

## **Statistical Analysis Plan (SAP)**

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED  
PARALLEL GROUP STUDY TO ASSESS THE EFFICACY AND SAFETY  
OF INDUCTION THERAPY WITH LYC-30937-EC IN SUBJECTS WITH  
ACTIVE ULCERATIVE COLITIS**

**Protocol LYC-30937-2001  
SAP Version 1.0 (Final)**

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**Statistical Analysis Plan Signature Page**

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## TABLE OF CONTENTS

TABLE OF CONTENTS.....	3
LIST OF TABLES.....	4
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS.....	5
1 INTRODUCTION.....	6
2 STUDY OVERVIEW.....	6
2.1 Study Population.....	6
2.2 Study Design.....	6
2.3 Assessments.....	7
2.4 Anticipated Number of Subjects.....	7
3 STUDY OBJECTIVES AND ENDPOINTS.....	7
3.1 Objectives.....	7
3.2 Efficacy Measures.....	8
4 ANALYSIS PLAN OVERVIEW.....	10
5 ANALYSIS SETS.....	10
5.1 Full Analysis Set (FAS).....	10
5.2 Per Protocol Population (PP).....	10
5.3 Safety Set.....	11
5.4 PK and PD Set.....	11
5.5 Protocol Deviations and Treatment Misallocation.....	11
6 STATISTICAL ANALYSES.....	11
6.1 Statistical Power and Sample Size Considerations.....	11
6.2 Baseline, Endpoint and Missing Value Definitions.....	12
6.2.1 Baseline Definition.....	12
6.2.2 Subgroups.....	12
6.2.3 Visit Windows.....	13
6.2.4 Replicate Data.....	14
6.2.5 Missing Data.....	14
6.2.6 Change From Baseline.....	15
6.3 Statistical Analyses.....	15
6.3.1 Subject Baseline Characteristics.....	15
6.3.2 Subject Disposition.....	16
6.3.3 Interim Analysis.....	17
6.3.4 Treatment Compliance and Exposure.....	17
6.3.5 Efficacy Endpoint Analyses.....	18
6.3.5.1 Primary Endpoint Efficacy Analysis.....	18
6.3.5.2 Additional Analyses of the Primary Efficacy Endpoint.....	19
6.3.5.3 Secondary Efficacy Endpoints Analyses.....	19

6.3.5.4	Exploratory Efficacy Endpoints Analyses .....	20
6.3.6	Safety Analyses.....	20
6.3.6.1	Adverse Events .....	20
6.3.6.2	Other Safety Data.....	20
6.3.7	Exploratory Analyses.....	22
7	APPENDICES .....	24
7.1	Appendix 1. Prior and Concomitant Medication Start/Stop Date Imputation .....	24
7.2	Appendix 2. Adverse Event Start/Stop Date Imputation .....	25
7.3	Appendix 3. Ulcerative Colitis Disease Assessment by Mayo Score.....	26

**LIST OF TABLES**

Table 1.	Visit Windows for Assessments Done at Baseline and Weeks 1, 2, 4, and 8 or Baseline and Weeks 1, 2, 4, 8, and 10 .....	13
Table 2.	Visit Windows for Assessments Done at Baseline and Weeks 2, 4, and 8 or Baseline and Weeks 2, 4, 8, and 10 .....	14
Table 3.	Visit Windows for Assessments Done at Baseline and Week 8.....	14

## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
5-ASA	5-aminosalicylic acid
CD	cluster of differentiation
DSMB	Data Safety Monitoring Board
EC	enteric coated
ECG	Electrocardiogram
FAS	Full Analysis Set
IFN- $\gamma$	interferon gamma
IL	Interleukin
MMS	modified Mayo score
PD	Pharmacodynamics
PGA	physician's global assessment
PK	Pharmacokinetic
PP	Per Protocol
SAE	serious adverse event
TEAE	Treatment-emergent adverse event
TMS	Total Mayo Score
UC	ulcerative colitis
ULN	upper limit of normal

## 1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to summarize the study design and objectives, and provide details of the outcome and statistical methods required for the statistical analysis of data from Protocol LYC-30937-2001. The statistical plan described is an a priori plan and no unblinded analysis prior to the preparation of this plan has been conducted.

## 2 STUDY OVERVIEW

### 2.1 Study Population

The study will include adult males and non-pregnant non-lactating females age 18-75 years (except Czech Republic where upper age is 65 years) with active ulcerative colitis (UC) diagnosed at least 6 months prior to Screening with a minimum disease extent of  $\geq 15$  cm from the anal verge (diagnosis confirmed by both endoscopic and histologic evidence). They will have active UC defined as a Total Mayo Score (TMS) of 4-11 inclusive, and Mayo endoscopic subscore of  $\geq 2$  and a Mayo rectal bleeding subscore of  $\geq 1$ . They may be receiving as treatment for UC, stable doses of oral aminosalicylates and/or thiopurines and/or corticosteroids prior to entering the trial.

### 2.2 Study Design

This study is a randomized, double-blind, placebo-controlled, parallel group Phase 2 study comparing LYC-30937-enteric coated (EC) 25 mg and placebo in subjects with active UC. All subjects who meet eligibility criteria will be randomized 1:1 to receive either LYC-30937-enteric coated (EC) 25 mg or placebo. Study drug will be administered as an oral capsule to be taken once daily. Approximately 120 subjects will be randomized in the trial.

Subject randomization will be stratified across treatment groups by type of biologic therapy (subjects that have received biologic therapy (e.g. anti-tumor necrosis factor (anti-TNF), anti-integrin) and those that are naïve to biologic therapy). The randomization will be stratified to ensure that at least 50% of subjects included in the study are biologic therapy naïve and that these subjects are assigned evenly between the 2 arms.

Subjects who complete the double-blind portion of the trial through Week 8 will have the option of receiving open-label treatment with LYC-30937-EC in a separate open-label extension study (LYC-30937-2002) which will have the objective of collecting long-term safety data on LYC-30937-EC in subjects with active UC.

## 2.3 Assessments

All subjects who are randomized will be monitored for adverse events (AEs) and serious (SAEs) from the time the subject signs informed consent through last subject visit. Assessments will include:

- Safety assessments: clinical laboratory tests; monitoring of AEs, medical history, and concomitant medications and procedures; vital signs including body temperature; physical examinations; Electrocardiograms (ECGs); monitoring of plasma LYC-30937 concentrations and compliance.
- Efficacy assessments: Mayo subscores of stool frequency, rectal bleeding, endoscopic evaluation, and physicians global assessment (PGA); fecal calprotectin.
- PK/PD assessments: plasma pharmacokinetic (PK) parameters; colon tissue PK parameters; and exploratory pharmacodynamics (PD) biomarkers.

## 2.4 Anticipated Number of Subjects

Approximately 120 subjects will be randomized into the study in a 1:1 ratio to LYC-30937-EC or placebo.

# 3 STUDY OBJECTIVES AND ENDPOINTS

## 3.1 Objectives

### Primary Objective

The primary objective will be to assess the efficacy of LYC-30937-EC in inducing remission compared with placebo in subjects with active UC over treatment duration of 8 weeks.

### Secondary Objectives

The secondary objectives will be to evaluate the safety and tolerability of LYC-30937-EC compared with placebo in subjects with active UC.

### Exploratory Objectives

The exploratory objectives will be to assess the plasma PK of LYC-30937-EC and its metabolite, determine the colon tissue exposure of LYC-30937-EC, evaluate PD biomarkers, and assess endoscopic improvement at Week 8 in subjects with active UC; and assess efficacy in a subset of subjects with previous exposure to biologic therapy.

## 3.2 Efficacy Measures

The individual Mayo subscore components will be summed to give a modified Mayo score (MMS) of 0-9 or a total Mayo score (TMS) of 0-12 with higher scores indicating more active disease. Endoscopy finding, stool frequency, and rectal bleeding will be summed to calculate MMS. PGA will not be used to calculate MMS. All 4 subscores including PGA, endoscopy finding, stool frequency, and rectal bleeding will be summed to calculate TMS. Efficacy will be assessed using both TMS and MMS.

### Primary Efficacy Endpoint

The primary efficacy endpoint is Clinical remission at Week 8 using MMS.

A responder for the Clinical remission using MMS is defined as any subject that has a Mayo stool frequency subscore of  $\leq 1$ , a Mayo rectal bleeding subscore of 0 and a Mayo endoscopy subscore of  $\leq 1$ . Subjects with a missing Week 8 response will be considered non-responders.

The Mayo score (total and modified) will use the Mayo endoscopy score assessed by the independent central reader. In the case that a centrally read endoscopic Week 8 result is missing, the Week 8 endoscopic subscore assessed by the investigator will be used.

Calculation of the Week 8 MMS for efficacy endpoints requires that the endoscopy score be available. In other words, if the endoscopy score is missing, the MMS will be considered missing. If the stool frequency score and/or the rectal bleeding score is missing at Week 8, these scores may be carried forward from the most recent post-baseline previous visit for which the score is available.

The primary endpoint will be analysed using the Full Analysis Set (FAS). An additional Per Protocol (PP) population analysis will be completed. FAS and PP are as defined in [Sections 5.1](#) and [5.2](#).

### Secondary Efficacy Endpoints

The secondary efficacy outcome is Clinical remission at Week 8 using TMS. A responder for the clinical remission using TMS is defined as any subject that has a TMS score of  $\leq 2$ , with no individual score  $> 1$  and with a rectal bleeding score of 0.

Calculation of the Week 8 TMS for efficacy endpoints requires that the PGA subscore and endoscopic subscore be available. In other words, if either the PGA score or endoscopic score is missing, the TMS will be considered missing. If the stool frequency score and/or rectal bleeding score is missing at Week 8, these scores may be carried forward from the most recent post-baseline previous visit for which the subscore is available.



The secondary endpoint of Clinical remission at Week 8 using TMS will be analysed using the Full Analysis Set (FAS) and Per Protocol (PP) populations as defined in [Sections 5.1](#) and [5.2](#).

Other secondary endpoints include:

- Clinical response at Week 8 using MMS. This is defined as a reduction from baseline MMS of  $\geq 2$  points and  $\geq 25\%$ , and a decrease from baseline in rectal bleeding subscore of  $\geq 1$  point or an absolute rectal bleeding subscore of  $\leq 1$  point.
- Clinical response at Week 8 using TMS. This is defined as a reduction from baseline TMS of  $\geq 3$  points and  $\geq 30\%$ , and a decrease from baseline in rectal bleeding subscore of  $\geq 1$  point or an absolute rectal bleeding subscore of  $\leq 1$  point.
- Change from baseline in TMS at Week 8.
- Change from baseline in MMS at Week 8.
- Change from baseline in fecal calprotectin at Week 8.

Change from baseline is defined in [Section 6.2.6](#). For efficacy endpoints using the change from baseline, if the baseline value or Week 8 value is missing, the subject will be excluded from the analysis.

### Exploratory Efficacy Endpoints

Additional exploratory efficacy endpoints will be considered, including the following:

#### **Endoscopy**

- Endoscopic improvement at Week 8, where a responder is defined as any subject with an endoscopic subscore of  $\leq 1$  point.
- Endoscopy subscore of 0 at Week 8.

As a post-hoc analysis, and dependent on the number of subjects in each randomized stratum an additional endpoint of endoscopic improvement at Week 8 by previous biologic therapy status might be considered.

#### **TMS**

- Clinical remission at Week 8 using TMS by previous biologic therapy status.
- Clinical response at Week 8 using TMS by previous biologic therapy status.
- Clinical remission at Week 8 using TMS by subgroup (subgroups defined in [Section 6.2.2](#)).

As a post-hoc analysis, and dependent on the number of subjects in each randomized stratum an additional endpoint of Change from baseline in TMS at Week 8 by previous biologic therapy status might be considered.

#### **MMS and MMS subscores**

- Absolute and percent change from baseline in MMS at Week 8.
- Absolute and percent change from baseline in Mayo subscores at Week 8.

### Safety Endpoints

- The incidence and type of AEs, SAEs, and AEs that led to discontinuation of study treatment

### PK and PD Endpoints

- PK parameters will be derived from measurements of plasma LYC-30937 concentrations, and its metabolite.
- Colon tissue concentrations of LYC-30937 and its metabolite.
- PD biomarkers in subjects who consent to biologic samples (blood, stool, colon tissue). Biomarkers that may be assessed where feasible and acceptable include:
  - inflammatory proteins and cytokines
  - enumeration of lymphocytes subtypes
  - lymphocyte infiltration and metabolic remodeling
  - expression of proteins associated with gut-homing and lymphocyte activation
  - expression of small nucleotide polymorphism associated with UC
  - transcriptional profiling for immune cell signatures
  - taxonomic composition of subject microbiomes

## **4 ANALYSIS PLAN OVERVIEW**

The final analysis will be performed after official database lock, once the last subject has completed the Week 10 follow-up visit. No adjustments will be made for multiplicity.

The analysis of safety, PK and PD endpoints will be limited to descriptive statistics.

## **5 ANALYSIS SETS**

### **5.1 Full Analysis Set (FAS)**

The FAS is defined as all randomized subjects. Subjects will be included in the treatment group to which they were randomized, regardless of the treatment they actually received. All efficacy analyses will be performed on the FAS.

### **5.2 Per Protocol Population (PP)**

The PP is defined as all randomized subjects who are at least 80% compliant with taking study medication and who completed the Week 8 efficacy assessments. Subjects will be included in the treatment group to which they were treated. The PP population will exclude those subjects who had specific major protocol violations that would impact the assessment of efficacy and these will be finalized before database lock. The patients excluded from the PP population will

be fully defined and documented in a separate memo with reasons for exclusion prior to database lock. Primary and key secondary efficacy analyses will also be performed on the PP. The FAS will be primary.

### **5.3 Safety Set**

The Safety Set is defined as all randomized subjects who received at least one dose of study drug. For summaries/listings where treatment group is included, subjects will be included in the treatment group to which they were actually treated. All safety analyses will be performed on the Safety Set.

### **5.4 PK and PD Set**

The Safety PK Set is defined as up to 20 randomized and LYC-30937-EC treated subjects who have at least one blood sample collection at Visit 3, 4, 5 or 6.

The Serial PK Set is defined as a subset of up to 12 randomized and LYC-30937-EC treated subjects with sufficient serial blood sample collections at Visit 5 to derive at least 1 PK parameter.

The Plasma PK Set is defined as all randomized and LYC-30937-EC treated subjects who are not in the Safety PK Set or the Serial PK Set and have one blood sample collection at Visit 5.

The PD Set is defined as all randomized and LYC-30937-EC treated subjects who consent to biologic samples (blood, stool, colon tissue) and have at least one colon tissue concentration or PD biomarker endpoint measurement. All PD analyses will be performed on the PD Set.

### **5.5 Protocol Deviations and Treatment Misallocation**

Key and non-key protocol deviations will be listed. Protocol deviations will be used to assess the quality of study conduct but there are no plans to use them to define an additional population for analyses. Decisions to exclude patients or data from any statistical analyses will be decided on a case-by-case basis before database lock and without knowledge of treatment assignment and reasons will be documented. Treatment misallocation will be handled as described in the analysis set definitions in [Sections 5.1](#) through [5.3](#).

## **6 STATISTICAL ANALYSES**

### **6.1 Statistical Power and Sample Size Considerations**

A total of approximately 120 subjects will be randomized into the study and using a 1:1 randomization ratio of LYC-30937-EC 25 mg or placebo.

A sample size of 60 subjects per group will achieve approximately an 88% power to detect superiority in the remission rate of the active treatment group compared to the placebo treatment group. The placebo treatment group remission rate is assumed to be 6.7%. The power was computed for the case when the actual treatment group remission rate is 25% for a delta of 18.33%. The test statistic used is the one-sided Z test (pooled). The alpha level of the test was targeted at 0.05. Additionally, a sample size of 54 subjects per group excluding drop-outs will achieve approximately a 78% power to detect non-inferiority in the remission rate of the active treatment group compared to the placebo treatment group where the placebo treatment group remission rate is assumed to be 7.41% and the actual treatment group remission rate is 25.92% for a delta of 18.51%. All sample size calculations were performed using the Power Analysis & Sample Size (PASS), version 11 software.

Assuming a drop-out rate of 10%, the study will enroll approximately 120 subjects in order to complete 108.

## **6.2 Baseline, Endpoint and Missing Value Definitions**

### **6.2.1 Baseline Definition**

Baseline for demographics; height; weight; body mass index (BMI); physical examination (PE); electrocardiogram (ECG); laboratory results (including chemistry, hematology, and coagulation panels, and urinalysis); stool (including fecal calprotectin); Mayo Score; stool frequency and rectal bleeding; physician's global assessment (PGA); and endoscopy and biopsy is defined as those assessments from Screening.

Baseline for vital signs; body temperature; and PD biomarkers is defined as those assessments from prior to drug administration at Week 0 / Study Day 1 / Visit 2. If a subject is missing a pre-dose assessment from Visit 2 then a previous measurement (from Visit 1 / Screening or an unscheduled visit, for vital signs or PD biomarkers) will be used as baseline, if available. If no previous measurement is available, then the baseline will be missing. If there are multiple assessments prior to Week 0 / Study Day 1 / Visit 2, then the measurement closest to Week 0 / Study Day 1 / Visit 2 will be used.

### **6.2.2 Subgroups**

The following subgroup variables will be used for efficacy analyses:

- Age at baseline (<65, >=65 years)
- Sex (Male, Female)
- Race (White, Non-White)
- Region ((Europe: Czech Republic, Hungary, Netherlands, Poland, and Serbia versus North America)

- Weight (<55, 55-<70, 70-<85, 85-<100, >=100 kg)
- Baseline TMS Score (4-6, 7-9, >-10)
- Duration of disease (<2, 2-<5, 5-<10, >=10 years)
- Concomitant use of corticosteroids at baseline (yes, no)
- Previous biologic therapy status (yes, no)
- Previous use of immunosuppressants (yes, no)

### 6.2.3 Visit Windows

Data at scheduled visits will be assigned to analysis visits as defined in this section and in the Visit Window tables below which are provided based on how frequently the assessments are done. To ensure that all visits have the possibility to be included in the summaries, the visit window will also classify all unscheduled and early termination visits. The analysis visits will be derived in terms of study days since the first dose of study treatment. These analysis visits will be utilized in the summary and analyses of efficacy and safety endpoints.

If a subject has more than 1 assessment in a visit window, only the assessment that is closest to the Scheduled Visit Day will be used for analysis. In case where 2 assessments have the same distance from the Scheduled Visit Day, the later assessment will be used for analysis. The early termination visit will be assigned to an analysis visit based on the window below.

The Week 8 efficacy endpoints will use the visit window for summarization of Day  $\geq$  44. The Week 8 safety assessments will use the window of Day 44 – Day 64, except for assessments which have only 1 scheduled post-baseline assessment, (eg, ECG) which will use the window of Day  $\geq$  2.

**Table 1. Visit Windows for Assessments Done at Baseline and Weeks 1, 2, 4, and 8 or Baseline and Weeks 1, 2, 4, 8, and 10**

Analysis Visit	Scheduled Visit Day	Visit Window for Summarization
Baseline	Day -28 to 1	$\leq$ Day 1
Week 1	Day 8	Day 2 – Day 11
Week 2	Day 15	Day 12 – Day 22
Week 4	Day 29	Day 23 – Day 43
Week 8	Day 57	Day 44 – Day 64
Week 10	Day 71	Day $\geq$ 65

**Table 2. Visit Windows for Assessments Done at Baseline and Weeks 2, 4, 8, and 10**

Analysis Visit	Scheduled Visit Day	Visit Window for Summarization
Baseline	Day -28 to 1	$\leq$ Day1
Week 2	Day 15	Day 2 – Day 22
Week 4	Day 29	Day 23 – Day 43
Week 8	Day 57	Day 44 – Day 64
Week 10	Day 71	Day $\geq$ 65

**Table 3. Visit Windows for Assessments Done at Baseline and Week 8**

Analysis Visit	Scheduled Visit Day	Visit Window for Summarization
Baseline	Day -28 to 1	$\leq$ Day1
Week 8	Day 57	Day $\geq$ 2

#### 6.2.4 Replicate Data

For each parameter, if two or more non-missing values are in the same visit window, then the one collected on the day that is closest to the target day will be used in the analysis irrespective of whether the data came from a planned or unplanned visit. If there are 2 study visits that are equally close to the target visit day, then the later assessment will be used. All data will be provided in the data listings.

#### 6.2.5 Missing Data

For efficacy analyses the primary time point of interest is Week 8. For efficacy endpoints using the proportion of responders, subjects with a missing Week 8 response will be considered non-responders (this includes subjects who discontinue early). For efficacy endpoints using the change from baseline, if the baseline value or Week 8 value is missing, the subject will be excluded from the analysis.

The Mayo score (total and modified) will use the Mayo endoscopy score assessed by the independent central reader. In the case that a centrally read endoscopic Week 8 result is missing, the Week 8 endoscopic subscore assessed by the investigator will be used.

Calculation of the TMS for efficacy endpoints requires that the PGA subscore and endoscopic subscore be available. If the stool frequency score and/or rectal bleeding score is missing, these scores may be carried forward from the most recent previous visit for which the subscore is available. If either the PGA score or endoscopic score is missing, the TMS will be considered missing.

Calculation of the MMS for efficacy endpoints requires that the endoscopy score be available. If the stool frequency score and/or the rectal bleeding score is missing, these scores may be carried forward from the most recent previous visit for which the score is available. If the endoscopy score is missing, the MMS will be considered missing.

Missing PK concentrations and PD data will be treated as missing in the calculation of summary statistic. For serial PK sampling, missing concentrations will be treated as missing in the calculation of PK parameters and concentrations below the lower limit of quantification (LLOQ) will be treated as zero or missing in the calculation of PK parameter and zero in the calculation of summary statistics.

### 6.2.6 Change From Baseline

Absolute change from baseline is defined as:

$$\text{Value of parameter post-treatment} - \text{Value of parameter at baseline}$$

Percent change from baseline is defined as:

$$(\text{Value of parameter post-treatment} - \text{Value of parameter at baseline}) / \text{Value of parameter at baseline} * 100$$

If the baseline value is missing for a subject, then change from baseline will not be calculated for that subject. The subject will not be included in the summarization / analysis of that parameter.

## 6.3 Statistical Analyses

The following general comments apply to all statistical analyses and data presentations.

- Summaries will include frequency, percentages, and missing for categorical data; and non-missing subjects, mean, standard deviation, and median, minimum and maximum for continuous data.
- Individual subject listings of all data represented on the electronic case report forms (eCRFs) will be provided to facilitate the investigation of tabulated values and to allow for the clinical review of all efficacy and safety parameters.
- Version 9.3 (or higher) of SAS® statistical software package will be used to provide all summaries, listings, graphs, and statistical analyses.

### 6.3.1 Subject Baseline Characteristics

**Demographic information and baseline subject characteristics** include:

- Age at baseline (years) defined as screening date year – birth year.
- Age at diagnosis (years) defined as diagnosis date year – birth year.

- Sex
- Ethnicity
- Race
- Region (Europe: Czech Republic, Hungary, Netherlands, Poland, and Serbia versus North America)
- History of tobacco, drug abuse, alcohol (Never, Current, Former)
- Baseline height, weight, BMI
- Biologic therapy status at baseline
- Baseline TMS and MMS score
- Duration of disease (years) – defined as screening date year – UC diagnosis date year.
- Baseline C-Reactive protein and C-Reactive protein categories (< 5, ≥ 5 mg/L)
- Baseline fecal calprotectin and fecal calprotectin categories (≤ 250, > 250 - ≤ 500, > 500 μg/g)
- Concomitant Medication Use at baseline (None, 5-ASA, Corticosteroids, Thiopurines, 5-ASA + Corticosteroids, 5-ASA + Thiopurines, 5-ASA + Corticosteroids + Thiopurines, Other)

Demographic information and baseline subject will be summarized by treatment group and overall.

### **Medical History**

Subjects with reported medical history will be listed by treatment group.

### **Prior and Concomitant Medications and Procedures**

Medications will be coded using World Health Organization Drug Dictionary Enhanced (WHO DDE) (Version MAR2016 or higher). Medications are considered concomitant if the medication start date is prior to the first dose of study drug. Both UC and non-UC medications are summarized by Anatomical Therapeutic Chemical Classification (ATC) level 3 (third level indicates the therapeutic/pharmacologic subgroup) and generic medication name. Concomitant procedures will be listed.

#### **6.3.2 Subject Disposition**

The overall number of subjects screened and screen failures will be presented. Screen failure reasons will be listed. A listing, grouped by randomized strata, will be provided that indicates the subject's date and time of informed consent and randomization, randomized treatment assignment, randomization number, first and last dose date. A listing will be provided of



randomized subjects who did not meet all inclusion/exclusion criteria, and which criteria were not met.

The number of subjects included in each of the analysis populations (ie, randomized, FAS, Safety, PP) will be listed and summarized by treatment group. Reasons for exclusion from each population will be documented in a memo that indicates each subject's inclusion in/exclusion from the populations and the reason for exclusion from each of the populations. Number of subjects entering the open-label extension study will be summarized.

The number and percentage of subjects completing the study will be presented for each treatment group and overall for the randomized subjects. Reasons for premature discontinuation of the study, as recorded on the eCRF will be summarized (number and percentage) by treatment group and overall. A listing of all FAS subjects who prematurely discontinued the study will be presented, and the primary reason for discontinuation of not completing the study will be provided.

### **6.3.3 Interim Analysis**

There is no plan to conduct an interim analysis.

However, a Data Safety Monitoring Board (DSMB), independent of the sponsor, will be established to review safety data as specified in the DSMB charter. The DSMB will be comprised of a pharmacokineticist, a therapeutic expert and a statistician. The DSMB's initial planned review will take place when the first 30 subjects treated have completed at least 4 weeks of treatment. Accumulated safety data (AEs, AEs of special interest, SAEs, withdrawals due to AEs, vital signs, body temperature) and available plasma PK data will be included for this initial review. Frequency of DSMB meetings will be specified in the DSMB charter. The DSMB may recommend changes to the trial due to safety concerns based on their review. Any necessary blinding plan to assure the study data remains blinded to sponsor personnel and others involved in the trial, and additional relevant details of DSMB review activities will be provided in the DSMB charter.

More detail related to the DSMB is contained in the DSMB Charter.

### **6.3.4 Treatment Compliance and Exposure**

Exposure summary by treatment group and overall will be presented for the Safety population. The distribution of subjects by the total number of days on treatment ( $\leq 1$ , 2 - 8, 9 - 15, 16 - 29, 30 - 57 and  $\geq 58$  days) will be presented as will descriptive statistics for the duration of treatment. Duration of treatment is calculated (in days) as last dose date – first dose date +1. Drug interruptions are expected to be minimal and will not be accounted for in the duration of treatment definition.

Drug compliance is calculated as (number of capsules taken)/(number of scheduled capsules) × 100. For a patient who drops out early, the number of scheduled tablets is the number the patient should have taken until the time subject dropped out. The compliance is only calculated for patients who had returned all the dispensed bottles. The percentage of subjects who were < 80%, 80% - < 100%, 100% - < 120%, and ≥ 120% compliant will be summarized for the Safety population.

### 6.3.5 Efficacy Endpoint Analyses

Mayo scores; subscores including stool frequency, rectal bleeding, PGA, and endoscopic findings; and fecal calprotectin will be listed and summarized by treatment group and scheduled visit window. TMS, MMS, and fecal calprotectin will be summarized descriptively in both continuous and categorical manner by treatment group and scheduled visit window. Line graphs will be produced to present mean MMS and TMS at baseline and Week 8.

A listing of individual outcomes for each of the efficacy endpoints will also be presented by treatment group. Listings will include a flag to designate subjects with and without prior biologic therapy exposure. Summaries of efficacy data will also be presented by prior biologic therapy exposure and by treatment group. The definition for subjects with prior biologic therapy exposure is described in [Section 2.2](#).

#### 6.3.5.1 Primary Endpoint Efficacy Analysis

The primary efficacy analyses will be based on the FAS population. The statistical test will be a one-sided hypothesis test performed at the 5% level of significance. The primary efficacy outcome is the percentage of subjects who achieve a clinical remission at Week 8 of treatment using MMS. The number and percentage of subjects in each treatment group will be tabulated. The null and alternative hypotheses are as follows:

$$H_0: p_1 \leq p_2 \text{ and, } H_a: p_1 > p_2$$

where  $p_1$  is the proportion of subjects who achieve clinical remission with LYC-30397-EC and  $p_2$  is the proportion of subjects who achieve clinical remission with placebo.

To test the null hypothesis a Pearson chi-square test will be used. In addition, the difference in proportion of subjects who achieve a clinical remission at Week 8 of treatment (LYC-30937 minus placebo) and corresponding 90% confidence interval will also be estimated.

The following SAS code will be used:

```
PROC FREQ;
  TABLES TREATMENT*MREMISS / CHISQ RISKDIFF ALPHA=0.1;
RUN;
```

Where TREATMENT=1 for LYC-30937-EC and =0 for placebo; MREMISS='Y' for subjects who achieve a clinical remission and ='N' for subjects who do not achieve a clinical remission.

### 6.3.5.2 Additional Analyses of the Primary Efficacy Endpoint

The above analysis will also be conducted on the PP population.

As a post-hoc analysis, an additional Cochran-Mantel-Haenszel statistical analysis might be considered to test the association between treatment and clinical remission at Week 8 using MMS after adjusting for the randomization strata (biologic therapy status).

### 6.3.5.3 Secondary Efficacy Endpoints Analyses

The following secondary efficacy endpoints: Clinical Remission using TMS, Clinical Response using MMS and Clinical Response using TMS will be summarized and analysed using the same statistical methodology as the primary endpoint described in [section 6.3.5.1](#). Clinical remission at Week 8 using TMS will also be presented by subgroup, where subgroups are as defined in [section 6.2.2](#).

#### Change from Baseline in MMS and TMS

The change from baseline in MMS and TMS at Week 8 will be summarized using descriptive statistics by treatment group. The change from baseline in TMS will be analysed using an analysis of covariance (ANCOVA) with a factor for treatment and a covariate for baseline scores. The difference in the change from baseline in TMS (LYC-30937 minus placebo) and corresponding 90% confidence interval will also be estimated. The following SAS code will be used:

```
PROC GLM;
  CLASS TREATMENT;
  MODEL tmschg = TMSBASE treatment;
  ESTIMATE 'lyc-pLA' -1 1 / CL ALPHA=0.1;
RUN;
```

Where TREATMENT=1 for LYC-30937-EC and =0 for placebo; TMSBASE is the baseline TMS; and TMSCHG is the change from baseline TMS at Week 8. Subjects who are missing the baseline or Week 8 TMS will be excluded from the analysis.

#### Change from Baseline in fecal calprotectin

The change from baseline in fecal calprotectin at Week 8 will be summarized and analysed using the same statistical methodology as the change from baseline in TMS described above.

### **6.3.5.4 Exploratory Efficacy Endpoints Analyses**

The exploratory efficacy endpoints that are categorical will be summarized and analysed using the same statistical methodology as the primary endpoint described in [Section 6.3.2](#). The continuous exploratory efficacy endpoints will be summarized and analysed using the same statistical methodology as the secondary efficacy endpoint change from baseline in TMS described above.

### **6.3.6 Safety Analyses**

#### **6.3.6.1 Adverse Events**

Verbatim descriptions of AEs will be coded using Version 19.0 or higher of MedDRA. Treatment-emergent adverse events (TEAEs) are defined as adverse events (AEs) that first occur, or worsen, after the first dose of study medication and within 14 days after the permanent discontinuation of the study medication. AEs that occur in subjects who fail screening will only be listed if they were the reason the subject was a screen failure.

An overall summary of AEs will include the number of subjects who experienced at least one AE of the following categories: any AE, any TEAE, any related TEAE, any severe TEAE, any serious TEAE, any related SAE, any serious TEAE leading to death, any TEAE leading to withdrawal of study treatment, any TEAE leading to premature discontinuation from the study, any TEAE leading to dose interruption of test article, and any serious TEAE leading to withdrawal of study treatment. Subjects who die will also be summarized.

The number and percentage of subjects reporting a TEAE in each treatment group will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity (National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.03). The incidence of TEAEs will be summarized by preferred term and treatment group, for all TEAEs, related TEAEs, serious TEAEs and TEAEs leading to treatment discontinuation. For all analyses of TEAEs, if the same AE (based on preferred term) is reported for the same subject more than once, the AE is counted only once for that preferred term and at the highest severity and strongest relationship to test article. Should there be any SAEs resulting in death, these will be listed and summarized separately.

#### **6.3.6.2 Other Safety Data**

#### **Laboratory Values**

Summaries of laboratory data will include hematology, chemistry, urinalysis and coagulation parameters. Descriptive statistics (based on standard international (SI) units) for chemistry, hematology and coagulation values will be summarized by treatment group at each time point.

Box-plots for chemistry and hematology laboratory values by visit and treatment group will be provided.

Subjects with chemistry and hematology laboratory values above 2 standard deviations (SD) of ULN will be listed. Laboratory abnormal values of special interest will be determined based on the criteria below. Any subjects meeting the criteria at any time post-baseline will be summarized by treatment group.

<b>Chemistry</b>
Alanine Aminotransferase (ALT) > 3x ULN a)
Aspartate Amino transferase (AST) > 3x ULN b)
Alkaline phosphatase (ALP) > 400 U/L
Lactate $\geq$ 2x baseline value and >25 mg/dL
Total Bilirubin >34.2 mmol/L
<b>Hematology</b>
Leukocytes < $2 \times 10^9/L$

- a) is the upper limit of the normal range (55 U/L)
- b) is the upper limit of the normal range (34 U/L)

**Vital Signs**

Seated blood pressure (systolic and diastolic), temperature, respiratory rate and heart rate will be summarized using descriptive statistics. Descriptive statistics of the absolute change from baseline to each post-baseline visit window will also be provided. For change from baseline, a subject must have a baseline measurement and a measurement at that visit window to be included in the summaries.

**Electrocardiogram (ECGs)**

The QTc interval will be presented by using the Fridericia ( $QTcF = QT/(RR)^{1/3}$ ) correction ( $RR = \text{heart rate}/60$ ). The QTcF values and absolute changes from baseline to Week 8 will be summarized using descriptive statistics. For change from baseline, a subject must have a baseline measurement and a measurement at Week 8 to be included in the summaries. All other ECG parameters will be listed.

By-subject listings of vital signs, ECG, lab data, physical examination, and abnormal findings on the physical examination will be provided.

**Special safety topics of interest**

Certain safety topics of special interest will be specifically evaluated and will be discussed in the Clinical Study Report (CSR). These include but are not limited to:

- Repeated episodes of vomiting - above the severity and/or frequency of the baseline ulcerative colitis symptoms

- Persistent abdominal pain that - above the severity and/or frequency of the baseline ulcerative colitis symptoms
- Elevated body temperature
- Elevations in liver related clinical lab parameters: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (ALP)
- Lactate and lactate dehydrogenase elevations

These topics will be assessed using existing listings and tables as relevant.

### 6.3.7 Exploratory Analyses

#### Plasma PK Data

Listings of LYC-30937 and metabolite concentrations will be generated for the Safety PK Set, the Serial PK Set and the Plasma PK Set separately by analyte and scheduled timepoint and/or visit window. LYC-30937 and metabolite concentrations will also be summarized by number of subjects, mean, standard deviation, median and minimum and maximum values by PK set, analyte, and scheduled timepoint and/or visit window.

For serial PK concentrations, individual concentration versus time plots will be produced using actual time from Visit 5 drug administration on a linear and semi log scale. Mean ( $\pm$ SD) concentration versus nominal time plots will also be produced for the Serial PK Set using a linear and semi log scale.

The following PK parameters for LYC-30937 and its metabolite will be derived for the Serial PK Set:

$C_{max}$	Maximum observed plasma concentration
$T_{max}$	Time at which maximum observed plasma concentration $C_{max}$
$AUC_{0-t}$	AUC up to time t using linear-log trapezoidal rule, where t is the last time point with concentrations above the lower limit of quantitation (LLOQ)

The PK parameters will be summarized by number of subjects, mean, standard deviation, median and minimum and maximum values by analyte.

#### Colon Tissue Concentrations

Individual LYC-30937 and metabolite concentrations from the 3 biopsies at Visit 6 (Week 8) from each colon segment (rectum, sigmoid, descending, transverse, ascending and in selected subjects the ileocecum) where disease is present will be listed by analyte and biopsy site for subjects in the PD Set. The LYC-30937 and metabolite concentrations from the 3 biopsies will also be averaged at each biopsy site and the average concentrations will be listed by analyte and biopsy site for subjects in the PD Set. If < 3 or > 3 biopsies are collected from a given site, all

biopsies collected will be averaged. The average LYC-30937 and metabolite concentrations in colon tissue will also be summarized by number of subjects, mean, standard deviation, median, minimum, and maximum values by analyte, biopsy site, and scheduled visit window.

**PD Biomarkers**

Listings of PD biomarkers from blood, stool, or colon tissue biopsy will be generated for subjects in the PD Set by treatment group and scheduled visit window. The PD biomarkers may also be summarized by biomarker, treatment group, and scheduled visit window.

The table below lists PD biomarkers by biologic sample type that may be selected for investigation from the biologic samples collected in this trial. The ultimate selection of biomarkers for evaluation may involve a review of feasibility and also may be based on relevant information regarding these biomarkers that emerge during the course of this study.

Sample type	Sample	Biomarker Analysis
Blood	Whole blood or PBMC	Leukocyte characterization by flow cytometry: including but not limited to $\alpha 4\beta 7$ , Treg, PD-1, Annexin V, CD62L, glucose/fatty acid uptake
	Plasma	Cytokine profile by immunocapture assays: including but not limited to IL8, IL10, IFN $\gamma$ , IL17, IL6, IL1 $\beta$
Stool	Soluble fraction	Cytokine profile by immunocapture assays: including but not limited to IL8, IL10, IFN $\gamma$ , IL17, IL6, IL1 $\beta$
	RNA	gene chip or nanostring analysis
	DNA	Sequencing for microbiome characterization
Biopsy	Lysate from whole biopsy	Cytokine profile by immunocapture assays: including but not limited to IL8, IL10, IFN $\gamma$ , IL17, IL6, IL1 $\beta$
	RNA	gene chip analysis
	Formalin fixed	H&E and Immunohistochemistry: including but not limited to CD3, PD-1, CD62L, Annexin V

CD3 = cluster of differentiation 3 protein complex; CD62L = Lselectin; IFN gamma = interferon gamma; IL = interleukin; PBMC = peripheral blood mononuclear cells; PD-1 = programmed cell death protein 1; Treg = regulatory T cells, DNA = deoxyribonucleic acid,; RNA = ribonucleic acid.



## 7 APPENDICES

### 7.1 Appendix 1. Prior and Concomitant Medication Start/Stop Date Imputation

<b>Imputation Rules for Partial Dates (D = day, M = month, Y = year)</b>			
<b>Parameter</b>	<b>Missing</b>	<b>Additional Conditions</b>	<b>Imputation</b>
Start date	D only	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	M and D	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y not same as Y of first dose of study drug	Use Jan 01 of Y
M, D, and Y	None - date completely missing	Day prior to date of first dose of study drug	
Stop date	D only	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Last day of month
	M and D	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31 of Y
M, D, and Y	None - date completely missing and NOT ongoing	Date of last dose of study drug	

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month. Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.



## 7.2 Appendix 2. Adverse Event Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)			
Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of study drug M and/or Y not same as date of first dose of study drug	Date of first dose of study drug First day of month
	D and M	Y same as Y of first dose of study drug Y prior to Y of first dose of study drug but same as Y of screening date	Date of first dose of study drug Date of screening date
	D, M, Y	None - date completely missing	Date of first dose of study drug
Stop date for AEs	D	M and Y same as M and Y of last dose of study drug M and/or Y not same as date of last dose of study drug	Date of last dose of study drug Use last day of month
	D and M	Y same as Y of last dose of study drug Y not same as Y of last dose of study drug	Date of last dose of study drug Use Dec 31 of Y
	D, M, Y	None - date completely missing	No imputation, but assume ongoing

Note: AE = Adverse Event

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month. Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

### 7.3 Appendix 3. Ulcerative Colitis Disease Assessment by Mayo Score

The TMS is a scoring system for the assessment of UC activity calculated based on 4 parameters (PGA, endoscopy findings, rectal bleeding, and stool frequency). The MMS is calculated based on 3 parameters (all the aforementioned parameters apart from the PGA).

The 4 components are described and scored as follows:

- stool frequency<sup>a</sup> (expressed in relation to the subject’s “normal” baseline number of stools when not having a flare and this will be documented at screening):
  - 0 = normal number of stools for the subject
  - 1 = 1-2 more stools than normal
  - 2 = 3-4 stools more than normal
  - 3 = 5+ stools more than normal
- rectal bleeding<sup>b</sup>:
  - 0 = no blood seen
  - 1 = streaks of blood < 50% of the time
  - 2 = obvious blood with stool most of the time
  - 3 = passes blood without stool
- PGA<sup>c</sup>:
  - 0 = normal
  - 1 = mild disease
  - 2 = moderate disease
  - 3 = severe disease
- endoscopic findings:
  - 0 = normal or inactive disease
  - 1 = mild disease (erythema, decreased vascular pattern)
  - 2 = moderate disease (marked erythema, absent vascular pattern, friability, erosions)
  - 3 = severe disease (spontaneous bleeding, ulcerations)

<sup>a</sup> Each subject serves as their own control to establish the degree of abnormality of stool frequency.

<sup>b</sup> The daily bleeding score represents the most severe bleeding of the day.

<sup>c</sup> The PGA acknowledges the three other criteria, the subject’s recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the subject’s performance status.

Each of these individual scores will be summed to give a MMS of 0-9 or a TMS of 0-12.

Subjects were requested to enter all stools and associated rectal bleeding daily in their diary starting at Screening. Mayo scores are calculated using the stool frequency and rectal bleeding data obtained from the subjects daily diary entries. Stool frequency and rectal bleeding data from the most recent 3 days prior to the study visit (consecutive 3 days is preferred or non-consecutive

are used, if the most recent 3 days are not consecutive). If 3 days of diary data were not available, data from the 2 most recent days prior to the study visit were used. Data were not to be used from the following days:

- a. The day medications for constipation, diarrhea, or bowel irregularity are taken
- b. The day(s) of a procedure or preparation for a procedure (eg, enemas, laxative, clear liquid diet) that would affect bowel frequency or blood content of stool
- c. The 48 hours following the use of anti-motility medication (eg, loperamide)
- d. The 48 hours following endoscopy.

Stool frequency subscore calculation: The number of stools each of the 3 days is totaled individually. The subject's normal number of stools is subtracted from each daily stool total. The Mayo subscore is assigned to each days "normalized" stool total. These Mayo subscores are totaled for the 3 days and averaged (rounded to the nearest integer). This average is used to calculate the Mayo score.

Rectal bleeding subscore: The worst bleeding score from each of the 3 days is selected, totaled and averaged (rounded to the nearest integer). This average is used to calculate the Mayo score.

The PGA was completed by the Investigator (or designee) at Screening and at Week 8.

A colonoscopy was performed at screening to assess disease severity. Depending upon disease extent, either a flexible sigmoidoscopy or colonoscopy was performed at Week 8. The screening colonoscopy was to image the entire colon to determine areas of inflammation and demarcation. If the inflammation identified at screening was determined to be left-sided disease, defined as extending  $\geq 15$  cm from anal verge and with clear demarcation at not higher than 5 cm below the splenic flexure, then the Week 8 endoscopy could be a flexible sigmoidoscopy instead of a colonoscopy. All endoscopies performed were conducted using the investigative site's standard practice including bowel preparation. The endoscopies (either colonoscopy or flexible sigmoidoscopy) were performed at the site and the endoscopy video recording was sent to the ICON Medical Imaging for blinded, independent central reader review and assignment of the Mayo endoscopy subscore. Central readers are experienced at reviewing and Mayo scoring endoscopies and they received study-specific training prior to their reading endoscopies for this trial. This training included ensuring their understanding that the presence of "friability" is not considered consistent with remission and therefore, if present, the Mayo endoscopic subscore must be at least 2.