohibited medication

Table 6-2 Prohibited medication

Medication	Required wash-out	Action taken (if taken during study treatment period)
Any UC biologic advanced therapies, in particular, anti-TNF alpha blockers, anti-integrin blockers, anti-IL-12/IL-23 blockers	Wash-out: 3 months or 5 half-lives (whichever is longer) prior to screening endoscopy	Discontinue study treatment
Any non-biologic advanced therapies, in particular JAK inhibitors	Wash-out: 4 weeks prior to screening endoscopy	Discontinue study treatment

Medication	Required wash-out	Action taken (if taken during study treatment period)
Any systemic immunosuppressant or immunomodulator, such as cyclosporine, methotrexate, cyclophosphamide, azathioprine	Wash-out: 6 weeks prior to screening endoscopy (except 3 months for cyclophosphamide)	Discontinue study treatment
Systemic corticosteroids with dose > 10 mg/day (equivalent prednisone)	Stable dose (up to 10 mg/d eq prednisone) for at least 4 weeks before screening endoscopy	Discontinue study treatment
Budesonide with dose > 9 mg/day	Stable dose (up to 9 mg/day for at least 4 weeks before screening endoscopy)	Discontinue study treatment
Topical anti inflammatory treatments (e.g. Topical 5-aminosalicylic acid (5-ASA) or topical steroids) for the treatment of ulcerative colitis	Washout: 2 weeks prior to screening endoscopy (not more than 2 single doses)	Discontinue study treatment
Systemic antibiotics such as metronidazole or ciprofloxacin	Washout: 4 weeks prior to screening endoscopy	Discontinue study treatment
Antidiarrheal, antimotility medications	NA	Discontinue study treatment

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6.2.3 Rescue medication

In cases where the investigator believes rescue medication is necessary, it may be administered but the subject must be discontinued from the study treatment. For example, if a subject's disease is worsening, a corticosteroid dose may be increased or an immunomodulatory agent may be introduced, and the subject should be discontinued from the study treatment.

If the ulcerative condition worsens after the treatment period is finished, any medically indicated rescue medications can be prescribed during the follow up period.

Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies after start of study drug in the (e)CRF.

6.2.4 Restriction for study subjects

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6.2.4.2 Other restrictions

Not applicable

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

The subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see 'Subject numbering' section in the Site Operations Manual.

6.3.2 Treatment assignment, randomization

Randomized treatment will be assigned to individual subjects on Day 1. Randomization of subjects will be carried out by Interactive Response Technology (IRT) system.

The randomization number is only used to identify which treatment the subjects have been randomized to receive.

Subjects who discontinued from study treatment before or after week 8 assessments will not be replaced.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treatment blinding

This is a subject, investigator-blinded study. Subjects and investigators will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

All site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 6.6.3)

Sponsor staff

The following unblinded sponsor roles are required for this study:

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Statisticians, statistical programmers and other personnel involved in study data analysis (e.g. drug supply manager) are allowed to access treatment assignment information for the purpose of any unblinded data analysis during or at the end of the study.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure unless otherwise allowed (Table 6-3).

Following final database lock all roles may be considered unblinded. See the blinding/unblinding table for an overview of the blinding/unblinding plan.

Table 6-3 Blinding levels

Role	Time or Event			CCI
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	
Subjects/Patients	B	B	UI	
Site staff	B	B	UI	
Drug Supply and Randomization Office	UI	UI	UI	
Unblinded sponsor staff (see text above for details)	B	UI	UI	
Statistician/statistical programmer/data analysts	B	B	UI	
All other sponsor staff not identified above	B	B	UI	

B Remains blinded

UI Allowed to be unblinded on individual patient level

6.5 Dose escalation and dose modification

Study treatment dose adjustments and/or interruptions are not permitted. Occasional interruptions in study treatment must be recorded on the Dosage Administration Record page of the CRF.

6.6 Additional treatment guidance

Not applicable

6.6.1 Recommended treatment of adverse events

There are no known expected AEs associated with LYS006 that would warrant specific treatment. Necessary medication as well as surgical or physical treatment used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.6.2 Treatment compliance

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The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

Compliance will be assessed by the investigator and/or study personnel using pill counts and information provided by the subject/use of the Patient Diary. This information should be captured in the source document at the respective visit and in eCRF. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- subject number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given subject.

6.7 Preparation and dispensation

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

Each study site will be supplied with study drug in packaging as described under the investigational and control drugs Section 6.1.1.

LYS006 will be administered to the subject via oral route of administration, at home/outpatient basis. See the Site Operations Manual.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

Refer to the Site Operations Manual for a complete list of ICFs included in this study.

8 Visit schedule and assessments

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8.1 Screening

In the case where a safety assessment at screening is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the subject must be excluded from the study.

It is permissible to re-screen a subject if he/she fails the initial screening e.g. due to washout period of concomitant medication; however, each case must be discussed and agreed with the sponsor on a case-by-case basis.

A new ICF will need to be signed if the investigator chooses to re-screen the subject after he/she has screen failed. All eligibility criteria must be re-checked, based on the most recent data available, and met prior to enrollment of the subject into the study.

All required screening activities must be performed when the subject is re-screened for participation in the study. An individual subject may only be re-screened once for the study.

Once the number of subjects screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the subjects who screen failed will not be permitted to re-screen.

If the re-screening is successful, the following information should be collected in the CRF:

- Date of the informed consent signature.
- All assessments done during the first screening period.
- All assessments repeated during the re-screening period (e.g. ECG, lab).
- Updated information as per latest status during the re-screening period, e.g., medical history, diagnosis.
- Adverse events based on the date of re-consent.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. See the SOM for the list of information to be collected for screening failures and further information on re-screening. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (Section 10.1.2, Section 10.1.3 for reporting details). If the subject fails to be randomized, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Data to be collected will include general patient demographics, relevant medical history and current medical conditions prior to study entry, diagnosis and other variables believed to influence UC severity or response to treatment, and any other assessments done for the purpose of determining eligibility for inclusion in the study. All medications and significant non-drug therapies (including herbal medicines, physical therapy and blood transfusions) taken within 4 weeks prior to first dose of study drug must be recorded on the CRF. Details are outlined in the Site Operational Manual.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3 Efficacy

Efficacy assessments are specified below, with the methods for assessment and recording specified in the Study Operations Manual. Efficacy assessments will be performed CCI at the timepoints defined in the Assessment schedule (Table 8-1). Follow instructions outlined in the SOM regarding sample collection, numbering, processing and shipment.

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8.3.1 Mayo Score

The Mayo score is an instrument designed to measure activity of UC. Mayo score comprises of four subscores: stool frequency, rectal bleeding, endoscopic findings and Physician's Global Assessment. Each subscore is graded from 0 to 3 with higher scores indicating more severe disease.

Table 8-2 Mayo score system for ulcerative colitis

Stool frequency	
0	Normal number of bowel movements for this patient
1	1 to 2 bowel movements more than normal
2	3 to 4 bowel movements more than normal
3	5 or more bowel movements more than normal
Rectal bleeding	
0	No blood seen
1	Streaks of blood with stool less than half the time
2	Obvious blood with stool most of the time
3	Blood alone passes
Endoscopic findings	
0	Normal or inactive disease
1	Mild disease (erythema, decreased vascular pattern)
2	Moderate disease (marked erythema, absent vascular pattern, any friability, erosions)

3	Severe disease (spontaneous bleeding, ulceration)
Physician's global assessment	
0	Normal
1	Mild disease
2	Moderate disease
3	Severe disease

The full Mayo score is the sum of four sub scores, ranging from 0 to 12.

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Clinical remission is defined in Section 12.4.1.

8.3.1.1 Subject diary: Stool frequency and Rectal bleeding

Stool frequency and rectal bleeding are the main clinical symptoms of ulcerative colitis. Calculation of the Mayo score requires an assessment of stool frequency and rectal bleeding. Data on these clinical symptoms will be recorded by subjects on a daily basis using a paper diary until the end of the treatment period. Subjects will be provided with instructions on how to complete the paper diary at the screening visit. These should be reviewed at each visit until EoT by site staff, with retraining provided to subjects if the diaries are not completed correctly.

See the Site Operations Manual for guidance on training the subjects in the use of the diary and using the diary data to complete the Mayo score.

8.3.1.2 Endoscopy

Assessment of clinical efficacy through longitudinal (repeated) endoscopic examination provides an objective readout and decreases the risk of having false positive results (based on clinical symptoms only). Endoscopy is the best means for assessment of extent and severity of colon mucosal inflammation.

Type of endoscopy

A screening colonoscopy is required if the patient has no documented colonoscopy within the preceding 12 months. If a documented report of colonoscopy performed within the 12 months preceding screening is available in the source notes, the patient can have a sigmoidoscopy performed at screening.

Sigmoidoscopies will be performed at all other visits.

The colonoscopy will require a bowel preparation with drinking a liquid that will trigger bowel-clearing diarrhea and will be performed with adequate sedation as per local clinical practice. The sigmoidoscopy will require enemas before the procedure to clean out the lower part of the colon.

The endoscopic report (historical colonoscopy or screening endoscopy) must be available in the source documents.

Scheduling of endoscopies

Subjects should be seen for all visits/assessments as outlined, or as close to the designated day as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

- Screening endoscopy: is to be performed between Day -7 and Day -4 before the baseline visit, to allow time to obtain endoscopic subscore report from the central read.
  Note: The endoscopic subscore from central read will be used to determine eligibility.

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Endoscopic subscore

The mucosal appearance during the sigmoidoscopic portion of endoscopic examination will be assessed for the Mayo endoscopic subscore based on the scoring system provided in the Section 8.3.1. The endoscopic appearance will be read by the central reader through video recorded during the procedure. Centrally-read endoscopic sub-scores will be transferred to the Sponsor electronically. A report will be provided to the site for the screening score to be used for eligibility purposes.

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8.3.1.3 Physician's Global Assessment

The physician's global assessment (PhGA) acknowledges the three other criteria of the Mayo score which includes, the patient's recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the patient's performance status. The grading will be 0, 1, 2, or 3, following the guidance in Table 8-2. PhGA must be performed by a qualified physician and it is recommended that the same physician performs this assessment for a particular subject throughout the study. Calculation of the full Mayo score requires a Physician's global assessment. This will be done at every visit of the subject to the site.

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8.3.4 Appropriateness of efficacy assessments

Ulcerative colitis is a chronic, relapsing disease characterized by diffuse mucosal inflammation of the colon involving the rectum and may extend proximally to part of the colon or the entire colon involving clinical manifestations of active disease involving blood and diarrhea.

As per FDA UC Draft Guidance (2016), the primary efficacy assessment tool used in clinical trials for the treatment of UC should consist of a combination of signs and symptoms assessment scales, best measures by a patient-reported outcome instrument, in combination with an endoscopic scale.

The Mayo scoring system is one of the most commonly used disease activity indices in placebo-controlled trials and registration trials in UC. In its complete form, it is composed of four parts: bleeding, stool frequency, physician assessment, and endoscopy findings.

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In addition, assessment of the clinical local severity through longitudinal (repeated) endoscopic examination provides an objective readout, decreases the risk of having false positive results (based on clinical symptoms only) and as a consequence is expected to limit the number of subjects to be exposed to the new investigational drug in this indication. .

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8.4 Safety

Safety assessments are specified below; methods of assessment and recording are specified in the SOM, with the assessment schedules (Table 8-1) detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 10.1

Table 8-4 Assessments & Specifications

Assessment	Description
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. Further examination may be required based on medical history and/or symptoms. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event on the Adverse event section of the CRF

Assessment	Description
Vital signs	Vital signs include body* temperature, Blood Pressure and pulse measurements. After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. *Oral body temperature must be measured at screening if the patient has ≥6 bloody stools per day and potentially meets exclusion criterion 5. Otherwise the site can use their standard method for collection of body temperature. Vital signs must be performed before dosing and as indicated in the Assessment schedule (Table 8-1)
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured. Height information will be collected at screening only.

The methods for each assessment and data recording details are specified in the SOM.

8.4.1 Laboratory evaluations

Central laboratories will be used for the analysis of scheduled hematology and clinical chemistry blood specimens collected as part of screening and safety monitoring (as detailed in the Assessment schedule (Table 8-1). Only laboratory results from the central laboratory can be used to determine subject's eligibility for the study. During the course of the study, unscheduled assessment can be performed if clinically indicated.

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside a **protocol-specified range** at screening, the assessment may be repeated once prior to randomization. If the repeat value remains outside of protocol specified ranges, the subject is excluded from the study.

In the case where a laboratory range is **not specified by the protocol**, but is outside the reference range of the laboratory at screening, a decision regarding whether the result is of clinical significance or not shall be made by the investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization.

In all cases, the investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the subject to continue in the study.

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant.

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Details of the collection and shipment of samples and the reporting of results by the central laboratory are provided to the investigators in a separate Laboratory Manual.

Blood Specimens

The following parameters will be analyzed from blood samples:

Table 8-5 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells (WBC), WBC morphology with differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry	Albumin, Alkaline phosphatase, ALT , AST , Gamma-glutamyl-transferase (GGT), Total Bilirubin, Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, CCI CCI Glucose, Estimated Glomerular Filtration Rate (eGFR) estimated by MDRD. For postmenopausal women, FSH is measured at screening to assist in confirming menopausal status. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.
HIV and hepatitis markers	Hepatitis B, Hepatitis C, HIV at screening
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Pregnancy Test	Serum / Urine pregnancy test

Urine specimens

Please see central lab manual for more information on sample collection and handling.

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8.4.2 Electrocardiogram (ECG)

A central reading of standard 12-Lead ECGs will be implemented. Full details of all procedures relating to the ECG collection and reporting are contained in the core laboratory technical manual or in the Site Operations Manual. At Baseline, local reading is allowed in order to assess the eligibility of the subject before randomization.

PR interval, QRS duration, heart rate, RR interval, QT interval, QTcF (Fridericia QT) will be collected.

The SOM has the preferred sequence of data collection during study visits, notably ECG collection (10 min rest, ECG recording over next 5 min suggested), precedes vital signs and blood sampling.

Clinically significant abnormalities must be reported as adverse events in the AE CRF.

8.4.3 Pregnancy and assessments of fertility

At screening and EoS (or last visit), a serum pregnancy test will be performed centrally.

Throughout the study, local urine pregnancy tests are sufficient. Additional urine pregnancy tests may be required, if a reason occurs such as subject reports delay in menstruation.

A positive urine pregnancy test requires immediate interruption of study drug until serum ß-hCG is performed and found to be negative. See Section 10.1.4 for guidance on pregnancy reporting and follow-up.

8.5 Additional assessments

No additional tests will be performed on subjects entered into this study.

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9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject is defined as when study treatment is stopped earlier than the protocol planned duration. Discontinuation of study treatment can be decided by either the subject or the investigator. Subjects may voluntarily discontinue the study for any reason and at any time. Investigator must discontinue the study treatment for a given subject, if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment **must** be discontinued under the following circumstances:

- Subject withdraws consent
- Pregnancy

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- Any protocol deviation that results in a significant risk to the subject's safety
- Major disease worsening requiring rescue medication Section 6.2.3) as judged by the investigator

Subjects who discontinue study treatment should NOT be considered withdrawn from the study UNLESS they withdraw their consent. Where possible, they should return for their End of Treatment visit as soon as possible after the last day of study medication, as defined in the Assessment schedule (Table 8-1). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact them for additional follow up as specified in Section 9.1.3.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table (Table 8-1).

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

For US: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For all other countries: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed and his/her scheduled end of the study visit have occured.

9.1.4 Study stopping rules

The study may be put on hold pending full safety data review if one or more of the following criteria are met:

- Two or more investigational drug (LYS006) related SAEs are reported
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- Other clinically significant events that in the opinion of the investigator or sponsor preclude to continue dosing Commercially Confidential Information

In these cases, ad hoc internal experts will carefully evaluate the safety data of the entire study. the experts will recommend whether the study can be continued, should be stopped or is other safety measures need to be taken.

In the event of the study stopping rules being met and the study being put on hold pending a full safety review, Novartis will promptly notify all concerned investigators/institutions, Ethics Committees/Review Boards and the Regulatory Authorities. The findings and recommendations of the internal experts will be documented and will be made available to the respective Ethics Committees/Review Boards and the Regulatory Authorities.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely discontinued subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. Study completion/ End of the clinical trial is defined as when the last subject completes his/her End of Study visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

All treated subjects should have a safety follow-up visit conducted 30 days after the last administration of study treatment. All SAEs reported during this time period must be reported as described in Section 10.1.3 and the SOM. The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See Section 10.1 for an overview of the reporting requirements.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by

the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events should be recorded on the Adverse Events CRF under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The Common Toxicity Criteria (CTC) AE grade: Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 of higher
2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose reduced/increased
- Drug interrupted/withdrawn

6. its outcome

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days (or 5 half-lives or end of study visit, whichever is longer) following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Commercially Confidential Information

Follow the instructions found in the Site Operations Manual for data capture methodology regarding AE collection for subjects that fail screening.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to ICH E2D Guideline FDA 2003).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an

emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guideline FDA 2003).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Chief Medical Office and Patient Safety (CMO & PS) as per Section 10.1.3

10.1.3 SAE reporting

10.1.3.1 Screen failures

SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

10.1.3.2 Randomized / Treated Subjects

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last administration of study treatment must be reported to Novartis within 24 hours of learning of its occurrence as described below.

Any SAEs experienced after this period should only be reported to Novartis if the Investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Follow-up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from the study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the Site Operations Manual regarding the submission process for reporting SAEs to Novartis. Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

10.1.4 Pregnancy reporting

If a female trial subject becomes pregnant, the study treatment should be stopped, and the trial subject must be asked to read and sign pregnancy consent form to allow the Study Doctor follow up on her pregnancy. To ensure subject safety, each pregnancy occurring after signing the informed consent must be **reported to Novartis within 24 hours** of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Chief Medical Office and Patient Safety (CMO&PS) Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient/subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Chief Medical Office and Patient Safety (CMO & PS) department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Chief Medical Office and Patient Safety (CMO & PS). As such, instances of misuse or abuse are also to be reported using the SAE form/CRF.

Table 10-1 summarizes the reporting requirements.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 10.1 respectively.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

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Additional details on actions required in case of liver events are outlined in Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unplanned local laboratory CRF.
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Section 9.1: Discontinuation of study treatment section), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event

- Thorough follow-up of the liver event should include
  - Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, PT/INR and GGT. If total bilirubin is elevated >2 x ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Resting should be continued up to resolution.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Exclusion of underlying liver disease, as specified in Table 16-3; Section 16.2
- Imaging such as abdominal US, CT or MRI, as appropriate
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

All follow-up information and procedures performed must be recorded as appropriate in the CRF. Refer to the SOM for additional details.

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11 Data Collection and Database management

11.1 Data collection

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF) using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected in the eCRFs by the investigator staff. .\

The investigator/designee is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate. After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis staff (or designated CRO working on behalf of Novartis) review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff are required to respond to the query and confirm or correct the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Patient reported outcomes will be collected via paper diaries. Relevant data will be entered into the CRF.

Randomization codes and data about all study drug(s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis or delegated CRO representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis or delegated CRO organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

Data analysis will be conducted on all subject data at the time the trial ends, or at the time of any interim analysis. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Full details will be described in Statistical Analysis Plan (SAP) document.

12.1 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.

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

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12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including Mayo scores/subscores, previous anti-TNFα treatment experience, baseline corticosteroid use/dose and disease duration will be summarized overall and also by treatment group for the safety analysis set.

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Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

12.3 Treatments

The safety set will be used for treatment compliance analysis.

Data for study drug administration and changes in dosage will be listed by treatment group and subject.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by treatment group and subject.

12.4 Analysis of the primary endpoint(s)

The primary aim of the study is to assess the induction of clinical remission by LYS006 compared to placebo in patients with mild to moderate ulcerative colitis. The PD analysis set will be used for the primary analysis.

12.4.1 Definition of primary endpoint: Clinical remission

The primary endpoint of this study is the clinical remission rate at the End of treatment (EoT) visit (CCI Week 8 for subsequent protocol amendments), i.e. the proportion of the patients who reach the status of clinical remission at the EoT visit.

Clinical remission is defined as a full Mayo score of 2 points or lower, with no individual subscore exceeding one point.

Subjects with early discontinuation for reasons other than COVID-19 before the EoT visit, or use of rescue/prohibited medication during the treatment period, or missing endoscopy score at EoT will be considered failed to reach remission.

Discontinuation prior to the defined treatment period, or subjects who were not able to complete endoscopy at EoT visit due to local COVID-19 related restrictions will be considered as missing data.

12.4.2 Statistical model, hypothesis, and method of analysis

The binary endpoint of clinical remission rate will be modelled with binomial distribution and analyzed via Bayesian approach. 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). The derivation of this informative prior can be found in the study sample size documentation. 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 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 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%.

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12.4.3 Handling of missing values/censoring/discontinuations

In the primary analysis, subjects who discontinue from the study for reasons other than COVID-19 prior to EoT visit, or have received rescue or prohibited medication for the treatment of ulcerative colitis during the treatment period will be considered failed to reach clinical remission. Discontinuation prior to the defined treatment period, or subjects who were not able to complete endoscopy at EoT visit due to local COVID-19 related restrictions will be considered as missing data. Any missing subscore at CCI Week 8 (subsequent protocol amendments) will lead to a non-evaluable clinical remission status and the subject will also be considered failed to reach 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.

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12.5 Analysis of secondary endpoints

Assessing safety and tolerability of LYS006 in this population is the secondary objective of the study.

12.5.1 Safety endpoints

For all safety analyses, the safety set will be used. All tables, figures and listings tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided, if there were death during the study. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

Adverse events

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

The number (and percentage) of subjects with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, and other significant adverse events leading to discontinuation.

The number and percentage of subjects with adverse events of infections, CCI will be summarized by treatment.

A subject with multiple adverse events within a primary system organ class/preferred term is only counted once towards the total of this primary system organ class/preferred term.

Summaries will also be provided for the number of adverse events by treatment.

Vital signs

Abnormalities (and relevant orthostatic changes) will be flagged and reported. The subjects with abnormal values will be visualized along with all subjects in overlaid individual plots by treatment group.

ECG

Abnormalities will be flagged and reported. For continuous ECG parameters, the subjects with abnormal values will be visualized along with all subjects in overlaid individual plots by treatment group. Clinically notable events such as those in Exclusion Criteria 24 will be summarized separately by treatment group.

Clinical laboratory evaluations

Shift tables using the low/normal/high classification based on laboratory normal ranges will be used to compare baseline to the worst on-treatment value. For continuous laboratory parameters, the subjects with abnormal values will be visualized along with all subjects in overlaid individual plots by treatment group.

In particular, abnormalities in selected liver, CCI function parameters/events (Section 10.2) will be summarized separately by treatment group. Graphical presentation will be used as needed.

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12.7 Interim analyses

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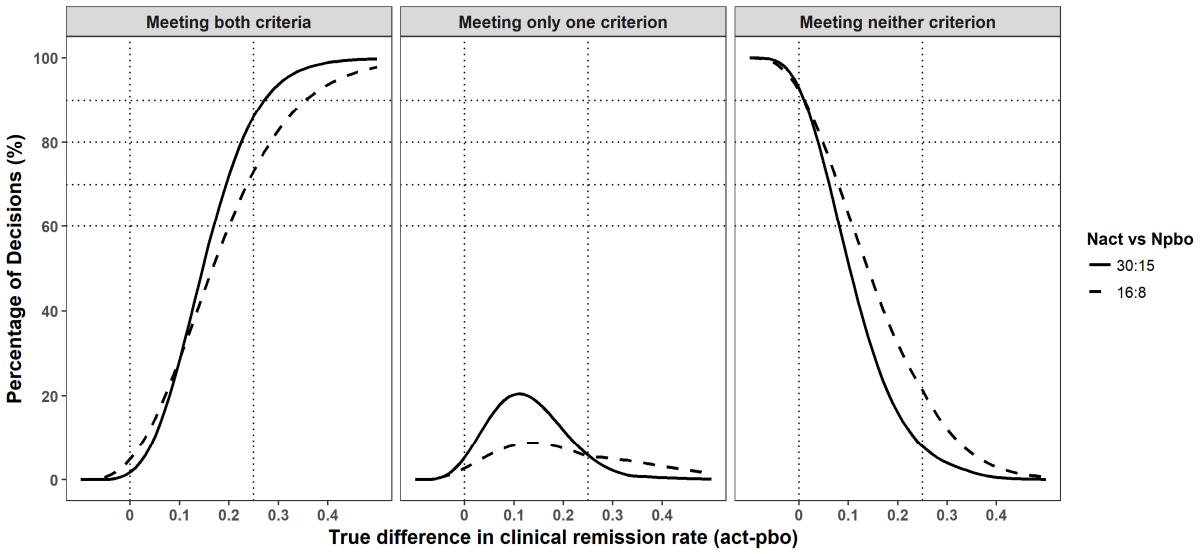
12.8 Sample size calculation

Approximately a total of 45 subjects are planned to be enrolled, with a randomization ratio of 2:1. Use of historical control data, as described in Section 12.4.2 helps to reduce the within-study control.

12.8.1 Primary endpoint(s)

Figure 12-2 below illustrates the operating characteristics for the design of 45 subjects with 2:1 randomization ratio. The outcome of approximately 50% data is also shown in the same figure. The informative prior for the placebo group is included in the analysis. Assuming the true treatment difference in remission rate is 25% between LYS006 and placebo CCI , the probability of meeting the dual efficacy criteria, stated in Section 12.4.2, is 86% with the full 45 subjects and 73%, for half the size. If there is no difference between LYS006 and placebo in clinical remission rate, the chance of meeting dual criteria is below 5% as shown in the left hand panel of the figure and the chance of meeting neither criterion is 92%, as shown in the right hand panel.

Figure 12-2 Operating charateristics for current design: 30 on LYS006 vs. 15 on placebo with historical placebo



12.8.2 Secondary endpoint(s)

Not applicable.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive

2001/20/EC, US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis by the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

13.3 Publication of study protocol and results

The key design elements of this protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (*defined as last patient last visit*) and finalization of the study report the results of this trial will either be submitted for publication and/or posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed or overseen by Novartis Pharma Auditing and Compliance Quality Assurance (or CRO working on behalf of Novartis), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including

incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 10 (Safety Monitoring) must be followed and the Study Lead informed.

15 References

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values

Please refer to the Central Laboratory Manual for a list of clinically significant laboratory values.

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