LYCERA

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 NUMBER: LYC-30937-2001

STUDY PHASE: 2

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LIST OF ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
5-ASA	5-aminosalicylic acid
AST	aspartate aminotransferase
ATP	adenosine triphosphate
ATPase	mitochondrial ATP synthase enzyme
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma (concentration-time) curve from time 0 to 24 hours post-dose
BLQ	below the limit of quantitation
BP	blood pressure
BUN	blood urea nitrogen
C.	*Clostridium*
CD	Crohn's Disease
CFR	Code of Federal Regulation
C_{max}	maximum observed plasma concentration
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology for Adverse Events
CYP	Cytochrome P450
DBP	diastolic blood pressure
DSMB	Data Safety Monitoring Board
EC	enteric coated
ECG	electrocardiogram
eCRF	electronic case report form
EIU	exposure in utero
ET	early termination
FAS	full analysis set
FDA	Food and Drug Administration
FE	food effect
FSH	follicle-stimulating hormone
GCP	good clinical practice

GLP	good laboratory practice
GMP	good manufacturing practice
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDL	high-density lipoprotein
HEENT	head, eyes, ears, nose and throat
hERG	human ether-a-go-go related gene
HIV	human immunodeficiency virus
HPMC	hydroxyl-propyl methyl-cellulose
HR	heart rate
hsCRP	high sensitivity C-reactive protein
IBD	inflammatory bowel disease
IC_{50}	50% inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IWRS	interactive web-based response system
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLOQ	lower limit of quantitation
MAD	multiple ascending dose
MCH	mean cell hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MMF	mycophenolate mofetil
MMS	modified Mayo score
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
OLE	open-label extension
OXPHOS	oxidative phosphorylation
PD	pharmacodynamics
PGA	Physician's Global Assessment

PK	pharmacokinetics
PT	prothrombin time
PVSS	Pharmacovigilance and Safety Services
q.d.	*quaque Die*, once daily
RBC	red blood cell
ROS	reactive oxygen species
RR	respiration rate
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SI	international system units
SUSAR	suspected unexpected serious adverse reaction
T	temperature
TEAE	treatment emergent adverse event
T_{max}	time at which maximum observed plasma concentration (C_{max})
TMS	total Mayo score
TNBS	trinitrobenzene sulfonic acid
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
WBC	white blood cell

1.0 PROTOCOL SUMMARY

Indication

Ulcerative Colitis (UC)

Study Rationale

Inflammatory bowel disease (IBD) is a complex autoimmune disorder that consists of UC, Crohn's Disease (CD), and nonspecific colitis that remains a disease of high unmet medical need. Current therapies are limited by either low response rates or poor tolerability. LYC-30937 enteric-coated (EC) acts to induce apoptosis of chronically activated lymphocytes such as those thought to drive the inflammation of UC. LYC-30937 demonstrated efficacy in animal models of IBD and selective induction of apoptosis in chronically activated human lymphocytes. LYC-30937-EC has also shown safety, tolerability, and a favorable pharmacokinetic (PK) profile in healthy subjects up to single doses of 300 mg and 7 days of daily dosing at 200 mg and in UC subjects in single doses of 25 and 100 mg. The mechanism of action of selective induction of apoptosis in chronically activated lymphocytes, the demonstration of efficacy in IBD models, and the safety, tolerability, and PK profile demonstrated in the Phase 1 program supports the further of assessment of the efficacy LYC-30937-EC in inducing remission in subjects with active UC.

Study Objectives

The objective of this study is to evaluate the efficacy, safety, and tolerability of LYC-30937-EC compared to placebo in subjects with UC. In addition, selected PK and pharmacodynamic (PD) parameters will be assessed. 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.

Primary Objectives

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 a 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

Exploratory objectives include determining plasma PK and the colon tissue exposure of LYC-30937-EC, assessment of endoscopic improvement at Week 8, evaluating PD biomarkers, and assessing efficacy in subjects with previous exposure to biologic (includes tumor necrosis factor [TNF]-alpha antagonist and integrin receptor antagonist agents) therapy.

Study Population

This study will include adult males and nonpregnant, nonlactating females with active UC.

Study Design and Assessments

All subjects who meet the eligibility criteria will be randomized in a 1:1 ratio to LYC-30937-EC 25 mg or matching placebo. The randomization will be stratified by previous treatment with biologic therapy such that at least 50% of the randomized subjects who have never received biologic therapy (ie, are biologic naïve).

Assessments

Safety assessments:

Adverse events (AEs) will be collected from the time of signing the informed consent. All subjects who are randomized will be monitored for AEs until the time they leave the study.

Additional safety assessments:

- Vital signs including body temperature
- Physical examinations
- Electrocardiograms (ECGs)
- Clinical laboratory assessments
- Monitoring of plasma LYC-30937 concentrations
- AEs of special interest

Efficacy assessments:

- Stool frequency
- Rectal bleeding;
- Disease severity assessed by endoscopy (either flexible sigmoidoscopy or colonoscopy)

PK assessment:

- Blood will be collected for determining plasma LYC-30937 concentrations and its metabolite LYC-53552.
- Colon tissue will be collected for exploratory analysis of colon tissue concentrations of LYC-30937 and its metabolite.

PD assessment (exploratory):

- Blood, stool, and colon tissue analysis for PD parameters may be performed in consenting subjects where feasible and acceptable.

Endpoints

Primary Efficacy Endpoint:

- The proportion of subjects who achieve a clinical remission at Week 8 using the modified Mayo score (MMS). Clinical remission using MMS is defined as Mayo stool frequency subscore of ≤ 1, Mayo rectal bleeding subscore of 0 and Mayo endoscopy subscore of ≤ 1

Secondary Efficacy Endpoints:

- The proportion of subjects who achieve clinical remission at Week 8 using the total Mayo score (TMS). Clinical remission using TMS is defined as a TMS of ≤ 2, with no individual score > 1, and rectal bleeding score of 0
- The proportion of subjects with a clinical response at Week 8, defined as a reduction from Baseline in MMS of ≥ 2 points and $\geq 25\%$, and a decrease from baseline in rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 point

- The proportion of subjects with a clinical response at Week 8, defined as a reduction from Baseline in TMS of ≥ 3 points and ≥ 30%, and a decrease from baseline in rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 point

- The change from baseline TMS at Week 8

- The change from baseline to Week 8 in fecal calprotectin

Exploratory Efficacy Endpoint:

- The proportion of subjects with endoscopic improvement at Week 8, defined by a Mayo endoscopic subscore of ≤ 1 point

- The proportion of subjects with clinical remission, response, and endoscopic improvement at Week 8 who had previously received biologic therapy; who were refractory to biologic therapy (during their initial course of biologic treatment), or who lost response to biologic therapy or were intolerant of biologic therapy

Safety Endpoint:

- The incidence and type of AEs, serious AEs (SAEs), and AEs that led to discontinuation of treatment

PK and PD Endpoints:

- PK parameters will be derived from plasma concentrations of LYC-30937 (and its metabolite); colon tissue (exploratory) will be assayed for concentration of LYC-30937 and its metabolite; exploratory PD biomarkers will be assayed from blood, stool, and colon tissue.

Anticipated Number of Subjects

Approximately 120 subjects will be randomized into the study and dosed in a 1:1 ratio to LYC-30937-EC 25 mg or matching placebo.

Anticipated Number of Sites

Approximately 66 sites

First Subject Screened

2nd quarter 2016

End of Study

Last subject last visit is expected to occur in approximately December 2017

Study Countries

The study is being conducted in North America (Canada, United States) and Europe (Czech Republic, Hungary, Netherlands, Poland, Serbia)

2.0 INTRODUCTION

2.1 Background

Inflammatory bowel diseases such as ulcerative colitis (UC), Crohn's Disease (CD), and nonspecific colitis are chronic autoimmune diseases with significant unmet medical need. Manifestations of the disease are unpredictable and can be progressive and, in certain cases, may result in life-threatening complications. Current small molecule therapies result in mainly symptomatic relief and current biologic therapies result in sustained remission in less than 25% of UC and 50% of CD patients, respectively.[1,2] All treatment options are associated with significant safety concerns, notably increased infection risk due to sustained immune suppression.[3] New treatment options are needed as surgical resection of the bowel remains a necessary intervention for a substantial portion of patients even after the introduction of biologic agents as treatments. Since the introduction of newer agents (2003-2011), the rates of surgery for patients with CD and UC have decreased, but remained at ~20% and ~8%, respectively.[4] Thus, there is a need for novel oral treatment options that will result in induction of remission as well as maintenance of remission over long-term dosing, with a reduced risk for immune suppression.

The rationale for assessing LYC-30937-EC starts with accumulating evidence that lymphocytes adopt a specific metabolic phenotype that supports their particular effector function. Thus, the energy required for normal lymphocyte activation is driven by aerobic glycolysis, whereas chronically activated pathogenic lymphocytes make their adenosine triphosphate (ATP) primarily via oxidative phosphorylation (OXPHOS) occurring in the mitochondria.[5,6] Oxidative phosphorylation is, in turn, dependent on the activity of the mitochondrial ATP synthase enzyme (F_1F_0-ATPase) that constitutes the final complex in the mitochondrial respiratory chain and is responsible for the formation of ATP.[7,8] Modulation of the F_1F_0-ATPase (ATPase) with small molecule allosteric agents such as LYC-30937 (ATPase modulators) has demonstrated increases in reactive oxygen species and hyperpolarization of the mitochondrial membrane, changes that, together with other bioenergetic and redox abnormalities, result in apoptosis of susceptible cells. ATPase modulators, therefore, selectively deplete chronically activated pathogenic lymphocytes while sparing normal lymphocytic function based on the distinct role of the ATPase in the differential metabolism of these lymphocyte subsets. In agreement with this mechanism of action, ATPase modulators have demonstrated efficacy in several preclinical rodent models of autoimmune disease (arthritis, lupus, psoriasis, graft-versus-host disease, and inflammatory bowel disease [IBD]) with no effect on normal immune responses (no effect on primary or secondary responses in murine T-Cell-Dependent Antibody Response and adoptive transfer immunization models).[9,10,11,12]

LYC-30937-EC is an orally administered EC small molecule ATPase modulator under development for treatment of IBD. LYC-30937 acts as a potent immune modulator through induction of cell death in chronically activated pathogenic lymphocytes and demonstrates efficacy in acute and chronic rodent models of colitis. Moreover, LYC-30937 distributes preferentially to the colon versus plasma at efficacious doses in these models and is therefore predicted to work predominantly through local effects in the gastrointestinal tract, with limited systemic exposure.

In initial dosing in healthy subjects, the pharmacokinetic (PK) profile in single ascending doses (SAD) was consistent with post-pyloric delivery (due to enteric coating) and the systemic exposures did not exceed 5.1 ng/mL, which is 50-fold below the no observed adverse effect level (NOAEL) in the rat, the most sensitive species. In the multiple ascending dose (MAD; 100 and 200 mg dose groups) part of the study, the time at which maximum observed plasma concentration (T_{max}) (> 4 hours) was also consistent with colonic delivery. Furthermore, after multiple dosing, the area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) in the 100 mg dose group increased from 25.4 ng·h/mL at Day 1 to 99.5 ng·h/mL on Day 7, and from 62.7 ng·h/mL at Day 1 to 173 ng·h/mL at Day 7 in the 200 mg dose group. The highest individual plasma concentration in the 200 mg dose group (maximum plasma concentration [C_{max}]: 21.4 ng/mL; AUC_{0-24}: 306 ng·h/mL) was still 10-fold below the NOAEL.

In the Phase 1 study in UC subjects, the AUC and C_{max} were very similar to healthy volunteers following a single administration of a single dose of 25 mg. At a dose of 100 mg, exposures were higher in UC subjects; however, there were no safety findings and exposures remained at least 20-fold (based on C_{max} and AUC) below the lowest NOAEL in the rat and monkey chronic toxicology studies.

In summary, LYC-30937-EC is a first-in-class oral ATPase modulator with a novel mechanism of action that is anticipated to demonstrate clinical efficacy free from generalized immune suppression. Overall, this profile could provide significant advantages for the treatment of IBD.

2.2 Rationale for the Study

Inflammatory bowel disease is a complex autoimmune disorder that consists of UC, CD, and nonspecific colitis that remains a disease of high unmet medical need. Current therapies are limited by either low response rates or poor tolerability. LYC-30937-EC has a unique mechanism of action, which results in induction of apoptosis in chronically activated lymphocytes such as those thought to drive the inflammation of UC. LYC-30937 demonstrated efficacy in animal models of IBD and selective induction of apoptosis in chronically activated human lymphocytes. LYC-30937-EC has also shown safety, tolerability, and a favorable PK

profile in healthy male volunteers up to single doses of 300 mg and 7 days of daily dosing at 200 mg and in UC subjects in single doses of 25 and 100 mg, which are the highest doses tested in humans to date. The mechanism of action of selective induction of apoptosis in chronically activated lymphocytes, the demonstration of efficacy in IBD models and the safety, tolerability, and PK profile demonstrated in the Phase 1 program supports further study of the compound in humans with IBD.

2.3 Nonclinical Studies

2.3.1 Nonclinical Pharmacology

LYC-30937 is an orally administered small molecule for the treatment of IBD. It functions as an allosteric modulator targeting the mitochondrial ATP synthase, also known as the F_1F_0-ATPase. Compounds that modulate F_1F_0-ATPase activity increase superoxide formation and mediate apoptosis of susceptible cells via a well-characterized apoptotic signaling cascade. Consistent with this mechanism of action, LYC-30937 slows the rate of ATP production in submitochondrial particles, increases reactive oxygen species (ROS) generation, and induces apoptosis in a lymphocyte cell line. In addition, LYC-30937 induces apoptosis of gut-tropic T-cells from subjects with IBD.

LYC-30937 and other ATPase modulator compounds are efficacious in acute and chronic rodent colitis models. Oral administration of LYC-30937 in rodent models of IBD is associated with a reduction in clinical signs and improvements in histology. LYC-30937 was selected for advancement based on its in vitro potency, in vivo immunomodulatory activity, and a PK profile characterized by high local tissue concentrations in the gastrointestinal tract. In rodent efficacy studies, LYC-30937 was efficacious at doses where plasma drug levels were below concentrations anticipated to be efficacious based on biochemical and cellular assays. In contrast, colonic drug levels exceeded the 50% inhibitory concentration (IC_{50}) values in enzymatic and cellular assays. These data suggest that efficacy was largely driven by drug in colon tissues rather than plasma.

2.3.2 Nonclinical Pharmacokinetics

LYC-30937 has low aqueous solubility and exhibits moderate apparent permeability in a Caco-2 cell model. Following administration of single oral doses of LYC-30937 as an emulsion in a lipid-based formulation, bioavailability is low to moderate in monkeys, mice, and rats (10%-38%). Plasma LYC-30937 exposures were similar in normal and trinitrobenzene sulfonic acid (TNBS)-treated rats indicating that colitis did not alter the PK of the drug. When administered as a powder blend in an enteric-coated capsule (the intended clinical formulation) to monkeys, the $AUC_{0\text{-}24}$ of LYC-30937-EC is approximately 10% of that achieved using a lipid-

based formulation. In mouse, rat, and monkey, LYC-30937 exhibits low to moderate plasma clearance, low to moderate volume of distribution, and a long terminal elimination half-life. Plasma protein binding is moderate in all species (13%-18% free).

LYC-30937 is moderately stable in hepatocytes from rat and human, and poorly stable in hepatocytes from monkey. Metabolite profiles are qualitatively similar across species and all human metabolites were produced in rat and monkey hepatocytes. The major metabolic pathways included glucuronidation and hydroxylation. In addition, a cyclodehydration product (LYC-53552) was observed that appears to be formed non-enzymatically. Conversion of LYC-30937 to LYC-53552 also was observed in simulated gastric fluid, consistent with the compound's known instability in the presence of acid. LYC-30937 is not predicted to be a direct inhibitor of human cytochrome P450 enzymes (CYPs) but may be a weak time-dependent inhibitor of CYP 2D6. LYC-30937 is unlikely to be associated with significant drug-drug interactions.

2.3.3 Safety Pharmacology and Toxicology

LYC-30937 is not genotoxic and does not produce adverse central nervous system, pulmonary or cardiovascular effects in single dose safety pharmacology studies. In rats and monkeys dosed for up to 28 days with LYC-30937, there was no evidence of generalized immune suppression.

In the rat 28-day good laboratory practice (GLP) toxicology study, an AUC of ≥ 5800 ng·h/mL was associated with sporadic instances of mortality. In the rat 91-day GLP toxicology study, the NOAEL was 10 mg/kg with a plasma AUC of 7750 ng·h/mL (combined sex mean). Since mortality was observed in previous studies at a lower AUC, the rat NOAEL across all studies was considered to be the mid dose in the 91-day study of 3 mg/kg with a C_{max} of 257 ng/mL and an AUC of 3060 ng·h/mL. In the 26-week chronic toxicology study, the NOAEL was also 3 mg/kg and was associated with a mean steady state C_{max} of 240 ng/mL and an AUC_{0-24} of 3000 ng·h/mL.

Due to the mitochondrial mechanism of action of LYC-30937, a study was conducted to explore uncoupling as a potential cause of mortality in rats at high plasma drug levels. As measured by indirect calorimetry, at doses ≥ 7 mg/kg, LYC-30937 produced dose-related increases in oxygen consumption and body temperature consistent with mitochondrial uncoupling. At a tolerated dose, measurable and reversible increases were observed for both parameters.

In the 28-day GLP monkey toxicology study, an exposure of 6340 ng·h/mL in the male high dose group (30 mg/kg) was associated with dose-limiting emesis and diarrhea leading to euthanasia of the group following 16-18 days of dosing. In surviving animals, complete recovery

from these clinical signs occurred following a reversal period of 28 to 38 days. The NOAEL in the 28-day monkey study was 10 mg/kg/day associated with an AUC of 4820 ng·h/mL (combined sex mean). In the 91-day GLP toxicology study, the NOAEL was 10 mg/kg with an AUC of 2580 ng·h/mL. Likewise, in the 39-week chronic toxicology study in monkeys, the NOAEL was 10 mg/kg and was associated with a mean C_{max} of 281 ng/mL and a mean AUC_{0-24} of 2760 ng·h/mL.

Comparing plasma drug levels at the NOAELs in the chronic rat and monkey toxicology studies to the efficacious exposure in a chronic TNBS-induced colitis model following an oral dose of 0.3 mg/kg, exposure ratios are > 20 based on C_{max} and > 50 based on AUC.

Additional information is provided in the Investigator's Brochure (IB).

2.4 Previous Human Experience

LYC-30937-EC has been studied in two Phase 1 studies.

The Phase 1a study was comprised of a SAD, MAD, and food effect (FE) component. A total of 57 healthy male subjects were randomized in the study, 34 subjects in the SAD component, 16 subjects in the MAD component, and 7 subjects in the FE component. A total of 40 subjects received LYC-30937-EC treatment (SAD = 21, MAD = 12, FE = 7).

A total of 52 treatment emergent adverse events (TEAEs) were reported. All TEAEs were of mild severity. There were no deaths or SAEs reported and no discontinuations due to AEs in any components of the study. A total of 6 TEAEs were considered by the investigator to be possibly related to study drug. All of these TEAEs were reported in the SAD component of the study, of which 5 TEAEs were reported by 3 placebo subjects and 1 TEAE (flatulence) by a subject receiving a single dose of 75 mg LYC-30937-EC.

There were no clinically significant findings with respect to clinical laboratory, vital signs (including body temperature), ECGs, continuous cardiac monitoring, PE, respirometry, and tissue or pulse oximetry.

In the SAD component of the study, the C_{max} reached a plateau of 3 to 4 ng/mL at the 75 mg cohort (at least 60-fold below NOAEL in rat, the most sensitive species) and the AUC began to plateau at the 150-mg dose (Table 1). In the MAD component of the trial, the mean C_{max} and AUC values were 10.3 ng/mL and 173 ng·h/mL on Day 7 following oral administration of 200 mg (Table 2). The extent of accumulation following multiple dosing was 3- to 4-fold.

Table 1: Pharmacokinetics of Healthy Subjects in the Phase 1 Single Ascending Dose Study

Cohort [a]	Dose (mg)	C_{max} (ng/mL)	T_{max} (hour)	$AUC_{0\text{-last}}$ (ng·h/mL)
1	2	0.3 (0.02)	6.0 (2.0)	1.1 (0.17)
2	8	2.1 (0.34)	4.0 (0.0)	20.7 (4.9) [b]
3	25	1.7 (1.08)	12.0 (10.39)	31.5 (7.4)
4	75	3.0 (2.02)	7.3 (4.16)	50.3 (27.9)
5	150	3.1 (1.09)	13.0 (10.54)	97.3 (56.4)
6	300	4.2 (0.73)	17.7 (15.96)	134 (56.6)

All data are presented as mean (SD)
AUC = area under the plasma (concentration-time) curve; C_{max} = maximum observed plasma concentration;
SD = standard deviation; T_{max} = time at which maximum observed plasma concentration C_{max}
[a] N = 3 healthy subjects per cohort except for N = 6 for the 300 mg cohort
[b] Last measurable exposure at 36 or 48 hours ($AUC_{0\text{-}36}$ and $AUC_{0\text{-}48}$)
Source: LYC-30937-1001 Clinical Study Report Table 15.2.4

Table 2: Pharmacokinetics of Healthy Subjects in the Phase 1 Multiple Ascending Dose Study

Dose	Day	C_{max} (ng/mL)	T_{max} (hour)	AUC_{τ} (ng·h/mL)	$t_{1/2}$ (hours)
100 mg	1	2.5 (1.75)	11.3 (9.85)	25.4 (12.1)	-
	7	6.3 (4.33)	6.0 (3.10)	99.5 (63.1)	87.6 (27.4)
200 mg	1	6.0 (2.3)	5.67 (1.51)	62.7 (20.6)	-
	7	10.3 (6.06)	8.3 (2.94)	173 (84.2)	66.6 (10.2)

All data are presented as mean (SD)
N = 6 healthy subjects per dose group
AUC = area under the plasma (concentration-time) curve; C_{max} = maximum observed plasma concentration;
SD = standard deviation; T_{max} = time at which maximum observed plasma concentration
Source: LYC-30937-1001 Clinical Study Report Table 15.2.4

In the FE component of the study, administration of a single 100-mg dose under fed conditions resulted in a 15-fold increase in mean C_{max} and a 6-fold increase in mean AUC versus the fasting exposures. The highest individual exposure in a fed subject was 2- to 3- fold below the NOAEL in the rat, the most sensitive species.

The Phase 1b study was an open-label, SAD study to evaluate the PK profile, safety, and tolerability in subjects with UC. A total of 6 subjects received LYC-30937-EC treatment at either 25 mg (3 subjects) or 100 mg (3 subjects). No AEs were reported for the study and exposures at the 25-mg dose were comparable to exposures in healthy volunteers. At a dose of 100 mg,

exposures were higher in UC patients but there were not associated safety findings and exposures remained at least 20-fold (based on C_{max} and AUC) below the lowest NOAEL in rat and monkey chronic toxicology studies.

Overall, oral administration of LYC-30937-EC as a single dose up to 300 mg and as a daily dose up to 200 mg for 7 days was safe and well tolerated. Administration of a single, 100-mg dose under fed conditions in the FE component of the study demonstrated a significant food effect. The increased exposures were not associated with any safety findings.

Additional information is provided in the IB.

2.5 Dose Selection Rationale

The proposed dose to be studied in this Phase 2 proof of concept trial is 25-mg daily oral dose. The rationale for this is based on the exposures required to demonstrate efficacy in the chronic TNBS IBD model, and the safety margins for the both the fasted and fed states.

From the SAD study, a dose of 25 mg was associated with a C_{max} of 1.7 ng/mL and the AUC_{0-72} was 31.5 ng·h/mL. Projection of steady-state exposure was based on the average accumulation observed following doses of 100 or 200 mg and using linear regression in relation to other doses studied. Using these methods, the steady state C_{max} and AUC following daily doses of 25 mg are projected to be approximately 2 ng/mL and 40 ng·h/mL. Both the C_{max} and AUC values exceed the exposures achieved in the mouse chronic TNBS model at 0.03 mg/kg where C_{max} was 1 ng/mL and AUC_{0-24} was $\leq$ 10 ng·h/mL. Furthermore, the colon tissue concentration of the compound is predicted to be at least 13-fold higher than in plasma, which will ensure adequate exposures at the site of action: chronically activated lymphocytes in the lamina propria.

The dose is also to ensure safety. Subjects in this trial will be instructed to take study drug in the fasted state. In the fasting state, the C_{max} and AUC are projected to be > 100-fold below and > 70-fold below the rat NOAEL, respectively. In the fed state, where there is significantly increased systemic exposure, the mean plasma C_{max} and AUC are projected to remain 10-fold below the NOAEL in the rat, the most sensitive species.

Thus, the selection of 25-mg daily dose is made to provide the optimal benefit-to-risk profile. This is achieved by the mechanism of delivering drug to the site of action while minimizing the systemic exposures.

2.6 Risks and Benefits

Based on the results from the first-in-human study described in Section 2.4, single doses of up to 300 mg were proven to be safe and tolerable (in the SAD part of the study) and single-dose exposures observed with once-daily dosing for 7 days in 100 and 200 mg dose groups in the MAD part of the study were similar to those observed in the SAD part of the study.

The EC capsule was developed to deliver study drug to luminal tissue in the ileum and colon. In addition, LYC-30937 is sparingly soluble in water and distributes preferentially to the colon versus plasma. It is therefore predicted to work predominantly through local effects in the gastrointestinal tract, with limited systemic exposure. It should be noted that with any clinical study drug, there is a risk of AEs. Based on the human exposures in the Phase 1 study in healthy subjects, there were no safety signals detected. There were no clinically significant laboratory abnormalities and the subjects tolerated the drug well.

In Phase 2, the subjects will be suffering from active UC and therefore will be a different subject population. They will also be administered study drug for 8 weeks. Subjects will be closely monitored for any potential AE or laboratory abnormality that may arise. Because of the effect of a high fat meal on absorption, observed in the FE component of the Phase 1 study, subjects will be instructed to take their study drug upon awakening in the morning after fasting overnight.

They should not eat until approximately 1 hour after taking study drug. This will ensure that the systemic exposures are predictable and low.

The colonoscopy/flexible sigmoidoscopy carries known risks including adverse reaction to the sedative, if used during the exam. Other risks of the procedure itself may include perforation, bleeding or irritation of the lumen of the colon. These risks are very small, especially in the hands of experts performing the procedures.

The benefits of the drug in subjects with active UC are being evaluated in this study, therefore any benefit is theoretical. There has not been an efficacy study yet. The rationale to study this drug in subjects with UC is based on the mechanism of action and preclinical animal models of IBD.

3.0 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Study 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 a treatment duration of 8 weeks.

3.1.2 Secondary Study Objectives

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

3.1.3 Exploratory Objectives

The exploratory objectives will be to determine plasma PK and the colon tissue exposure of LYC-30937-EC, evaluate pharmacodynamic (PD) biomarkers, assessment of endoscopic improvement at Week 8, and assessing efficacy in subjects with previous exposure to biologic therapy.

3.2 Endpoints

3.2.1 Efficacy Endpoints

Primary Efficacy Endpoint:

- The proportion of subjects who achieve a clinical remission at Week 8 using the modified Mayo score (MMS). Clinical remission using the MMS is defined as a Mayo stool frequency subscore of ≤ 1, a Mayo rectal bleeding subscore of 0 and a Mayo endoscopy subscore of ≤ 1.

Secondary Efficacy Endpoints:

- The proportion of subjects who achieve a clinical remission at Week 8 using the total Mayo score (TMS). Clinical remission using the TMS is defined as a TMS score of ≤ 2, with no individual score > 1, and rectal bleeding score of 0

- The proportion of subjects with a clinical response at Week 8, defined as a reduction from baseline MMS of ≥ 2 points and ≥ 25%, and a decrease from baseline in rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 point

- The proportion of subjects with a clinical response at Week 8, defined as a reduction from baseline TMS of ≥ 3 points and ≥ 30%, and a decrease from baseline in rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 point

- The change from baseline TMS at Week 8

- The change from baseline to Week 8 in fecal calprotectin

Exploratory Efficacy Endpoints:

- The proportion of subjects with endoscopic improvement at Week 8, defined by an endoscopic subscore of ≤ 1 point

- The proportion of subjects with clinical remission, response, and endoscopic improvement at Week 8 who had previously received biologic therapy; who were refractory to biologic therapy (during their initial course of biologic treatment), or who lost response to biologic therapy or were intolerant of biologic therapy

3.2.2 Safety Endpoint

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

3.2.3 PK and PD Endpoints

- PK parameters will be derived from measurements of plasma LYC-30937 concentrations, and its metabolite, using noncompartmental PK analyses.

- Colon tissue concentrations of LYC-30937, and its metabolite, will be measured for exploratory analyses.

- Where feasible and acceptable and in subjects who consent, biologic samples (blood, stool, colon tissue) will be assessed for a series of exploratory PD biomarkers aimed at helping understand the effects of LYC-30937-EC in subjects with active UC (see Appendix C). Biomarkers that may be assessed 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

4.0 STUDY DESIGN

4.1 Design Overview

This study is a Phase 2 multicenter, multinational, randomized, double-blind, placebo-controlled, parallel group study designed to evaluate the efficacy, PK, PD, safety, and tolerability of LYC-30937-EC in subjects with UC. Male and female adult subjects with a previous diagnosis of UC will be screened to determine eligibility as per the inclusion and exclusion criteria (see Sections 4.4.1 and 4.4.2, respectively). The screening period will be up to 28 days (4 weeks).

There are 3 distinct phases of this study as outlined below:

Screening: The screening visit will take place up to 28 days (4 weeks) prior to randomization and the subject's first dose of study drug. Screening will take place over multiple days to complete and obtain results for all assessments. Subjects who meet all eligibility requirements will return for the next phase of the study.

Double-Blind Treatment Period: Subjects meeting all entry criteria will be randomized in a 1:1 ratio to LYC-30937-EC 25 mg once daily [q.d.] or placebo q.d. Randomization will be stratified by previous treatment with biologic therapy such that at least 50% of randomized subjects are biologic naïve. Subjects will receive their first dose of study drug at the clinic after randomization has occurred. Subjects will return to the clinic at Weeks 1, 2, 4, and 8 for efficacy assessments, safety monitoring and study drug receipt.

Follow-Up: There will be 1 follow-up visit performed at Week 10 for final safety monitoring purposes.

All subjects will thus be followed for approximately 14 weeks, which includes up to 4 weeks between screening and Study Day 1 (first dose of study drug), 8 weeks for treatment and 2 weeks for follow-up. Subjects will visit the clinic at Screening (Days -28 to -1), baseline (Day 1), Week 1 (Day 8), Week 2 (Day 15), Week 4 (Day 29), and Week 8 (Day 57) or at the Early Termination (ET) Visit. In addition, a follow-up visit will be planned 2 weeks after the last administration of study drug (Week 10 [Day 71]).

The assessments planned at each visit are detailed in the double-blind schedule of events (Table 3).

After all subjects complete the Week 10 follow-up visit, the study database will be locked to allow for the analysis of data collected up through the Week 10 visit.

The subjects, site personnel following the subject, and the Sponsor will remain blinded to treatment until after the database lock.

Optional Open-Label Treatment: An optional open-label extension study will be available to subjects under a separate protocol to subjects who complete the double-blind trial. The open-label extension will allow up to 44 weeks of treatment with LYC-30937-EC.

4.2 Number of Subjects and Sites

A total of approximately 120 subjects will be randomized into the study and treated at approximately 66 sites (refer to Section 8.1 for sample size estimation).

4.3 Assignment of Subject Numbers

Subjects will be assigned a 6-digit unique identification number sequentially as they sign the informed consent document (ICD) and agree to participate in the study. The first 3 numbers will identify the site number (eg, 200, 201, 202) and the next 3 numbers will be assigned consecutively starting with “001” then “002.” Subject identification numbers will be captured on the electronic case report forms (eCRFs) and will serve as the primary method of identifying each subject on the eCRFs and on the site’s source documents throughout the study. Each site will prepare and maintain a “Master List” of each subject participating in the study.

A randomization number will be assigned to each subject who has met entry criteria and is randomized into the study. The treatment that the subject is assigned to receive will be linked to the randomization number. A list of randomization numbers will be generated before enrollment begins. The subject identification number and randomization number will be assigned by an interactive web-based (IWRS) response system.

Rescreening of subjects, who previously failed screening, may be allowed once after consultation and approval by the study sponsor. Depending on the timing of the rescreening, the subject may need to repeat certain screening assessments to confirm eligibility into the study.

4.4 Subject Selection

The following entry criteria are designed to select subjects for the study for whom protocol treatment is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.4.1 Inclusion Criteria

Each of the following inclusion criteria must be met for entry into the study.

1. Consenting adults aged 18–75 years.
2. Have had UC diagnosed at least 6 months prior to screening and with a minimum disease extent of ≥ 15 cm from the anal verge. The diagnosis of UC must be confirmed by endoscopic and histologic evidence (histology may be confirmed at screening based on biopsy collection during the screening colonoscopy with histological evaluation done by the site).
3. Have active UC defined as a TMS of 4–11 (inclusive) with endoscopic subscore of ≥ 2 and rectal bleeding subscore of ≥ 1 at screening.

4. Male and female subjects of childbearing potential must agree to use adequate birth control measures during the study. Female subjects of childbearing potential must use 2 highly effective forms of contraception, unless surgically sterilized, partner has had a vasectomy, or they will be abstinent, during study participation and for 30 days after their last dose of study drug. Highly effective methods of birth control in this study include: intrauterine device, hormonal contraceptives (oral, patch, long acting injectable, implant), double - barrier method (condom or diaphragm with spermicide). (Postmenopausal defined as lack of menses for ≥ 6 months prior to screening confirmed with serum FSH > 25 mIU/mL at screening.)

5. If currently receiving any of the following UC treatments, the duration and dose prior to the screening endoscopy must be as specified below and a stable dose should be maintained throughout the double-blind trial:

    a. 5-aminosalicylates (5-ASA) (eg, mesalamine, sulfasalazine, olsalazine, balsalazide) for ≥ 6 weeks with the dose stable for ≥ 3 weeks prior to the screening endoscopy.

    b. Prednisone (dose ≤ 20 mg daily) or equivalent for ≥ 4 weeks and receiving a stable dose for ≥ 2 weeks prior to the screening endoscopy.

    c. Thiopurines (azathioprine or 6-mercaptopurine) provided the dose has been stable for ≥ 8 weeks prior to screening endoscopy.

6. If 5-ASA, or corticosteroids have been recently discontinued, they must have been stopped for ≥ 2 weeks prior to the screening endoscopy (eg, if recently tapered off corticosteroid). If a thiopurine has recently been discontinued, it must have been stopped for ≥ 4 weeks prior to the screening endoscopy.

7. Ability to provide written informed consent and to be compliant with the schedule of events, provided in Section 6.2 (Table 3).

4.4.2 Exclusion Criteria

Subjects presenting with any of the following will not be randomized:

1. Known mitochondrial disorder.

2. History of CD or indeterminate colitis or the presence or history of a fistula consistent with CD.

3. History of bleeding disorders (eg, complement disorders, hemophilia, history of uncontrolled bleeding).

4. Severe extensive disease that in physician judgment the subject is likely to require colonic surgery during the 8-week double-blind course (eg, fulminant colitis, toxic megacolon, bowel perforation, evidence of an acute abdomen).

5. Positive test for *Clostridium (C.) difficile*, positive stool culture for enteric pathogens (eg, Salmonella, Shigella, Campylobacter), or presence of ova or parasites at screening.

   Note that *C. difficile* may be treated and the subject may be retested for screening after he/she completed this treatment.

6. Any of the following laboratory abnormalities:

   a. liver function tests > 1.5 x the upper limit of normal (ULN) or direct bilirubin > 1.5 x ULN.

   b. hemoglobin < 8.5 g/dl (international system units [SI]: < 85 g/L).

   c. neutrophils < 1500/mm^3 (SI: < 1.5 x 10^9/L).

   d. white blood cell (WBC) count < 3,000/mm^3 (SI: < 3.0 x 10^9/L).

   e. Platelets < 80,000 mm^3 (SI: 80 x 10^9/L).

   f. international normalized ratio (INR) > 1.5.

   g. serum creatinine > 1.4 mg/dL for women or > 1.6 mg/dL for men.

7. Treatment with non-thiopurine immunosuppressant agents within 4 weeks prior to screening endoscopy (eg, cyclosporine, methotrexate, tacrolimus, sirolimus, or mycophenolate mofetil [MMF]).

8. Pregnancy, lactation, or a positive serum beta human chorionic gonadotropin (hCG) at screening. Female subjects should not be planning to become pregnant while enrolled in the trial.

9. Clinically relevant hepatic, neurological, pulmonary, ophthalmological, gastrointestinal, endocrine, psychiatric, or other major systemic disease making implementation of the protocol or interpretation of the study difficult or that would put the subject at risk by participating in the study.

10. This criterion has been removed as part of the Amendment 4 revision.

11. Current active or history of clinically significant, recurrent bacterial, viral, fungal, mycobacterial or other infections (including but not limited to tuberculosis and atypical mycobacterial disease and herpes zoster), human immunodeficiency virus, or any major episode of infection requiring hospitalization or treatment with intravenous antibiotics within 4 weeks prior to the screening visit and at any time during the screening period, up through the first dose of study drug. Note that recurring urinary tract infections are allowed.

12. History of cancer within the 5 years prior to screening including solid tumors and hematological malignancies, unless approved by the study medical monitor (exception: no approval needed for basal cell and in situ squamous cell carcinomas of the skin that have been adequately treated with no re-occurrence for at least 1 year prior to screening).

13. Presence of adenomatous colon polyps that have not been removed.

14. History of alcohol or drug abuse within 1 year prior to randomization.

15. History of or currently active primary or secondary immunodeficiency.

16. Previous exposure to more than 2 biologic agents to treat UC and these treatments were considered not efficacious (eg, the subject was refractory to the therapies or they lost response to the therapies). "Biologic agents" for this criterion includes approved biologics or biosimilars of approved biologics (either approved or in an investigational clinical trial; eg, TNF-alpha antagonist, integrin receptor antagonist).

17. History of UC treatment with a biologic agent within 12 weeks or 5 elimination half-lives, whichever is shorter, prior to initiating the screening endoscopy (refer to Appendix D: Biologic Medication Restriction).

18. Treatment with an investigational agent within 30 days prior to initiating screening procedures.

19. Treatment with rectal steroids within 2 weeks of initiating screening procedures.

20. Treatment with a fecal transplant within 3 months of initiating screening procedures.

4.5 Subject Withdrawals

Subjects will be encouraged to complete the study; however they may voluntarily withdraw at any point during the study without prejudice. Lycera, or the designated contract research organization (CRO), must be notified immediately if a randomized subject is withdrawn from the study, and every effort should be made to inform Lycera prior to withdrawing the subject.

Subjects may be withdrawn from the study for the following reasons:

- screen failure: subject does not meet entry criteria and was not randomized
- occurrence of any AE (if the subject withdraws due to an AE the investigator should follow the subject until the AE resolve or stabilizes), concurrent illness, laboratory abnormality or other concern which, in the opinion of the investigator or Lycera, warrants the subject's permanent withdrawal
- subject noncompliance, defined as refusal or inability to adhere to the study schedule or procedures
- at the request of the subject (withdraw consent)
- at the request of the investigator, Lycera (sponsor), or regulatory authority(ies) for safety, behavioral, or administrative reasons
- subject is lost to follow-up
- If a subject does not return for a scheduled visit, every effort should be made to contact the subject and/or the subject's family. This effort must be clearly documented.
- other (eg, subject moved)

If a subject withdraws before completing Visit 6 (Week 8) every effort should be made to have the subject undergo final visit procedures (Visit 6/Week 8) in order to document subject outcome, if possible. The investigator or site staff should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved AEs. The reason for the withdrawal will be documented in the source documents and in the appropriate eCRF. If a

subject withdraws due to an AE or other safety reason, the subject should be asked to also return for follow-up Visit 7/Week 10 to have final safety assessments completed.

If a subject withdraws from the study, and withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. Lycera may retain and continue to use any data collected before such withdrawal of consent.

5.0 STUDY TREATMENTS

5.1 Description

- active Substance: LYC-30937
- activity: Modulator of mitochondrial F_1F_0 ATPase
- indication: UC
- strength: 25 mg
- dosage Form: oral, delayed release, enteric coated hydroxyl-propyl methyl-cellulose (HPMC) capsule
- inactive placebo: matching oral, enteric coated HPMC capsule containing the same inactive excipients as the LYC-30937 active treatment capsules
- manufacturer: QS Pharma (Boothwyn, USA)

5.2 Treatment Regimen

The treatment (LYC-30937-EC or placebo) will be administered orally q.d. from Study Day 1 through the end of the double-blind treatment phase (Visit 6/Week 8) for a total of 57 days of treatment. The capsules must be administered in the morning upon awaking after fasting overnight. Subject should not eat for approximately 1 hour (or more) after taking study drug. The exception to this is the Visit 2/randomization visit when the first dose of study drug is administered in the clinic. Subjects may have eaten their morning meal prior to coming for this visit. They should note the time they ate their last meal prior to this clinic visit and study drug should not be administered until at least 2 hours after that meal.

- LYC-30937-EC 25 mg q.d.: one 25-mg capsule of LYC-30937-EC, administer upon awaking in the morning after fasting overnight and do not eat within the next approximately 1 hour after dosing

- placebo q.d.: 1 matching placebo capsule, administer upon awaking in the morning after fasting overnight and do not eat within the next approximately 1 hour after dosing

At the clinic, the study drug supplies must be handled and stored safely and properly, and kept in a secured location to which only the investigator and authorized staff have access.

5.3 Randomization

Subjects will be randomized on the same day (Visit 2) and just prior to the subject's first dose of study drug. The first dose of study drug will be taken while in the clinic under medical supervision. Randomized subjects will receive LYC-30937-EC 25 mg or placebo in a 1:1 ratio.

The randomization will be stratified by previous treatment with biologic therapy such that at least 50% of the randomized subjects are biologic naïve.

5.4 Maintaining and Breaking the Blind

The 2 capsules developed for the trial (LYC-30937-EC 25 mg and placebo) are indistinguishable (identical in size, shape, color and appearance; all EC) and are packaged identically.

To minimize the potential for bias, treatment information will be kept confidential and will not be available for release to the investigator, site staff, and Lycera until after database lock at the end of the double-blind study (Visit 7/Week 10).

The study site will be instructed on the method for breaking the treatment blind prior to study start (ie, the actual treatment received by the subject). The treatment blind is to be broken only in emergency situations when medical/supportive care cannot be provided without determining if the subject was treated with the study drug. In the event that the treatment blind needs to be broken prior to the completion of the study, the investigator must contact Lycera or designee. The investigator will explain and document in writing why the blind was broken, how the blind was broken, and how the integrity of the remaining blinded subjects was maintained.

5.5 Drug Supplies

5.5.1 Packaging and Labeling

All study drug will be supplied in bottles.

All manufacturing, packaging, and labeling operations will be performed according to Good Manufacturing Practices (GMP) for Medicinal Products and the relevant regulatory requirements.

The study drug is to be dispensed according to the protocol. The distribution will only occur after all required documentation is obtained including study approval by the Competent Authorities and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

Each bottle will be identified with a unique number. The subject will be given bottles containing sufficient capsules for the subject until the next scheduled study visit. The bottles will be labeled according to local requirements.

5.5.2 Product Accountability, Storage, Dispensing, and Return

Upon receipt of the study drug, the investigator or authorized designee will inspect the amount and condition of the medication, review for appropriate language in the label, and acknowledge receipt and condition in the IWRS. All study drug supplies will be stored in a locked and secure location accessible only to those authorized by the investigator to dispense the study drug. The study drug supply will need to be stored under controlled room temperature conditions (15°C-25°C/59°F-77°F). A detailed inventory log of study drug received and dispensed will be maintained by the investigator or authorized designee.

The first dose of study drug will be taken while in the clinic under medical supervision. Subsequent dosing will take place at the subject's home including on the days of study clinic visits (unless otherwise specified in Section 6.0). Subjects are to take their study drug dose in the morning upon awaking after fasting overnight and they should not eat for approximately 1 hour after taking study drug. Selected subjects who provide blood samples for PK analysis and LYC-30937 plasma concentration monitoring may be instructed to not take their study drug at home the morning of specified clinic visit(s). They instead will be asked to take their study drug in the clinic. During each study visit, the subject will receive a new medication supply containing sufficient study drug for the period until the next visit.

A study drug accountability record will be maintained by the study site. The investigator will not destroy unused study drug unless Lycera or designee provides written authorization.

5.5.3 Treatment Compliance

For each study drug dose taken, the date, time, and number of capsules taken should be recorded in the subject's electronic diary (see Section 6.3 for additional information).

Subject compliance with taking study drug will be assessed by counting the number of returned capsules at each visit. Subjects should take study drug as directed by the investigator without stopping or interrupting it on their own, unless they experience an adverse event (AE) and in this case they should be instructed to contact the investigator immediately. The investigator (or designee) must complete the appropriate eCRF pages to document the data.

Subjects will return any unused study drug and empty bottles at each study visit and/or early discontinuation visit (if applicable). Missed doses of study drug should be discussed to try to ascertain the reason(s). Every effort should be made to ensure proper subject dosing.

All unused study drug and empty bottles will be returned to the study drug supplier/CRO depot as applicable at the closure of the study site or will be destroyed at the site, upon sponsor decision.

5.6 Concomitant Medications

Subjects will not be permitted to use biologics or non-thiopurine immunomodulatory medications during the study. Subjects are allowed to remain on 5-ASA products, oral corticosteroids, and thiopurines (azathioprine, 6-mercaptopurine) as specified in Section 4.4.1 (corticosteroid tapering is not allowed during this study). They will not be permitted to use newly prescribed or increased dosages of these medications during the double-blind portion of the study. Also, rectal preparations of corticosteroids are not permitted. Inhaled or topical corticosteroids are permitted to be used as medically indicated.

Apart from the above, subjects are allowed any medications necessary for the treatment of concomitant medical disorders as deemed necessary by the treating physician and according to standard practice guidelines. No therapeutic interventions that the investigator feels are clinically indicated will be withheld, independent of whether those compounds, procedures, or therapies were excluded in the eligibility criteria. Following randomization, addition of

concomitant medications or any change in the dosage should be limited to those considered medically essential. All concomitant medication administration should be recorded as specified on the eCRF.

6.0 STUDY PROCEDURES

6.1 Visit Timing

The schedule of study assessments is described below (Table 3); however, a subject may be seen at any time for safety reasons. Routine clinic visits outlined in the protocol should occur whenever possible at the same time of day throughout the study to decrease variation in assessments and procedures. It's recommended that study visits be scheduled in the morning. Morning visits will be necessary for subjects who participate in the safety PK exposure monitoring or serial PK substudies (refer to Section 6.6.1.1 and 6.6.1.2). Prior to each clinic visit, subject activities should remain consistent with their normal routine (eg, meals, medications, caffeine ingestion). Subjects should take prescribed and over-the-counter medications at the same time of the day throughout the study.

- The day the subject receives the first dose of study drug is considered Study Day 1. The timing of all study visits should be based on Study Day 1.
- Study visit timing and windows are as follows:
  - screening (Visit 1) – approximately Study Day -28 to Day -1
  - randomization/treatment (Visit 2) – Study Day 1
  - Visit 3 (Week 1 – Study Day 8) – window ± 3 days
  - Visit 4 (Week 2 – Study Day 15) – window ± 3 days
  - Visit 5 (Week 4 – Study Day 29) – window ± 3 days
  - Visit 6 (Week 8 – Study Day 57) – window ± 4 days
  - Follow-up (Visit 7) (Week 10 – Study Day 71) – window ± 3 days

Unplanned visits may occur at any time for reasons of safety. These visits and associated procedures must be documented on the eCRF.

6.2 Schedule of Events

Table 3: Schedule of Events

Protocol Activity	Screening	Randomization and 1st Dose	Treatment				Follow-up
		Week 0	Week 1	Week 2	Week 4	Week 8/ ET	Week 10
Study Day	**-28 to -1**	**1**	**8 ± 3 days**	**15 ± 3 days**	**29 ± 3 days**	**57 ± 4 days**	**71 ± 3 days**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Informed consent	X						
Demography	X						
Medical/surgical history [a]	X						
Serology [b]	X						
Prior UC medications	X						
Serum pregnancy test (premenopausal females)	X						
FSH (postmenopausal females) [c]	X						
Assess protocol eligibility	X	X					
Randomization		X					
Dispense study drug		X	X	X	X		
Administer study drug at the clinic		X	(X) [n]		(X) [o]	(X) [n]	
Review study drug compliance		X [s]	X	X	X	X	
Mayo Score	X					X	
Stool frequency and rectal bleeding [d]	X		X	X	X	X	
Physician's Global Assessment	X					X	
Endoscopy and biopsy [e, f]	X					X	
Vital signs [g]	X	X	X	X	X	X	X
Body temperature collected by subject [h]		X					
Urine pregnancy test (women of childbearing potential only)		X	X	X	X	X	X

Table 3: Schedule of Events

Protocol Activity	Screening	Randomization and 1st Dose	Treatment				Follow-up
		Week 0	Week 1	Week 2	Week 4	Week 8/ ET	Week 10
Study Day	**-28 to -1**	**1**	**8 ± 3 days**	**15 ± 3 days**	**29 ± 3 days**	**57 ± 4 days**	**71 ± 3 days**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Height	X						
Weight	X			X	X	X	X
Physical examination	X			X	X	X	X
12-Lead ECG	X					X	
Chemistry panel [i]	X			X	X	X	X
Hematology panel [j]	X			X	X	X	X
Coagulation panel [k]	X					X	
Urinalysis [l]	X					X	
Stool collection [m]	X			X	X	X	
Safety PK exposure monitoring sub-study [n]			X	X	X	X	
Serial PK sub-study [o]					X		
Plasma PK (all subjects who are NOT participating in safety PK exposure monitoring or serial PK substudies) [p]					X		
Exploratory PD biomarker blood sample [q]	X	X		X		X	
Concomitant medications	X	X	X	X	X	X	X
Assess AEs	X [r]	X	X	X	X	X	X

AE = adverse event; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; LDH = lactate dehydrogenase; CPK = creatine phosphokinase; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HBsAg = hepatitis B surface antigen; HCV = hepatitis C; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; hsCRP = high sensitivity C-reactive protein; LDL = low-density lipoprotein; MCH = mean cell hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PD = pharmacodynamic; PK = pharmacokinetics; PT = prothrombin time; RBC = red blood cell; TBD = to be determined; UC = ulcerative colitis; WBC = white blood cell.

[a] Including smoking status, drug and alcohol consumption, and date of UC diagnosis.

[b] HBsAg, HCV antibodies, and HIV 1/2 antibodies.

[c] Postmenopausal defined as no menses for ≥ 6 months prior to screening and serum FSH > 25 mIU/mL at screening.

[d] Subject will collect rectal bleeding and stool frequency every day between clinic visits through Visit 6 (Week 8) in electronic diary.

[e] Colon tissue samples are collected at screening and Visit 6 as part of the endoscopy procedures and will be analyzed for drug concentration levels and may be used for PD purposes.

[f] This screening endoscopy will be a colonoscopy and it will be centrally read and used to determine eligibility. The Visit 6 endoscopy can be a colonoscopy or flexible sigmoidoscopy (left-sided disease only) and it will also be centrally read.

[g] Vital signs will be collected after the subject has been sitting quietly for ≥ 5 minutes and include blood pressure (systolic and diastolic), heart rate, respiratory rate, and temperature.

[h] At Days 1-7, subjects should take their body temperature at 4 and 8 hours after administration of the study drug. In case their temperature reading is > 101°F (or 38.3°C), they are to call the investigator for evaluation of possible infection. After Day 7, subjects should report any elevated temperatures to the investigator (all elevated temperatures > 101°F (or 38.3°C) will be reported as AEs).

[i] Chemistry panel includes: glucose, calcium, sodium, albumin, total protein, potassium, bicarbonate, chloride, BUN, creatinine, lactate, LDH, ALT, AST, reflexive bilirubin (total, direct, indirect), ALP, cholesterol, triglycerides, CPK, hsCRP, HDL, and LDL.

[j] Hematology Panel includes: platelets, WBCs with differential if abnormal (% and absolute counts), hematocrit, RBCs, hemoglobin, MCV, MCHC, and MCH.

[k] Coagulation Panel includes: PT, fibrinogen and INR.

[l] Urinalysis (dipstick) includes: color, appearance, specific gravity, leukocyte esterase, pH, protein, glucose, ketones, blood, and nitrite. Microscopic urinalysis will be performed on samples with abnormal blood, leukocyte esterase, protein, and nitrate.

[m] Stool collected will be analyzed for fecal calprotectin and may be analyzed for PD biomarkers. The stool collected at screening will also be tested for presence of pathogens and *C. difficile*.

[n] A subset of up to 20 subjects will have blood collected at Visits 3, 4, 5, and 6 at the time points specified in Section 6.6.1.1. At Visit 3 and at Visit 6 these subjects will take their study drug dose in the clinic after the pre-dose blood draw.

[o] A subset of up to 12 subjects will have 5 serial blood samples collected at Visit 5. Samples will be collected pre-dose and 4, 6, 10, and 24 hours post-dose (± 30 minutes). These subjects will have their daily study drug dose administered in the clinic at Visit 5. See Section 6.6.1.2.

[p] All subjects who are not participating in the safety PK exposure monitoring sub-study or the serial PK sub-study will have 1 blood sample collected at Visit 5 (any time point) to measure plasma LYC-30937 concentration. See Section 6.6.1.3.

[q] Optional PD Biomarker blood sample - collected where feasible and from subjects who consent to having this sample collected for exploratory PD assessments.

[r] After informed consent is signed.

[s] Telephone subject on Study Day 2 (the day following Visit 2) and again later during the week following Visit 2 to ensure subject is compliant with taking study drug on an empty stomach (fasted overnight).

6.2.1 Screening Visit 1

No study-related procedures will be performed until each subject has been completely informed of the details of the study including its nature, risks, and procedures, and has signed and dated IRB/IEC-approved ICD. A subject who satisfies all eligibility criteria during the screening visit may proceed to the next visit.

A laboratory test (eg, alanine aminotransferase [ALT], aspartate aminotransferase [AST], platelets) or procedure that does not meet eligibility criteria can be repeated once at the discretion of the investigator in order to determine eligibility. A subject who does not satisfy all entry requirements that can be assessed during the screening phase will require no further visits and will be identified as a screen failure in the source documents and eCRFs.

Re-screening of subjects initially not meeting all selection criteria may be allowed once after consultation with the sponsor (eg, subjects infected with *C. difficile* may be re-screened after completing treatment).

Subject Screening will be divided over at least 2 days (all counted under Visit 1) with the recommendation that the easier and less invasive screening procedures be completed first to ensure subject meets these criteria prior to performing the more invasive endoscopy. There will be at least 5 days between Part 1 and Part 2 (endoscopy visit) of the screening visit in order for the subject to collect baseline rectal bleeding and stool frequency information for use in calculation of the Mayo score. If a subject meets the first set of eligibility criteria assessed at the first screening day, an endoscopy will be performed to complete the assessment of the subject's eligibility. (Sites should follow the scheduling practice at their site to determine timing of scheduling the endoscopy in order to complete the screening eligibility within the 28-day screening period).

In the event that a potential study subject is already scheduled for a colonoscopy, it is acceptable to vary from the recommended screening procedure sequence and to consent the subject at the time of their colonoscopy visit and complete the rest of the screening procedures after this time point.

Recommended processes and procedures occurring during Screening Visit 1 (Part 1) are detailed below:

- Inform subject of the study details and obtain the subject's signed ICD.

- Obtain Subject Identification Number through IWRS.
- Obtain demographic information.
- Obtain subject's medical and surgical history including smoking status, drug and alcohol consumption and date of diagnosis for UC.
- Obtain prior medication use for UC.
- Provide subject with electronic diary and train on its use. Instruct subject to begin recording stool frequency and rectal bleeding. Subject's should being collecting this information daily and they will bring their diary with them to all subsequent visits, including Part 2 of the screening visit.
- Obtain vital signs after sitting quietly for at least 5 minutes (includes systolic and diastolic blood pressure [SBP and DBP], heart rate [HR], temperature [T], respiration rate [RR]).
- Measure height and weight.
- Conduct a physical examination.
- Perform a 12-lead ECG.
- Collect samples for serum chemistry, hematology, coagulation laboratory analysis as well as serology tests and follicle-stimulating hormone (FSH) measurement (in postmenopausal female subjects) and a urine sample for urinalysis.
- Collect sample for serum pregnancy test (hCG) in premenopausal female subjects.
- Collect exploratory PD biomarker sample in consenting subjects.
- Collect a stool sample for fecal calprotectin and enteric pathogens.
- Review and document concomitant medication use.
- Assess for AEs (after informed consent has been signed) and/or determine if medical history should be updated.
- Assess eligibility by carefully reviewing each inclusion/exclusion criteria.

Recommended processes and procedures occurring during Screening Visit 1 (Part 2) are detailed below:

- Ensure rectal bleeding subscore ≥ 1 and that other eligibility criteria completed during screening visit Part 1 are met.
- Perform a colonoscopy and biopsy collection (colonoscopy will be centrally read to determine eligibility).
- Collect information on rectal bleeding, stool frequency, and Physician's Global Assessment (PGA) in order to calculate the TMS and MMS.
- Review and document any changes in concomitant medication use since the initial screening visit.
- Assess for AEs (after informed consent has been signed) and/or determine if medical history should be updated occurring after the initial screening visit.
- Assess eligibility by carefully reviewing each inclusion/exclusion criteria.

6.2.2 Visit 2 (Randomization and Dosing)

Subjects who satisfy all inclusion/exclusion criteria assessed during the screening period will return to the clinic for Visit 2 for randomization and dosing. Review all eligibility criteria and ensure the subject remains appropriate for study entry.

Procedures completed at this visit are outlined below:

- Assess protocol eligibility.
- Obtain vital signs after sitting quietly for at least 5 minutes (includes SBP, DBP, HR, T, RR).
- Review concomitant medication use.
- Query for AEs.
- Obtain urine sample for urine pregnancy test (women of childbearing potential only).
- Collect exploratory PD biomarker sample in consenting subjects.

- Randomize subject.
- Administer first dose of study drug at the clinic (dose should be taken at least 2 hours after last meal) and subject should wait approximately 1 hour before eating.
- Dispense study drug and instruct subjects to take 1 capsule per day in the morning upon awaking (fasting overnight) and to wait for approximately 1 hour before eating; remind subject to record the time they take study drug in subject diary each day.
- Remind the subject to measure his/her body temperature daily (at 4 and 8 hours after administration of the study drug) and record in the subject diary. Body temperature may be measured using any method (eg, oral, temporal, etc.). Instruct subject to measure their body temperature using the same method each time.
- Post Visit 2 Telephone Follow-up with Subject – telephone the subject on Day 2 (the day following Visit 2) and a second time during the week following Visit 2 to remind the subject to take study drug on an empty stomach (fasted overnight) and to ensure they are completing their electronic diary.

Randomization will be managed through IWRS. Any subject failing to meet enrollment criteria prior to randomization will be considered a screen failure.

All subjects who are randomized will be counted as part of the Full Analysis Set (FAS) population.

6.2.3 Visit 3 (Week 1)

Subjects will return to the clinic for Visit 3, 1 week post Study Day 1. Procedures completed at this visit are outlined below:

- Obtain vital signs after sitting quietly for at least 5 minutes (includes SBP, DBP, HR, T, RR).
- Collect information on rectal bleeding and stool frequency.
- Obtain urine sample for urine pregnancy test (women of childbearing potential only).
- Review concomitant medication use.

- Query for AEs.
- Review study drug compliance.
- Register visit in IWRS and dispense study drug and remind subjects to take 1 capsule per day in the morning upon awaking (fasting overnight), and to wait for approximately 1 hour before eating and remind subjects to record the time they take study drug in diary.
- Remind the subject to report any increases in body temperature.
- Note: A selected subset of consenting subjects will provide blood samples to assess of plasma concentrations of LYC-30937 as part of the safety PK exposure monitoring sub-study. These subjects should have their study visit scheduled for the morning because they will take their dose of study drug in the clinic (not at home) after collection of a pre-dose blood sample. A second blood sample will be collected 4-6 hours post-dose. Refer to Section 6.6.1.1.

6.2.4 Visit 4 (Week 2)

Subjects will return to the clinic for Visit 4 which occurs 2 weeks after Study Day 1. Procedures completed at this visit are outlined below:

- Obtain vital signs after sitting quietly for at least 5 minutes (includes SBP, DBP, HR, T, RR).
- Measure weight.
- Conduct a physical examination.
- Collect a serum sample for chemistry and hematology laboratory analysis.
- Collect exploratory PD biomarker sample in consenting subjects.
- Obtain urine sample for urine pregnancy test (women of childbearing potential only).
- Collect information on rectal bleeding and stool frequency.
- Collect a stool sample for fecal calprotectin.
- Review concomitant medication use.

- Query for AEs.
- Review study drug compliance.
- Register visit in IWRS and dispense study drug and remind subjects to take 1 capsule per day in the morning upon awaking (fasting overnight) and to wait for approximately 1 hour before eating and remind subjects to record the time they take study drug in diary.
- Remind the subject to report any increases in body temperature.
- Note: A selected subset of consenting subjects will provide blood samples to assess of plasma concentrations of LYC-30937 as part of the safety PK exposure monitoring sub-study. A blood sample will be collected 4-6 hours after the subject has taken their daily study drug dose. Refer to Section 6.6.1.1.

6.2.5 Visit 5 (Week 4)

Subjects will return to the clinic for Visit 5, which occurs 4 weeks after Study Day 1. Procedures completed at this visit are outlined below:

- Collect information on rectal bleeding and stool frequency.
- Obtain vital signs after sitting quietly for at least 5 minutes (includes SBP, DBP, HR, T, RR).
- Measure weight.
- Conduct a physical examination.
- Collect a serum sample for chemistry and hematology analysis.
- Obtain urine sample for urine pregnancy test (women of childbearing potential only).
- Collect a stool sample for fecal calprotectin.
- Collect serum sample for PK analysis – also see Section 6.6.1.3. This sample will be collected from all subjects who are not participating in the safety PK exposure monitoring or serial PK substudies.
- Review concomitant medication use.

- Query for AEs.
- Review study drug compliance.
- Register visit in IWRS and dispense study drug and remind subjects to take 1 capsule per day in the morning upon awaking (fasting overnight) and to wait for approximately 1 hour before eating and remind subjects to record the time they take study drug in diary.
- Remind the subject to report any increases in body temperature.
- Note: A selected subset of consenting subjects will provide blood samples to assess of plasma concentrations of LYC-30937 as part of the safety PK exposure monitoring sub-study. A blood sample will be collected 4-6 hours after the subject has taken their daily study drug dose. Refer to Section 6.6.1.1.
- Note: A subset of consenting subjects will provide serial blood samples to assess PK parameters as part of the serial PK sub-study. These subjects should have their study visit scheduled for the morning. Their dose of study drug will be taken in the clinic at this visit (not at home). Blood samples will be collected pre-dose and at 4, 6, 10, and 24 hours post-dose (± 30 minutes). Refer to Section 6.6.1.2.

6.2.6 Visit 6 or Early Termination (Week 8)

Subjects will return to the clinic for Visit 6 which occurs 8 weeks after Study Day 1. Any subjects who terminate from the study prior to completing Week 8 should also complete the assessments required at this visit. Procedures completed at this visit are outlined below:

- Collect information on rectal bleeding, stool frequency, and PGA in order to calculate the TMS and MMS.
- Perform an endoscopy and colon biopsy collection.
- Obtain vital signs after sitting quietly for at least 5 minutes (includes SBP, DBP, HR, T, RR).
- Measure weight.
- Conduct a physical examination.
- Conduct a 12-lead ECG.

- Collect a serum sample for chemistry, hematology, coagulation laboratory analysis and a urine sample for urinalysis.
- Collect exploratory PD biomarker sample in consenting subjects.
- Obtain urine sample for urine pregnancy test (women of childbearing potential only).
- Collect a stool sample for fecal calprotectin.
- Review concomitant medication use.
- Query for AEs.
- Review study drug compliance.
- Collect electronic diary.
- Remind the subject to report any increases in body temperature.
- Note: A selected subset of consenting subjects will provide blood samples to assess plasma concentrations of LYC-30937 as part of the safety PK exposure monitoring sub-study. These subjects should have their study visit scheduled for the morning because they will take their dose of study drug in the clinic (not at home) after collection of a pre-dose blood sample. A second blood sample will be collected 4-6 hours post-dose. Refer to Section 6.6.1.1.
- Subjects may elect to participate in the optional open-label extension (OLE) study LYC-30937-2002. Refer to that protocol for details of the OLE study. Subjects who enter the OLE upon completion of Visit 6 (Week 8) procedures and prior to follow-up Visit 7 (Week 10) will not return for the Visit 7 (Week 10). Subjects who elect to participate in the OLE study but who do not start OLE treatment prior to Visit 7 (Week 10) must return for Visit 7 (Week 10). Subjects who will not enter the OLE study will return for follow-up Visit 7 (Week 10).
- The Visit 6 date is the date of study completion (and will be recorded in the e-CRF).

6.2.7 Follow-up Visit 7 (Week 10)

Subjects returning for Visit 7 (Week 10) will undergo the following procedures:

- Obtain vital signs after sitting quietly for at least 5 minutes (includes systolic and diastolic BP, HR, T, RR.
- Measure weight.
- Conduct a physical examination.
- Collect a serum sample for chemistry and hematology laboratory analysis.
- Obtain urine sample for urine pregnancy test (women of childbearing potential only).
- Review concomitant medication use.
- Query for AEs.

6.2.8 Unplanned Visits

Unplanned visits may occur at any time for reasons of safety.

6.3 Subject Diary

Subjects will be given and instructed on the use of an electronic diary at screening to record the following:

- From Day 1 through Day 57 (or ET), subjects will be asked to record the date and time study drug is ingested.
- From Day 1 through Day 7 (or ET), subjects will be asked to record their body temperature (measured 4 and 8 hours post dosing). The method of taking body temperature is optional (eg, oral, temporal, etc.) but subjects should use the same method for the duration of this trial.
- From screening Visit 1 to Visit 8 (or ET), subjects will be asked to record daily their stool frequency and rectal bleeding. This stool frequency and rectal bleeding information will be used to calculate the screening and Week 8 Mayo scores.

Information recorded in the diary will be reviewed by site personnel before or at each study visit. Subjects will enter diary information daily throughout the study in order to encourage consistency in diary recording.

6.4 Efficacy Assessments Performed

6.4.1 Ulcerative Colitis Disease Activity by Mayo Score

At the time points indicated in the double-blind schedule of events (Table 3), the subject will be asked to record their stool frequency and rectal bleeding and the Investigator will be asked to complete the PGA.

A colonoscopy will be performed at screening to assess disease severity. Depending upon disease extent, either a flexible sigmoidoscopy or colonoscopy will be performed at end of double-blind treatment visit (Visit 6/Week 8). The screening colonoscopy will image the entire colon to determine areas of inflammation and demarcation. If the inflammation identified at screening is left-sided disease, defined as extending ≥ 15 cm from anal verge and with clear demarcation at not higher than 5 cm below the splenic flexure, then the Week 8 endoscopy can be a flexible sigmoidoscopy instead of a colonoscopy. All endoscopies performed will be based on the investigative site's standard practice including bowel preparation. The endoscopies (either colonoscopy or flexible sigmoidoscopy) will be performed at the site and the endoscopy video recording will be sent to the central reader for evaluation. The Mayo endoscopy subscore component will be assigned based on review by a central reader. Central readers are experienced at reviewing and scoring endoscopies and they will receive study-specific training prior to their reading endoscopies for this trial. This training will include 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. Additional details for performing and submitting endoscopy images for the central read will be described in a separate imaging manual.

Based on these parameters, the subject's Mayo score will be calculated.

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 aforementioned parameters apart from the PGA).

- stool frequency [a] (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 [b]:

  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 [c]:

  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)

[a] Each subject serves as their own control to establish the degree of abnormality of stool frequency.

[b] The daily bleeding score represents the most severe bleeding of the day.

[c] 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.

Mayo scores are calculated using the stool frequency and rectal bleeding data obtained from the subjects via their direct daily diary entries. Stool frequency and rectal bleeding data from the

most recent consecutive 3-day period prior to the study visit will be used for the Mayo score, excluding:

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.

The investigator (or designee) will select the most recent consecutive 3-day period and the stool frequency scores over those 3 days will be totaled and the average calculated. This average score will be used to calculate the Mayo score. Similarly the rectal bleeding scores over the 3-day period will be averaged and this average score will be used to calculate the Mayo score.

Note that in order to be eligible for the study, a subject must have a TMS of 4-11 inclusive at screening with an endoscopy subscore of ≥ 2 and a rectal bleeding subscore of ≥ 1.

6.5 Safety Assessments Performed

6.5.1 Physical Examinations

A physical examination will be conducted at the time points indicated in the schedule of events (Table 3).

Standard physical examination will be performed by the Investigator or by an appropriately trained individual and will include a review of body systems outlined below.

- general appearance
- head, eyes, ears, nose, and throat (HEENT)
- respiratory examination
- circulatory system
- abdominal examination

- musculoskeletal
- neurological examination to record the presence of abnormalities in mental status, motor, and sensory function (includes reflexes)
- any additional assessments necessary to establish baseline status or evaluate symptoms or adverse experiences

Every effort should be made to have the same examiner perform each physical exam for a given subject to minimize variability in the examinations. Clinically significant changes from screening should be noted as AEs.

6.5.2 Medical and Surgical History

Medical history will be obtained and reviewed to ensure the subject is appropriate for study entry. During the Screening period, site personnel may become aware of additional events or procedures which should be added to medical or surgical history.

6.5.3 Vital Signs Measurements

Vital signs will be measured at the time points indicated in the schedule of events (Table 3).

Vital signs measurements consist of SBP, DBP, HR, RR, and T. Subjects should sit quietly with feet flat on the floor or be supine (lying down) for at least 5 minutes prior to measurements.

- Subject must remain seated or lying down for the entire measurement.
- The use of automated devices for measuring BP and HR is acceptable. If done manually, HR must be measured in the brachial/radial artery for at least 30 seconds.
- BP determinations must be performed using calibrated and appropriately maintained equipment and the same equipment should be used on the same subject throughout the study as much as possible.
- The same size BP cuff, which has been properly sized and calibrated, will be used to measure BP each time.
- Subject's arm must be at the same height (at the level of the heart) during each BP measurement.

6.5.4 12-Lead ECG

A 12-lead ECG will be conducted at the time points indicated in the schedule of events (Table 3).

A standard 12-lead ECG will be performed after 5 minutes of rest in the supine position using a standardized automated device. The following ECG parameters will be recorded by the study site: HR, PR-interval, QRS-duration, QT and QTc intervals, and the investigator's assessment of the ECG profile (note that QTcF, the QT interval corrected for heart rate according to Fredericia's formula, will be programmatically calculated and the site does not need to calculate this value). Clinically significant changes from screening should be recorded as AEs.

6.5.5 Laboratory Assessments

Serum samples for laboratory assessments and urine samples for urinalysis will be collected at the time points indicated in the schedule of events and be analyzed by a central laboratory (Table 3). The details on the serum and urine sampling procedures will be described in a separate laboratory manual.

The investigator at the site must assess the clinical significance of all laboratory values outside the laboratory reference ranges. All laboratory abnormalities considered to be clinically significant by the investigator should be repeated. Confirmed, clinically significant laboratory abnormalities should be further evaluated by the investigator and captured as an AE.

Chemistry Panel Sample

The chemistry panel includes: glucose, calcium, sodium, albumin, total protein, potassium, bicarbonate, chloride, blood urea nitrogen (BUN), creatinine, lactate, ALT, AST, reflexive bilirubin (total, direct, indirect), alkaline phosphatase (ALP), high sensitivity C-reactive protein (hsCRP), creatine phosphokinase (CPK), cholesterol, triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL), lactate dehydrogenase (LDH).

Hematology Panel Sample

The hematology panel includes: platelets, WBCs with differential if abnormal (% and absolute counts), hematocrit, red blood cells (RBCs), hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and mean cell hemoglobin (MCH).

Coagulation Panel Sample

The coagulation panel includes: prothrombin time (PT), fibrinogen, and INR.

Urine Sample (Dipstick)

The urinalysis test includes: color, appearance, specific gravity, leukocyte esterase, pH, protein, glucose, ketones, blood, and nitrites. Microscopic urinalysis will be performed on samples with abnormal blood, leukocyte esterase, protein, and nitrite. This test will be evaluated by dipstick at the central laboratory.

Childbearing Potential Evaluation and Pregnancy Tests

Serum FSH in postmenopausal female subjects and a serum hCG (pregnancy test) in premenopausal females will be evaluated at the central laboratory at screening. At Visits 2 through 7, urine pregnancy tests will be performed in women of childbearing potential.

Stool Sample

Stool samples will be collected at the time points indicated in the schedule of events (Table 3). These samples will be analyzed for the presence of fecal calprotectin, a marker of bowel inflammation. Fecal calprotectin is being assessed as a secondary efficacy endpoint. Additionally, the screening stool sample will be evaluated for the presence of *C. difficile* and enteric pathogens.

6.5.6 Inflammation monitoring

Subjects are to take their body temperature at the time points indicated in the schedule of events (Table 3) (ie, 4 and 8 hours after taking the study drug on Days 1-7). The subject should complete their temperature reading in the electronic diary.

If the subject's temperature reading is > 101°F (or 38.3°C) they must call their investigator and this should be recorded as an AE.

If a subject calls with an elevated body temperature, the subject is to present to the clinic and be evaluated for a possible bacterial or viral infection. This assessment is to be completed per the investigator's best clinical judgment (eg, if there is suspicion of a urinary tract infection, then the subject is to have a urinalysis performed; if the subject has signs and symptoms of a classic viral

upper respiratory tract infection, then the subject can be treated symptomatically without being evaluated).

If there are no signs or symptoms of infection, then the subject is to present to the clinic. The study drug should be withheld and the subject should be evaluated for other sources of increased temperature as medically indicated. Study drug may be re-started if study drug has been interrupted for no more than 3 days and the source of the elevated temperature is determined, or it resolves, and in the clinical judgement of the investigator and Study Medical Monitor it is safe for the subject to continue study drug. If the subject is off drug for more than 3 days the investigator should withdraw the subject from the study.

6.5.7 Monitoring Subjects for Adverse Events of Special Interest

Subjects will be monitored throughout the study for the occurrence of AEs and for abnormal clinical laboratory values.

AEs of special interest include those that may be related to LYC-30937's mechanism of action of mitochondrial modulation and those AEs which may indicate hepatotoxicity. Investigators should be particularly mindful of these AEs, which include vomiting, abdominal pain, elevated lactate, and abnormal liver function tests indicative of possible hepatotoxicity (AST, ALT, total bilirubin, ALP, LDH). Guidance for monitoring for these AEs of special interest is outlined below:

Vomiting or Abdominal Pain:

If a subject exhibits repeated episodes of vomiting or persistent abdominal pain above the severity and/or frequency they experience as part of their underlying UC, they must contact their investigator. [It's understood that subjects will experience these symptoms as part of their UC. It is therefore very important to understand and document at screening the "normal" severity and frequency of these symptoms experienced by the subject]. They should present to the clinic as soon as possible to be evaluated for potential source of the symptom and liver function testing should be performed. The study medical monitor should be contacted. If a source is not readily identified then study drug should be withheld and the subject should continue to be evaluated for the source and managed as medically indicated. Study drug may be re-started if it has been interrupted for no more than 3 days and the source of the vomiting or abdominal pain is determined, or if these symptoms resolve, and in the clinical judgement of the investigator and

study medical monitor it is safe for the subject to continue study drug. If the subject is off drug for more than 3 days the investigator should withdraw the subject from the study.

Monitoring Lactate and Liver Function:

If a subject exhibits any of the following elevations, study drug should be withheld at least until evaluation of the subject:

- ALT or AST > 8 x ULN
- ALT or AST > 5 x ULN for more than 2 weeks
- ALT or AST > 3 x ULN and total bilirubin > 2 x ULN (or INR > 1.5)
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)
- ALP > 1.5 x ULN
- Lactate ≥ 3 mmol/L
- LDH > 2 x ULN

If any of the above occur the investigator must contact the subject to request they stop taking study drug and report to the clinic as soon as possible for evaluation (do not wait for the next scheduled study visit). As dehydration and heavy physical exertion can cause elevations (eg, of blood lactate levels), the clinical lab should be repeated with the subject instructed to ensure hydration and avoid heavy physical activity. The study medical monitor should be contacted to discuss the subject. If the elevation is confirmed by the repeat lab and neither dehydration nor heavy physical exertion explains the elevation, study drug must continue to be withheld. Close observation of the subject should be initiated. Repeat liver enzyme and serum bilirubin testing should be performed 2 to 3 times weekly until the values return to baseline. Frequency of this retesting can decrease to once per week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. The investigator should obtain a detailed history of symptoms, prior or concurrent diseases, concomitant drug use, alcohol use, recreational drug use, special diets, and exposure to environmental chemical agents. Evaluation should be performed to rule out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract

disease. Obtain additional tests to evaluate liver function as appropriate (eg, INR, direct bilirubin). Consider gastroenterology or hepatology consults. If a source of the abnormal value is not readily identified the subject should continue to be evaluated for the source and managed as medically indicated. Study drug may be re-started if study drug has been interrupted for no more than 3 days and the source of the abnormal value(s) is determined, or if upon repeating the clinical lab the value returns to normal, and in the clinical judgement of the investigator and study medical monitor it is safe for the subject to continue study drug. If study drug cannot be ruled out as the cause of the abnormal value then study drug should be permanently discontinued. Additionally, if study drug is interrupted for more than 3 days, then study drug should be permanently discontinued.

6.6 Pharmacokinetic Assessments

6.6.1 Biological Samples

Blood samples for plasma PK analysis will be collected as outlined in the schedule of events and as specified below. Because PK results would unblind investigators, this data will not be reported to sites or to Lycera during the double-blind portion of the trial (except as noted in Section 6.6.1.1).

6.6.1.1 Safety Pharmacokinetic Exposure Monitoring Sub-study Sample Collection

Up to 20 consenting subjects will have blood samples collected for determination of plasma concentrations of LYC-30937. These samples will be collected at the following visits and time points:

- Visit 3* (Week 1): fasting pre-dose and 4-6 hours post-dose
- Visit 4 (Week 2): 4-6 hours post-dose
- Visit 5 (Week 4): 4-6 hours post-dose
- Visit 6* (Week 8): fasting pre-dose and 4-6 hours post-dose

* Note that in preparation for Visit 3 and Visit 6, subjects will be asked to come to these study clinic visits after having fasted overnight and they will be instructed not to take their study drug that morning. Study drug will be administered in the clinic after having the pre-dose

blood sample collected. They will wait approximately 1 hour after administration of their study drug before they eat.

PK samples from these subjects will be collected, sent to the central clinical laboratory for evaluation and will be available for Data Safety Monitoring Board (DSMB) review.

6.6.1.2 Serial Pharmacokinetic Sub-study Sample Collection

Up to 12 consenting subjects will participate in a PK sub-study to assess LYC-30937 plasma PK parameters (and PK parameters of its metabolite). These subjects will have 5 serial blood samples collected at Visit 5 (Week 4). Blood samples will be collected at:

- Visit 5 (Week 4): pre-dose (fasted) and post-dose at 4, 6, 10, and 24 hours (window ± 30 minutes at each time point).

These subjects will take their study drug dose on the day of Visit 5 at the clinic and not at home. They will come to the clinic for Visit 5 assessments after having fasted overnight and will have their pre-dose blood sample collected before taking their daily dose of study drug. They will then take their study drug dose and have the other study visit procedures performed. Note: they should not eat for approximately 1 hour after taking their study drug dose. Additional blood samples will be collected at 4, 6, and 10 hours post-dose. They will return to the clinic the following day to have a 24-hour blood post-dose sample collected after fasting overnight and prior to taking their daily dose of study drug. After the 24-hour blood sample is collected, they will take their study drug dose and they will be able to eat after waiting approximately 1 hour after taking study drug. These serial PK blood samples may be collected ± 30 minutes from the specified collection times.

6.6.1.3 Plasma Pharmacokinetic Sample Collection

All subject who are not participating in either the safety PK exposure monitoring sub-study (Section 6.6.1.1) or the serial PK sub-study (Section 6.6.1.2) will have a single blood draw at Visit 5 (Week 4). This sample will be assessed for plasma concentration of LYC-30937 and its metabolite.

6.6.1.4 Exploratory Colon Tissue Concentration

In addition, colon tissue biopsies will be collected to determine the tissue concentration of LYC-30937 and its metabolite and for exploratory PD assessments (see Section 6.7). These

tissue biopsies will be collected at screening and at Visit 6 (Week 8) from all subjects as part of the endoscopy procedures performed at these visits. At screening tissue biopsies will be collected from segments in which disease is present, with 3 biopsies collected from each of these segments. These will be mucosal biopsies collected from the most inflamed areas of inflammation (avoid ulcerated mucosa). At Visit 6, 3 mucosal biopsies will be collected from the same segments that were biopsied at screening.

At selected sites, an additional 3 mucosal biopsies will be collected at Visit 6 from the ileocecal junction to assess LYC-30937 tissue concentrations.

The details on the plasma and colon tissue PK sampling and processing procedures will be described in a separate laboratory manual.

6.6.2 Pharmacokinetic Parameters

The PK parameters to be calculated from the plasma and colon tissue concentration data for LYC-30937 and its metabolite are outlined in Appendix A. The study drug concentration measurements in plasma and colon tissue will be performed by a validated method.

6.7 Exploratory Pharmacodynamic Assessments

6.7.1 Biological Samples for Pharmacodynamic Evaluations

Where feasible and acceptable and in subjects who consent, exploratory PD analysis will be performed on biologic samples collected in the study. This aspect of the trial is optional and subjects may participate in this trial even if they don't consent to have their biologic tissue used for the PD evaluation. Evaluation of these exploratory PD biomarkers will aid in understanding the effects of LYC-30937 in subjects with active UC. Because these are exploratory, the samples may be evaluated in batches by the central lab or by Lycera and the results will not be reported to the study sites during the study.

Biologic samples, including blood, stool, and colon biopsy tissue, will be collected at the time points indicated in the schedule of events (Table 3). Refer to Appendix C for biomarker analyses that may be performed.

Collection of approximately 12 mL of blood for exploratory PD assessments will be collected from consenting subjects as noted in the schedule of events (Table 3) at screening and at Visits 2, 4, and 6.

Colon tissue biopsies will be collected (required for study participation) as noted in the schedule of events (Table 3). Colon biopsy tissue will used to assess for LYC-30937 PK concentrations. If biopsy tissue is available after assessment of drug levels, this tissue may be used for assessing exploratory PD biomarkers.

Stool samples will be collected (required for study participation) as noted in the schedule of events (Table 3). Stool will be used to assess for fecal calprotectin, an intestinal inflammatory marker. Additionally, stool collected at screening will be used to assess for enteric pathogens (for eligibility). Stool remaining after these required evaluations may be used for PD assessments.

6.7.2 PD Parameters

Refer to Appendix C for exploratory PD biomarker parameter analyses that may be performed.

Serum from blood will be used to assess for inflammatory proteins; cells will be analyzed by flow cytometry for enumeration of lymphocyte subtypes and expression of proteins associated with gut homing and lymphocyte activation; expression of small nucleotide polymorphism associated with UC will be assessed.

Stool samples will be processed to determine the presence of inflammatory cytokines, and transcriptional profiling for immune cell signatures and taxonomic composition of subject microbiomes.

Colon biopsy tissue available after measurement of LYC-30937 tissue concentrations will be processed to assess for inflammatory proteins, transcriptional profiling, and assessment of lymphocyte infiltration and metabolic remodeling.

7.0 ADVERSE EVENTS AND SAFETY MONITORING

7.1 Adverse Event Definition

Defined by 21 Code of Federal Regulation (CFR) 312.32(a) and consistent with International Council for Harmonisation (ICH) E2A guidance, an AE means untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable or unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. Examples of AEs include but are not limited to:

- abnormal test findings
- clinically significant symptoms and signs
- changes in physical examination findings
- hypersensitivity
- progression/worsening of underlying disease

Events related to the underlying disease(s), which have not worsened in intensity (severity) or frequency since screening, are not AEs.

7.2 Serious Adverse Events Definition

Defined by 21CFR 312.32(a) and consistent with ICH E2A guidance, an AE is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- death
- life threatening (ie, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does NOT include an event, that had it occurred in a more severe form, might have caused death.)
- in-subject hospitalization or prolongation of existing hospitalization

- persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- congenital anomaly/birth defect

- other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (eg, an allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency)

7.3 Adverse Event Reporting

Adverse events, both serious and nonserious, should be collected on source documents from the time the subject has signed informed consent through last subject visit. The investigator is to collect all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs. For all randomized subjects, AEs should be recorded on case report forms (CRFs) from the time the subject has signed informed consent. For subjects not randomized, only SAEs and AEs leading to screen failure will be collected on the CRFs from the time the subject has signed informed consent.

Each AE is to be assessed to determine if it meets the criteria for SAE, see Section 7.2 above. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

AEs should be reported using concise medical terminology on the CRFs.

Diagnostic and therapeutic noninvasive procedures should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE and procedure would be the treatment and recorded as “action taken” of the AE.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Lycera or its designated representative. For all AEs, sufficient information should be obtained to determine the causality of the AE.

All AEs that occur from the time of informed consent, regardless of whether the particular event is expected and regardless of relatedness, will be recorded as an AE.

7.4 Assessment of Severity of Adverse Events

The investigator or blinded physician will assess subjects at each visit for the occurrence of AEs. In order to avoid bias in eliciting AEs, subjects should be asked the following nonleading questions: "How are you feeling?" All AEs (serious and nonserious) reported by the subject must be recorded on the CRFs regardless whether a causal relationship to the study drug is suspected.

Severity of AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.

Adverse events that are not included in the NCI CTCAE lists will be graded according to the NCI CTCAE general guideline for grades as follows:

Grade 1 Mild, asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate, minimal, local intervention, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL), eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL, eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed in Section 7.2.

7.5 Serious Adverse Event Reporting

All observed or volunteered SAEs regardless of treatment group or suspected causal relationship to the study drug will be reported as described below.

If an SAE occurs, ICON Pharmacovigilance and Safety Services (PVSS) is to be notified within 24 hours of awareness of the event by the investigator or subinvestigator. The initial SAE report form should be completed and faxed to ICON PVSS using one of the following:

North America:

Email: icon-mads@iconplc.com
Facsimile: +1-215-616-3096
Telephone: +1-888-723-9952

Europe:

Email: icon-safety-centralreceipt@iconplc.com
Facsimile: +44 (0)208 100 5005

In particular, if the SAE is fatal or life threatening, notification must be made immediately, irrespective of the extent of available AE information.

This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure in utero (EIU) cases. The investigator should continue to report any significant follow-up information to ICON PVSS up to the point of resolution.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient trial subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and the document the time of his/her first awareness of the SAE.

The study sponsor medical monitor will perform final medical review of SAEs. Full details of the SAE processing and review procedures will be documented in a safety management plan and medical monitoring plan. Serious adverse events, including any deemed as suspected unexpected serious adverse reactions (SUSAR) will be reported according to timeframes as per country regulatory guidance, including to United States (US) Food and Drug Administration

(FDA) within 15 calendar days of ICON PVSS notification and within 7 calendar days if the SUSAR is considered life threatening or resulted in death. Non-SUSAR SAEs will be reported to country regulatory authorities annually as per regulatory guidance.

For all SAEs, the investigator is obligated to pursue and provide information to Lycera or designee in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Lycera to obtain specific additional follow-up information in an expedited fashion. In general, the SAE form will include a description/narrative of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Lycera or its designated representative. Expedited safety reports on all unexpected SAEs that are at least possibly related to study procedures will be provided to the FDA.

Subjects with unresolved previously reported SAEs, or new SAEs identified on the last scheduled visit, should be followed by the investigator until the events are satisfactorily resolved. Resolution means the subject has returned to the baseline state of health, the investigator does not expect any further improvement or worsening of the AE, or upon agreement with Lycera or designee.

7.6 Post-Week 10 Reporting of Serious Adverse Events

Any SAEs reported by the subject to the investigator that occur after the last visit and are determined by the investigator to be associated with the use of LYC-30937-EC or with associated study procedures (biopsies), should be reported to Lycera or designee.

7.7 Exposure in Utero

For investigational products within clinical trials, an EIU occurs if:

- A female becomes, or is found to be, pregnant after receiving the study drug (eg, after Study Day 1).

If any study subject becomes pregnant during their participation in the study, the subject will stop study drug and withdraw from the study. The investigator must submit this information to Lycera or designee on EIU Form. This must be done irrespective of whether an AE has occurred

and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to an induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all EIU reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (ie, induced abortion) and then notify Lycera or designee of the outcome. The investigator will provide this information as a follow up to the initial EIU Form. The reasons(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable.

If the pregnancy outcome meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including resulting in an aborted fetus, stillbirth or neonatal death]), the investigator should follow the procedures for reporting SAEs.

In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (ie, no minimum follow-up period of a presumably normal infant is required before an EIU Form can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

Additional information about pregnancy outcomes that are classified as SAEs follows:

- "Spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regards to causality as SAEs. In addition, any infant death after 1 month that the investigator assesses as possibly related to the in utero exposure to the investigational medication should be reported.

7.8 Relationship/Causality of Adverse Events/Serious Adverse Events

The investigator's assessment of causality must be provided for all AEs (serious and nonserious). The causality assessment is the determination of whether there exists a reasonable possibility that the study drug itself (eg, LYC-30937-EC or placebo) caused or contributed to an AE.

If the final determination of causality is unknown and the investigator does not know whether the study drug caused the event, then the event will be handled as "related to study drug" for

reporting purposes. If the investigator's causality assessment is "unknown, but not related to study drug", this should be clearly documented on study records.

Relationship of an AE to the study drug will be assessed as follows:

Unrelated [Not Related or Unlikely Related]: There is not a temporal or causal relationship to the study drug. If the AE is "unrelated" to the study drug, the investigator must assess whether the event is thought to be related to the disease under study, concomitant medication, exacerbation of pre-existing condition, other illness, or unknown.

Related [Definite]: There is reason to conclude that the study drug caused the AE.

Suspected [Possible or Probable]: There is evidence to suggest a causal relationship between the study drug and the AE.

7.9 Withdrawal Due to Adverse Events

Withdrawal due to AEs must be recorded on the appropriate AE CRF page.

When a subject withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements as defined.

7.10 Medical Monitoring

Medical monitoring of the study will be performed by Lycera or designee in cooperation with the investigator(s) at the participating sites. Review of laboratory data, AEs, vital signs, physical exam data, and ECG data will be at regular intervals throughout the study. When additional information is required, Lycera or designee will contact the investigator or designee.

The sponsor Medical Monitor for the trial is:

H. Jeffrey Wilkins, MD
Lycera Corp.
Plymouth Meeting, Pennsylvania USA
Office: +1-484-243-6222
Mobile: +1-610-457-5095
Facsimile: +1-734-207-3178

7.11 Data Safety Monitoring Board (DSMB)

A 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 AEs) and plasma PK data will be available for this initial review. Frequency of DSMB meetings will be specified in the 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.

7.12 Stopping Rules

The sponsor has the right to terminate the study prematurely for safety or administrative reasons. In all cases, necessary measures will be taken to ensure appropriate safety follow-up of all subjects in the trial.

Individual subjects may interrupt or stop study drug at the discretion of the investigator or medical monitor any time for safety reasons. Individual subjects must discontinue if they experience a study drug-related Grade 3 (CTCAE version 4.0) AE of special interest – see Section 6.5.7 for list of AEs of special interest.

ECGs are scheduled to be performed at baseline and end of study. An additional ECG should be performed if a subject reports symptoms of recurrent palpitations, recurrent, persistent lightheadedness or faintness, or any symptom that the investigator deems for cause. Subjects should report these symptoms to the investigator immediately and return to the clinic as soon as possible for evaluation including an ECG. Subjects will discontinue study drug if marked QT/QTc prolongation of > 500 ms or > 60 ms over baseline is present (a repeat ECG should be performed within 24 hours to confirm the QT/QTc prolongation).

7.12.1 Suspension of Study

The study will be suspended if any subject experiences a drug-related AE that meets Grade 4 or 5 CTCAE (version 4.0) criteria or if 2 or more subjects experience a study drug-related

Grade 3 AE of the same type. Adverse event reports will be submitted to regulatory agencies and clearance received before any further dosing takes place.

The study will be suspended if 50% of subjects experience clinically important drug-related AEs with a determined intensity of CTCAE Grade 2. The clinical data must be unblinded and reviewed by the unblinded medical monitor for safety before proceeding with the study.

8.0 STATISTICAL AND ANALYTICAL PLAN

8.1 Sample Size Rationale

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 dropouts 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%.

Assuming a dropout rate of 10%, the study will enroll 120 subjects in order to complete 108.

8.2 Analysis Populations

8.2.1 Full Analysis Set

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.

8.2.2 Safety Set

The Safety Set is defined as all randomized subjects. 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.

8.2.3 Other Population Sets

Other population sets for the PK and PD analyses will be defined in the statistical analysis plan (SAP).

8.3 General Statistical Considerations

Baseline will be defined as the last observation prior to dosing unless otherwise specified.

Continuous endpoints will be summarized using at least mean, standard deviation, median, minimum, and maximum. Categorical endpoints will be summarized by the number and percent of subjects in each category. Additional details of the statistical analyses will be detailed in the SAP.

8.4 Demographic and Subject Characteristics

Demographic information and subject characteristics such as gender, race, age, baseline weight, baseline Mayo score, and subjects with and without previous biologic therapy will be summarized by treatment group and overall.

8.5 Efficacy Analysis

8.5.1 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint, ie, the proportion of subjects who achieve a clinical remission at Week 8 of treatment using the MMS, defined as a Mayo stool frequency subscore of ≤ 1, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of ≤ 1, will be reported for the LYC-30937-EC and placebo treatment arms. Statistical comparisons between the LYC-30937-EC treatment arm and placebo will be done using a one-sided Pearson chi-square test. 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. Subjects who are missing the Week 8 Mayo score assessment will be assumed to have not achieved clinical remission.

8.5.2 Secondary Efficacy Endpoint Analyses

The following secondary efficacy endpoints will be summarized and compared between the LYC-30937-EC treatment arm and placebo:

- the proportion of subjects who achieve a clinical remission at Week 8 using the TMS, defined as a TMS score of ≤ 2, with no individual score > 1 and rectal bleeding score of 0
- the proportion of subjects with a clinical response at Week 8, defined as a reduction from baseline MMS of ≥ 2 points and ≥ 25%, and a decrease from baseline in rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 point
- the proportion of subjects with a clinical response at Week 8, defined as a reduction from baseline in TMS of ≥ 3 points and ≥ 30%, and a decrease from baseline in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 point
- the change from baseline in TMS at Week 8
- the change from baseline to Week 8 in fecal calprotectin

8.5.3 Exploratory Efficacy Endpoint Analyses

The following exploratory efficacy endpoint will be summarized and compared between the LYC-30937-EC treatment arm and placebo:

- the proportion of subjects with endoscopic improvement at Week 8, defined by a Mayo endoscopic subscore of ≤ 1 point
- the proportion of subjects with clinical remission, response, and endoscopic improvement at Week 8 who had previously received biologic therapy; who were refractory to biologic therapy (during their initial course biologic treatment), or who lost response to biologic therapy and were intolerant of biologic therapy

8.6 Safety Analysis

AE collection begins after the subject signs the ICD and continues until Week 10 or ET. For all randomized subjects, AEs should be recorded on CRFs from the time the subject has signed informed consent through Week 10. For subjects not randomized, only SAEs and AEs leading to screen failure will be collected from the time the subject has signed informed consent through screen failure. Treatment-emergent AEs (TEAEs) are defined as AEs that start after study drug administration (LYC-30937-EC or placebo). AEs that occur in subjects who screen fail will only be listed if they were the reason the subject was a screen failure.

AEs and SAEs will be summarized by system organ class, by severity, and by relationship; this will be done by treatment group and overall. SAEs resulting in death will be listed and summarized separately. TEAEs and treatment-emergent SAEs will also be summarized by system organ class, by severity, and by relationship; this will be done by treatment group and overall.

Other safety data, such as physical examinations, vital signs, ECGs, clinical laboratory data, and body temperature will be summarized by study visit and treatment group. Where appropriate, change from baseline in safety data will also be summarized by study visit and treatment group.

8.7 Pharmacokinetic and Pharmacodynamic Analyses

Pharmacokinetic concentrations in plasma and colon tissue for LYC-30937 and its metabolite will be listed and summarized by time point for the active treatment group. Pharmacokinetic parameters calculated from the plasma concentrations for LYC-30937 and its metabolite outlined in Appendix A will be listed and summarized for the active treatment group. The handling of concentrations that are missing or below the limit of quantitation (BLQ) will be described in the SAP.

Pharmacodynamic markers will be listed and summarized by treatment group using descriptive statistics.

9.0 ETHICAL CONSIDERATIONS

9.1 Basic Principles

The study will be performed in accordance with the protocol, ICH good clinical practice (GCP) guidelines, and applicable local regulatory requirements and laws.

9.2 Institutional Review Board/Independent Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, eg, advertisements, if applicable from the IRB or IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Lycera or designee.

9.3 Informed Consent

Written informed consent is to be obtained prior to the subject entering the study (before initiation of protocol-specified procedures). The investigators, or other study personnel, explain the nature, purpose, and risks of the study to each subject. Each subject is to be informed that he/she could withdraw from the study at any time and for any reason. Each subject is to be given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate will sign an ICD.

9.4 Study Termination

Premature termination of this study or part of the study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, safety problems, or at the discretion of Lycera. In addition, Lycera retains the right to discontinue development of LYC-30937-EC at any time.

If a study is prematurely terminated or discontinued, Lycera will promptly notify the investigator. After notification, the investigator must notify all subjects currently participating in the study within a specific timeframe designated by Lycera. As directed by Lycera, study materials will be collected and all CRFs completed to the greatest extent possible.

10.0 DATA HANDLING AND RECORD KEEPING

10.1 Study Monitoring

The investigator will allow representatives of Lycera (or their designee) to periodically monitor all CRFs, source documents, informed consent documents, and clinical laboratory records for each subject. The purpose of the monitoring visits will be to:

- evaluate the progress of the study

- verify the accuracy and completeness of the CRFs
- verify the signed informed consent document, the Regulatory binder, and study drug storage and records
- resolve any inconsistencies in the study records
- ensure that all protocol requirements are being fulfilled
- ensure GCPs are being followed

The study site may be subject to review by the IRB/IEC, and/or to quality assurance audits performed by Lycera (or designee), and/or to inspection by appropriate Regulatory Authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

10.2 Study Documentation

Electronic CRFs are required and should be completed for all subjects signing informed consent. Subjects who screen fail will have demographic and disposition CRF with the reason for screen fail (if they screen fail due to an adverse event, the AE CRF will also be collected). For this trial, the CRFs are an electronic data record. The completed original CRFs are the sole property of Lycera and should not be made available in any form to third parties, except for authorized representatives of Lycera or appropriate regulatory authorities, without written permission from Lycera.

It is ultimately the investigator's responsibility to ensure completion and to review and approve all CRFs. Individual CRFs may be signed by the investigator or by an authorized staff member (and may be an electronic signature). A final CRF must be signed by the investigator to attest that the information contained on the CRF is true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs. Subject source documents are the investigator's subject records maintained at the study site. In most cases, the source documents will be the hospital's or the investigator's chart. In cases where the source documents are the hospital or the investigator's chart, the information collected on the CRFs must match those charts.

The CRF for questionnaires may serve as the source document.

10.3 Record Retention

Food and Drug Administration/ICH regulations require all investigators participating in clinical drug studies to maintain detailed clinical data for one of the following periods:

FDA/ICH

- A period of at least 2 years following the date on which a marketing application (eg, biological license application) is approved by the FDA
- A period of 2 years after Lycera notifies the investigator that no further application is to be filed with the FDA.

ICH

- Subject identification codes must be retained for at least 15 years following the completion or discontinuation of the study.

To enable evaluations and/or audits from regulatory authorities or Lycera, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, SAE forms, source documents, and detailed records of treatment disposition (at the end of the study). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the study, Lycera should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to Lycera. The investigator must obtain Lycera's written permission before disposing of any records, even if retention requirements have been met.

11.0 CONFIDENTIALITY AND PUBLICATION PLAN

11.1 Confidentiality

Subject's medical information obtained as a result of this study is considered confidential, and disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify subjects only by subject number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated in this study are to be available for inspection on request by the FDA or other government regulatory agency inspectors, and the IRB/IEC but should otherwise remain confidential.

11.2 Publication of Data and Protection of Intellectual Property

Any information about the study drug and company operations at Lycera is confidential, and shall remain the sole property of Lycera. The investigator agrees to use this information only in conducting this study, and to not use it for other purposed without prior written consent from Lycera.

The information developed in this clinical study will be used by Lycera in the clinical development of its compound and therefore, may be disclosed by Lycera, as required, to other clinical investigators, pharmaceutical companies, the FDA, and other government agencies.

12.0 REFERENCES

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13.0 APPENDICES

13.1 Appendix A: Pharmacokinetic Measurements

Pharmacokinetic (PK) parameters that may be calculated from the plasma concentration data and colon tissue for LYC-30937-EC and its metabolite (LYC-53552) are outlined below:

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)

13.2 Appendix B: Total of Blood Volume

The table below displays the approximate number and approximate volume of blood that will be collected per subject throughout the study.

Total Blood Volume by Assessment

Assessment	Maximum # Samples	mL of Blood per Sample	Total Volume of Blood (mL)	Lab to Analyze
Safety, PK, and PD				
Hematology	6	3	18	Central Lab
Chemistry	6	4	24	Central Lab
Coagulation	2	3	6	Central Lab
Serology	1	5	5	Central Lab
PK of -30937 and Metabolite -53552 (subjects not participating in Safety PK or Serial PK substudies)	1	6	6	Central Lab
Optional Exploratory PD	4	12	48	Central Lab/Lycera/ Specialty Lab
TOTAL			107	
Additional samples collected from a subset of subjects:				
Safety PK exposure monitoring sub-study (up to 20 subjects treated)	6	6	36	Central Lab
Serial PK sub-study (up to 12 subjects)	5	6	30	Central Lab

PD = pharmacodynamic; PK = pharmacokinetic.

13.3 Appendix C: Exploratory PD Biomarkers

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 α4β7, Treg, PD-1, Annexin V, CD62L, glucose/fatty acid uptake
	Plasma	Cytokine profile by immunocapture assays: including but not limited to IL8, IL10, IFN γ, IL17, IL6, IL1β
Stool	Soluble fraction	Cytokine profile by immunocapture assays: including but not limited to IL8, IL10, IFN γ, IL17, IL6, IL1β
	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 γ, IL17, IL6, IL1β
	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 = L-selectin; IL = interleukin; IFN gamma = interferon gamma; PBMC = peripheral blood mononuclear cells; PD-1 = programmed cell death protein 1; Treg = regulatory T cells.

13.4 Appendix D: Biologic Medication Restriction

Biologic medications to treat UC are not to be used during this study. They should not be used within 5 elimination half-lives or within 12 weeks prior to the initiation of screening procedures, whichever time period is shorter. Biologic medications and the time period prior to screening for which they should be stopped are listed below. This list is not exhaustive. If you have questions regarding these or biologic medications not listed below, please contact the Medical Monitor.

Infliximab (Remicade)	≥ 6 weeks (based on 5 half-lives)
Adalimumab (Humira)	≥ 12 weeks
Golimumab (Simponi)	≥ 11 weeks (based on 5 half-lives)
Certolizumab (Cimzia)	≥ 11 weeks (based on 5 half-lives)
Vedolizumab (Entyvio)	≥ 12 weeks
Natalizumab (Tysabri, Antegren)	≥ 12 weeks
Ustekinumab (Stelara)	≥ 12 weeks
Rituximab (Rituxan)	≥ 12 weeks

14.0 DOCUMENT HISTORY

		Summary of Changes	
Document	**Version Date**	**Description of Change**	**Rationale**
Original Protocol	01 March 2016	N/A	N/A
Amendment 1	09 May 2016	• Revised Section 6.5.7: Monitoring Subjects for AEs of Special Interest; • Revised Section 7.12: Stopping Rules and added Section 7.12.1: Suspension of Study; • Reduce LFT exclusion to 1.5 x ULN; • New Lycera facsimile number added to cover page; • Minor revisions/clarifications throughout	• FDA request that safety monitoring and stopping rules for hepatotoxicity be consistent with recommendations as described in FDA's industry guidance on drug-induced liver injury. • FDA request to reduce LFT exclusion criteria level. • New facsimile number received. • Minor revisions and clarifications determined as useful to include since protocol was to be amended for other reasons.
Amendment 2	22 June 2016	• Exploratory efficacy endpoint referencing "mucosal healing" changed throughout to "endoscopic improvement" since histologic evaluation of mucosa to validate healing will not be performed in this trial.; • Secondary efficacy endpoint Week 8 TMS clinical remission definition revised throughout to include rectal bleeding score of 0; • Section 4.4.1: Inclusion criteria 4 revised to require that women of childbearing potential use 2 highly effective forms of birth control;	• Revised per FDA guidance regarding labeling requirement for "mucosal healing." • Occurrences in the protocol of this endpoint definition were not consistent. Therefore revised to ensure consistency. • Inclusion criteria 4 revised to align with FDA guidance related to including women of childbearing potential in trials prior to completion of reproductive toxicity studies.

		Summary of Changes	
Document	**Version Date**	**Description of Change**	**Rationale**
		• Section 4.4.2: Exclusion criteria 6 revised to add elevated serum creatinine as an exclusion to exclude patients with renal impairment;	• Revised based on FDA request. FDA felt current data provided at this time did not adequately support including subjects with impaired renal function.
		• Section 6.4.1 revised to add definition of left-sided disease to clarify which subjects can have a flexible sigmoidoscopy at week 8 based on demarcation of inflammation observed in screening colonoscopy;	• Revised to clarify/define subjects who may have Week 8 sigmoidoscopy instead of a full colonoscopy based on demarcation of disease at screening.
		• Section 6.4.1 revised to clarify that endoscopy video recording will be provided for central reading and clarified that central readers will have study specific training, which will include that Mayo endoscopic score of 0 or 1 cannot include any degree of "friability" as this is not consistent with remission;	• Clarification to align with FDA guidance that endoscopic finding of friability is not consistent with Mayo endoscopy subscores of "0" or "1." Also revised to clarify that central readers will receive study-specific training and will use endoscopy videos for their review and assessment of endoscopy subscores.
		• Section 6.4.1 revised to clarify that stool frequency and rectal bleeding data for Mayo scoring will be obtained from the diary completed by the subjects. Also clarified that the average stool frequency and average rectal bleeding score will be calculated from the individual 3 consecutive days will be used for the Mayo score;	• Revised to specify that the Mayo score will be calculated using the stool frequency and rectal bleeding subscores obtained from patients through their daily diary entries.
		• Section 6.5.7 revised to state that study drug will be withheld in subjects who exhibit any of the listed lab elevations in liver biochemical parameters and lactate;	• Revised per FDA request.

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		• Section 7.5 revised to add SAE reporting information including time frame for reporting SAEs to US FDA;	• Revised to provide detail of the SAE reporting process.
		• Section 6.6.1.2 revised to clarify serial PK sub-study blood sample collection;	• Minor revisions to provide clarity.
		• Section 7.10 revised to add sponsor medical monitor name and contact information;	• Medical Monitor contact information added for completeness.
		• Section 7.12 revised to add individual subject stopping criteria based on abnormal ECG findings of prolonged QT/QTc interval;	• Revised per FDA request.
		• Section 11.1 revised to remove statement that subjects will be identified by their initials. Subject initials are not being collected.	• Revised due to error in protocol.

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Amendment 3	07 December 2016	• Throughout protocol: revised all references to "anti-TNF" therapy to state "biologic" therapy; • Section 1.0 revised to add countries participating in trial and the estimated last subject last visit; • Sections 1.0 - 2.5 updated and reorganized; • Section 4.1 revised language related to open-label extension protocol; • Section 4.4.1 Inclusion criteria #2 revised to add clarity to histological evaluation if done at screening; • Section 4.4.1 Inclusion criteria #4 revised to add clarity to effective birth control; • Section 4.4.1 Inclusion criteria #5 revised to add clarity; • Section 4.4.1 Inclusion criteria #6 revised to add clarity; • Section 4.4.2 Exclusion criteria #3 revised for clarity regarding bleeding disorders; • Section 4.4.2 Exclusion criteria #10 revised to define history of uveitis; • Section 4.4.2 Exclusion criteria #12 revised to define type of colon polyp being referenced; • Section 4.4.2 Exclusion criteria #19 revised to	• Throughout protocol: revised to clarify that both anti-integrin and anti-TNF agents are included in the "biologic" definition; • Section 1.0 revised for clarity; • Sections 1.0 - 2.5 updated based on recently finalized toxicology and phase 1 data; also reorganized for clarity and conciseness; • Section 4.1 Updated based on revised duration of open-label extension of up to 44 weeks; • Section 4.4.1 IC #2 revised to add clarity based on site feedback; • Section 4.4.1 IC #4 revised to add clarity based on site feedback; • Section 4.4.1 IC #5 revised to add clarity based on site feedback; • Section 4.4.1 IC #6 revised to add clarity based on site feedback; • Section 4.4.2 EC #3 revised to add clarity based on site feedback; • Section 4.4.2 EC #10 revised to provide clarity based on site feedback; • Section 4.4.2 EC #12 revised provide clarity based on site feedback; • Section 4.4.2 EC #19 revised due to error;

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		remove reference to use of "topical" 5-ASA and steroids; • Section 5.5.2-5.5.3 revised to add clarity related to IWRS and compliance; • Section 5.6 revised to be consistent with other sections of protocol and to specify that corticosteroid taper is not allowed during trial; • Section 6.2.1 revised wording related to timing for screening procedures when a subject is already scheduled for a colonoscopy; • Section 6.5.4 revised to clarify calculation of QTcF will not be done by sites; • Section 6.5.7 revised to specify that baseline abdominal pain and vomiting should be carefully assessed; • Section 7.4 revised to include the CTCAE criteria for assessment of AE severity; • Section 7.12.1 study suspension criteria revised to state that if 50% of subjects experience clinically important drug-related AEs (instead of TESAEs) with severity of CTCAE grade 2; • Appendix B revised: hepatitis blood sample removed.	• Section 5.5.2-5.5.3 revised to add clarity; • Section 5.6 revised for consistency and to add clarity based on site feedback; • Section 6.2.1 revised to provide flexibility to screening visit based on site feedback; • Section 6.5.4 revised to clarify based on site feedback; • Section 6.5.7 revised based on site feedback and based on patient population under study; • Section 7.4 revised per FDA request to assess AE severity using CTCAE criteria; • Section 7.12.1 revised because previous language (referencing TESAEs) was in error; • Appendix B revised to remove hepatitis blood sample because this sample is included in the "serology" blood sample.

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Amendment 4	05 June 2017	• Section 4.4.1 Inclusion criteria #5 revised to allow inclusion of subjects on concomitant thiopurine UC treatment and to allow subjects on no UC treatment.	• Section 4.4.1 IC #5: In recruiting the trial, it has been learned that some patients are either intolerant of or frustrated with current first line UC therapies. Thus, this change allows for the fact that patients may be on a baseline first line therapy; but does not require it. Therefore, those patients who were intolerant of or resistant to 5-ASA or steroid products and those with poorly controlled UC will be eligible for the trial. Safety data from the Phase 2 study, completed Phase 1 studies and preclinical data support the use of LYC-30937-EC without concomitant UC treatment. It was also learned that many patients are symptomatic despite being on azathioprine or 6-mercaptopurine. Safety data from this Phase 2 study, previously completed Phase 1 studies and preclinical data demonstrates no evidence of immune suppression with the study drug. Additionally, the completed *in vitro* interaction studies (cyps, transporters) demonstrate that there is little chance for interaction with 5-ASA products, corticosteroids and azathioprine or mercaptopurine based upon the very low systemic exposures achieved (C_{max} of approximately 0.004 µM following a single 25 mg dose).

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		• Section 4.4.1 Inclusion criteria #6 revised to include thiopurine.	• Section 4.4.1 IC #6 revised in conjunction with the revision of IC #5.
		• Section 4.4.2 Exclusion criteria #7 revised to remove reference to thiopurines and to reduce the washout of other immunomodulatory medications to 4 weeks prior to the screening endoscopy.	• Section 4.4.2 EC #7 – This revision will allow sufficient time for washout of immunosuppressant medications without making it onerous for patients to be off UC treatments. The new timing is supported by safety data from this Phase 2 study, completed Phase 1 studies and preclinical data which demonstrate no evidence of immune suppression with the study drug. It also considers that the time from screening to randomization is ~2-4 weeks.
		• Section 4.4.2 Exclusion criteria #10 removed (history of uveitis).	• Section 4.4.2 EC #10 – This criterion removed because comorbid uveitis is not a safety concern with respect to the study drug mechanism and therefore subjects with uveitis may be included in the trial.
		• Section 4.4.2 Exclusion criteria #12 revised to allow subjects with a history of cancer that is in remission for ≥ 5 years and excludes subjects with cancer diagnosed within the past 5 years unless approved by the study medical monitor.	• Section 4.4.2 EC #12 - Cancer in remission for 5 years or more has low probability of recurrence therefore these subjects may be considered for the trial. Subjects with cancer diagnosed within the past 5 years are excluded unless approved by the study medical monitor based on the cancer, its treatment and clinical course.

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		• Section 4.4.2 Exclusion criteria #17 biologic washout period determination revised and Appendix D added.	• Section 4.4.2 EC #17 – This criterion revised to use specific biologic elimination half-life to determine washout period for some biologics.
		• Section 4.4.2 Exclusion criteria #19 revised to allow use of rectal 5-ASA medications.	• Section 4.4.2 EC #19 – This criterion revised because rectal 5-ASA pharmacokinetics and pharmacodynamics are similar to those of oral 5-ASA medications.
		• Section 5.6 revised to allow concomitant use of a stable dose of thiopurines.	• Section 5.6 revised in accordance with the Section 4.4.1 IC #5 revision.
		• Section 6.2.6 revised to specify that the Visit 6 date is the date of study completion.	• Section 6.2.6 revised to clarify the study completion date.
		• Section 6.6.1.1, Table 3 footnote and Appendix B revised to specify that up to 20 subjects will participate in the safety PK sub-study.	• Section 6.6.1.1 safety PK sub-study participation is optional for sites and subjects therefore allowance is made in case fewer than 20 subjects consent to participate.
		• Section 6.6.1.2, Table 3 footnote and Appendix B revised to specify that up to 12 subjects will participate in the serial PK sub-study.	• Section 6.6.1.2 serial PK sub-study participation is optional for sites and subjects; therefore, allowance is made in case fewer than 12 subjects consent to participate.
		• Section 7.12 revised to specify that a repeat ECG should be performed if QT/QTc prolongation stopping criteria are noted for confirmation.	• Section 7.12 revised to request a 2nd ECG to confirm QT/QTc prolongation and that this repeat ECG be performed within 24 hours.