Clinical Protocol
LYC-30937-2002
Amendment 2, 22 November 2016

A MULTICENTER OPEN-LABEL EXTENSION STUDY TO ASSESS THE SAFETY AND TOLERABILITY OF LYC-30937-EC IN SUBJECTS WITH ACTIVE ULCERATIVE COLITIS

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***Sponsor*:**

Name: Lycera Corp.
Address: 2800 Plymouth Rd. NCRC, Building 26; Ann Arbor, MI 48109
Telephone: 610.457.5095
Facsimile: 734.207.3178

Approval:

22 Nov 2016

H. Jeffrey Wilkins, MD
Lycera Corp.
Chief Medical Officer

Date

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LIST OF ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASA	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 postdose
BP	blood pressure
BUN	blood urea nitrogen
CD	Crohn's Disease
CFR	Code of Federal Regulation
C_{max}	maximum 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
EC	enteric coated
ECG	Electrocardiogram
EIU	exposure in utero
FDA	Food and Drug Administration
FE	food effect
GCP	good clinical practice
GLP	good laboratory practice
HDL	high density lipoprotein
HEENT	head, eyes, ears, nose and throat
HPMC	hydroxyl-propyl methyl-cellulose
HR	heart rate
hsCRP	high sensitivity C-reactive protein
IB	Investigator's brochure
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
IP	investigational product
IRB	institutional review board
IWRS	interactive web-based response system
LDH	lactate dehydrogenase
LDL	low density lipoprotein
MAD	multiple ascending dose
MCH	mean cell hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
OL	open-label
OLE	open-label extension
OXPHOS	oxidative phosphorylation
PE	physical examination
PK	pharmacokinetics
PT	prothrombin time
PVSS	Pharmacovigilance and Safety Services
q.d.	*Quaque Die*, once daily
QTcF	QTc interval corrected for heart rate according to Fredericia's formula
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
SUSAR	suspected unexpected serious adverse reaction
T	Temperature
TEAE	treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
t_{max}	time to maximum plasma concentration
TNBS	trinitrobenzene sulfonic acid
UC	ulcerative colitis

ULN	upper limit of normal
US	United States
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 non-specific 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, 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 assessment of the efficacy of LYC-30937-EC in inducing remission in subjects with active UC.

Study Objectives

The objective of this open-label extension study is to allow subjects who complete the randomized, double-blind, placebo-controlled Phase 2 study, LYC-30937-2001, the opportunity to receive LYC-30937-EC and it will allow collection of additional information on the safety and tolerability of LYC-30937-EC in subjects with UC.

Primary Objectives

The primary objective will be to assess the safety and tolerability of LYC-30937-EC in subjects with UC.

Exploratory Objective

An exploratory objective will assess symptoms of UC.

Study Population

Eligible subjects for study are those who completed study LYC-30937-2001.

Treatment and Duration

All subjects who meet the eligibility criteria will receive treatment with LYC-30937-EC 25 mg once daily (q.d.) and taken orally in a fasted state. The treatment period is up to 44 weeks followed by a 2-week safety follow-up period.

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 (PEs)
- 12-lead Electrocardiograms (ECGs)
- Clinical laboratory assessments
- AEs of special interest

Endpoints

Safety Endpoint:

- The incidence and type of AEs, serious AEs (SAEs), and AEs that led to discontinuation of treatment, laboratory assessments, vital sign measurements, ECGs, and PEs.

Anticipated Number of Subjects

Up to approximately 120 subjects will have the opportunity to receive LYC-30937-EC 25 mg.

Anticipated Number of Sites

Up to approximately 66 sites

First Subject Enrolled

4th Quarter 2016

End of Study

Last subject visit approximately November 2018

Study Countries

North America (Canada, United States), Europe (Czech Republic, Hungary, Netherlands, Poland, Serbia)

2.0 INTRODUCTION

2.1 Background

Inflammatory bowel diseases such as UC, CD, and non-specific 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 remain 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] OXPHOS 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 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 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 of 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 (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 patients, 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 patients; 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 non-specific 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 volunteers up to single doses of 300 mg and 7 days of daily dosing at 200 mg, which are the highest doses tested in humans to date. LYC-30937-EC has also been given to

subjects with UC in single doses of 25 and 100 mg and safety, tolerability, and a favorable PK profile was observed. 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.

Because of the above stated background and rationale for evaluation, LYC-30937-EC will be assessed in a separate Phase 2 double-blind, placebo-controlled study (Protocol LYC-30937-2001). The here described open-label extension (OLE) study is a follow-on extension to that double-blind study and will allow subjects who complete the LYC-30937-2001 study the opportunity to receive active treatment with open-label (OL) LYC-30937-EC and to obtain additional information on safety and tolerability of LYC-30937-EC in subjects with UC.

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 sub-mitochondrial 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 IBD 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 EC capsule (the intended clinical formulation) to monkeys, the AUC_{0-24} 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 immunosuppression.

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 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 dose cohort (at least 60-fold below the NOAEL in rats, the most sensitive species) and the AUC began to plateau at the 150-mg dose. 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. The extent of accumulation following multiple dosing was 3- to 4-fold.

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 OL, 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 subjects but there were no 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 single dose up to 300 mg and as once 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 can be found in the current LYC-30937 IB.

2.5 Dose Selection Rationale

The proposed dose to be used in this trial is 25 mg daily oral dose, which is the same dose being used in the companion double-blind trial (LYC-30937-2001). The rationale for this is based on the exposures required to demonstrate efficacy in the chronic TNBS IBD mouse model, and the safety margins for 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, respectively. 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 ≤ 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 25-mg 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, exposures are projected to remain 10-fold below the lowest exposure associated with mortality in rats, the most sensitive species.

Thus, the selection of the 25 mg daily dose is intended 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 well tolerated (in the SAD part of the study) and 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 and in the Phase 1b study in subjects with active UC, 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. 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. The Phase 2 double-blind study (LYC-30937-2001), that subjects

will complete before entering this OLE study will employ a data safety monitoring committee to provide additional safety oversight.

The benefits of the study drug in subjects with active UC are being evaluated in this study, therefore any benefit is theoretical at this point in time. There have been no previous efficacy studies prior to the Phase 2 double-blind study and this extension study. The rationale to study this drug in subjects with UC is based on the mechanism of action of LYC-30937 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 evaluate the safety and tolerability of LYC-30937-EC in subjects with UC.

3.1.2 Exploratory Objective

An exploratory objective will be to assess symptoms of UC for up to 44 weeks.

3.2 Endpoints

3.2.1 Safety Endpoint:

- The incidence and type of AEs, SAEs, and AEs that led to discontinuation of treatment, laboratory assessments, vital sign measurements, ECGs, and PEs.

3.2.2 Exploratory Endpoint:

- The change in Mayo stool frequency subscore at Weeks 4, 8, 20, 32, and 44 as compared to the study LYC-30937-2001 Week 8 stool frequency subscore
- The change in Mayo rectal bleeding subscore at Weeks 4, 8, 20, 32, and 44 as compared to the study LYC-30937-2001 Week 8 rectal bleeding subscore

4.0 STUDY DESIGN

4.1 Design Overview

This study is a Phase 2 multicenter, multinational, OLE study designed to evaluate the safety and tolerability of LYC-30937-EC in subjects with UC. Eligible subjects are male and female adult subjects who completed study LYC-30937-2001 and who meet the eligibility criteria as per the inclusion and exclusion criteria (see Sections 4.4.1 and 4.4.2, respectively).

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

Eligibility: Eligibility is determined at Visit 6/Week 8 of the double-blind study LYC-30937-2001. Subjects who meet all eligibility requirements, including completing the LYC-30937-2001 Visit 6/Week 8 procedures including endoscopy, will be dispensed OL study drug and instructed to start taking OL study drug the following morning.

Open-Label Treatment Period: Subjects will receive LYC-30937-EC 25 mg q.d. Subjects will return to the clinic at Weeks 2, 4, 6, 8, 20, 32, and 44 for completion of the assessments detailed in the schedule of events (Table 1).

Follow-Up: There will be 1 follow-up visit performed at Week 46 for final safety monitoring purposes.

Therefore, all subjects will be followed for approximately 46 weeks, which includes 44 weeks for treatment and 2 weeks for follow-up.

The assessments planned at each visit are detailed in the schedule of events (Table 1).

4.2 Number of Subjects and Sites

Up to approximately 120 subjects may receive OL study medication at up to approximately 66 sites. The 3-digit site number will remain the same as that assigned in study LYC-30937-2001.

4.3 Assignment of Subject Numbers

Subjects will retain the same 6-digit unique identification number that they received in study LYC-30937-2001. Subject identification numbers will be captured on the case report forms (CRFs) and will serve as the primary method of identifying each subject on the CRFs 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.

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. Completed the 8-week double-blind treatment period of study LYC-30937-2001.

2. Males and females 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).

3. Non-pregnant, non-lactating females who are not planning to become pregnant while enrolled in this study.

4. Investigator considers it safe and potentially beneficial to participate.

5. Ability to provide written informed consent and to be compliant with the schedule of events, provided in Section 6.2.

4.4.2 Exclusion Criteria

Subjects presenting with any of the following will not participate in this study:

1. Subjects who completed LYC-30937-2001, but who experienced an SAE that was considered related to investigational product (IP), or have an unstable medical condition, or for any other reason, in the opinion of the investigator, should not participate in this study.

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.

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

- occurrence of any AE (if the subject withdraws due to an AE, the investigator should follow the subject until the AE resolves 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, or
- Other (eg, subject moved)

If a subject withdraws for any reason before completing Visit 8 (Week 44) every effort should be made to have the subject undergo final visit safety procedures at Visit 8/Week 44. 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 CRF.

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, EC hydroxyl-propyl methyl-cellulose (HPMC) capsule
- Manufacturer: QS Pharma (Boothwyn, USA)

5.2 Treatment Regimen

LYC-30937-EC will be administered orally q.d. from Study Day 1 through Visit 8/Week 44. 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. Subjects will take their first dose the morning after the LYC-30937-2001 Visit 6/Week 8 study visit, which is the visit at which OL study drug is dispensed.

- 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.

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 Drug Supplies

5.3.1 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 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.

5.3.2 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 interactive web-based response system (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 / 59-77°F). A detailed inventory log of study drug received and dispensed will be maintained by the investigator or authorized designee.

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.

5.3.3 Treatment Compliance

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. Subjects should not stop or interrupt study drug on their own unless they experience an adverse event and in this case they should be instructed to contact the investigator immediately. The investigator (or designee) must complete the appropriate CRF 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 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/contract research organization (CRO) depot as applicable at the closure of the study site or will be destroyed at the site, upon Sponsor decision.

5.4 Concomitant Medications

Subjects will not be permitted to use biologics and immunomodulatory medications during the study. Subjects are allowed to remain on oral aminosalicylic acid (ASA) products that they were receiving during the double-blind study LYC-30937-2001. Decrease of the corticosteroid use is allowed during this OL study using a tapering regimen per best clinical practice by the investigator. If tapering is initiated, the daily dose of prednisone (or equivalent) should not be decreased by more than 5 mg per week until reaching 10 mg, then not more than 2.5 mg per week until discontinuation. Subjects will not be permitted to use newly prescribed or increased dosages of ASA products or oral or injectable corticosteroids. 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 CRF.

6.0 STUDY PROCEDURES

6.1 Visit Timing

The schedule of study assessments is described below (Table 1); 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. 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:
  - Visit 1 (Study Day (-)1)

- Visit 2 (Week 2 – Study Day 14) – window ± 3 days
- Visit 3 (Week 4 – Study Day 28) – window ± 3 days
- Visit 4 (Week 6 - Study Day 42) – window ± 3 days
- Visit 5 (Week 8 – Study Day 56) – window ± 3 days
- Visit 6 (Week 20 – Study Day 140) – window ± 4 days
- Visit 7 (Week 32 – Study Day 224) – window ± 4 days
- Visit 8 (Week 44 – Study Day 308) – window ± 4 days
- Visit 9 (Week 46 – Study Day 322) – window ± 4 days

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

6.2 Schedule of Events

Table 1 Schedule of Events

Protocol Activity	Eligibility and 1st Dose [a]	Treatment							Follow-up
		Week 2	Week 4	Week 6	Week 8	Week 20	Week 32	Week 44	Week 46
OLE Study Day	**(-)1**	**14 ± 3 days**	**28 ± 3 days**	**42 ± 3 days**	**56 ± 3 days**	**140 ± 4 days**	**224 ± 4 days**	**308 ± 4 days**	**322± 4 days**
Visit Number	**1 [a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Informed consent	X								
Assess OLE protocol eligibility	X								
Dispense study drug using IWRS	X [i]	X	X		X	X	X		
Review study drug compliance		X	X	X	X	X	X	X	
Dispense temperature log (to record body temperature taken by subjects during 1st week of dosing)	X [j]								
Telephone reminder to subject regarding fasted dosing and body temperature monitoring	X [k]								
Vital signs [b]		X	X	X	X	X	X	X	X
Urine pregnancy test (women of childbearing potential only)		X	X	X	X	X	X	X	X

Table 1 Schedule of Events

Protocol Activity	Eligibility and 1st Dose [a]	Treatment							Follow-up
		Week 2	Week 4	Week 6	Week 8	Week 20	Week 32	Week 44	Week 46
OLE Study Day	**(-)1**	**14 ± 3 days**	**28 ± 3 days**	**42 ± 3 days**	**56 ± 3 days**	**140 ± 4 days**	**224 ± 4 days**	**308 ± 4 days**	**322± 4 days**
Visit Number	**1 [a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Weight		X	X	X	X	X	X	X	X
Physical examination		X	X	X	X	X	X	X	X
12-Lead ECG				X				X	
Dispense paper diary for collection of stool and rectal bleeding information	X	X	X	X	X	X	X		
Stool frequency and rectal bleeding [g]		X	X	X	X	X	X	X	
Telephone reminder to Subject to complete diary		X [h]	X [h]	X [h]	X [h]	X [h]	X [h]		
Chemistry panel [c]		X	X	X	X	X	X	X	X
Hematology panel [d]		X	X	X	X	X	X	X	X
Coagulation panel [e]			X					X	
Urinalysis [f]			X					X	
Concomitant medications		X	X	X	X	X	X	X	X
Assess AEs		X	X	X	X	X	X	X	X

AE = adverse event; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; ECG = electrocardiogram; ET = early termination; HDL = high-density lipoprotein; hsCRP = high sensitivity C-reactive protein; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MCH = mean cell hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; OLE = open label extension; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell.

[a] OLE Visit 1 (Study Day -1) is intended to occur at study LYC-30937-2001Visit 6/Week 8 after completion of all Visit 6 procedures. OLE eligibility will be assessed. Eligible subjects will have OLE medication dispensed and they will take their first dose the following morning which will be Study Day 1. Refer to Section 6.2.1 for information related to situations when subjects enter the OLE study at a time later than at Visit 6/Week 8 of the double-blind study.

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

[c] 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.

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

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

[f] 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 nitrite.

[g] Subjects will collect stool frequency and rectal bleeding in a paper diary on each of the 5 days immediately prior to the clinic visit starting at Visit 2. Diaries will be dispensed at each visit through Visit 7/Week 32. Note that at Visit 4/Week 6 stool and rectal bleeding information will be recorded in the source, but not in the eCRFs. This information will be included in the eCRFs for all other visits.

[h] Telephone subject approximately 7 days prior to the next visit to remind subject to record daily stool and rectal bleeding information on each of the 5 days prior to the next clinic visit.

[i] The first dose of OLE study drug is to be taken the morning following the Visit 6/Week 8 double-blind visit at which drug is dispensed. The first dose day will be Study Day 1.

[j] Subjects will be instructed to take their body temperature approximately 4 and 8 hours after taking study drug during the first 7 days of dosing. Subjects will be given a temperature log in which to record their body temperature and time of dosing for the first 7 days.

[k] Telephone subject on Day 1 (first day of dosing) and again later during the first week of dosing to remind subject of dosing directions to take study drug after fasting overnight and not to eat for approximately 1 hour after taking study drug. Also remind the subject to take their temperature each day, approximately 4 and 8 hours after dosing for the first 7 days of dosing and to call the investigator if their temperature is ever above 38.3°C/101°F.

6.2.1 Eligibility Visit 1

Visit 1 is intended to occur at the same clinic visit as Visit 6/Week 8 of the double-blind study LYC-30937-2001. NOTE: All Visit 6/Week 8 procedures (including endoscopy) must be completed before moving into the OLE. Subjects who enter the OLE at the double-blind Visit 6/Week 8 will not complete the double-blind study Visit 7/Week 10 post-treatment follow-up visit. Subjects will have signed the OLE informed consent document (ICD) and will have met all eligibility criteria (specified in Sections 4.4.1 and 4.4.2). They will retain the same subject identification number that they were assigned in double-blind study LYC-30937-2001.

A subject who declines to participate in the OLE or who does not meet the eligibility criteria will not participate in any visits for this OLE study. They should return for the Follow-up Visit 7/Week 10 of double-blind study LYC-30937-2001 to complete final safety assessments.

Processes and procedures occurring during Eligibility Visit 1 are detailed below:

- Inform subject of the OLE study details and obtain the subject's signed ICD
- Investigator confirms his/her eligibility and clinical belief that it is safe for subject to participate in OLE (refer to Inclusion and Exclusion Criteria in Sections 4.4.1 and 4.4.2)
- Register visit in interactive web-based response system (IWRS), dispense study drug and instruct the subject to take their first dose the following morning. Remind subjects to take 1 capsule per day in the morning upon waking (fasting overnight), approximately 1 hour before eating
- Dispense paper diary and instruct on its use for collection stool and rectal bleeding information
- Dispense temperature log in which subjects will record their body temperature taken twice daily at approximately 4 and 8 hours after taking their dose of study drug on the first 7 days of dosing as well recording the time they take their study dose

Post Visit 1 Telephone Follow-up Reminder with Subject – telephone the subject on Study Day 1 (the day following Visit 1 and the first day of OLE study drug dosing) and a 2nd time during the first week of dosing following Visit 1 to remind the subject to take study drug on an empty stomach (fasted overnight) and to wait approximately 1 hour after dosing before eating. Also remind subject to take body temperature approximately 4 and 8 hours after taking morning dose each day during the first week of dosing, to record the time study drug was taken and record temperatures in the log, and to call investigator immediately if body temperature is over 101°F/38.3°C.

Reminder – site will telephone subject approximately 7 days prior to each subsequent visit to remind them to record daily stool and rectal bleeding information in the diary on each of the 5 days prior to each visit.

6.2.1.1 Subjects Entering the OLE Study after Visit 6/Week 8 of the double-blind study

Subjects who desire to participate in the OLE, but are unable to begin the OLE at double-blind study Visit 6/Week 8 for any reason should return and complete the double-blind study Visit 7/Week 10 follow-up visit. They should start OLE study at this visit (preferred) or within the 3 weeks following completion of double-blind Visit 7/Week 10.

- Subjects who start the OLE study at or within 3 weeks of completing double-blind study follow-up Visit 7/Week 10 will complete the procedures listed for Eligibility Visit 1 (Section 6.2.1) and additionally should have the following performed:
  - Query for AEs since last visit
  - Review concomitant medication use
- Subjects who start OLE study more than 3 weeks after completing double-blind study follow-up Visit 7/Week 10 will require agreement of the PI and the Medical Monitor. If it is agreed that they may participate in the OLE, then the following additional procedures will be completed, except procedures listed for Eligibility Visit 1 (Section 6.2.1):
  - Obtain vital signs after sitting quietly for at least 5 minutes (includes systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate [HR], temperature [T], respiration rate [RR])
  - Collect samples for chemistry and hematology laboratory analyses
  - Obtain sample for urine pregnancy test (women of childbearing potential only)

6.2.1.2 Subjects who transition from OLE Protocol Amendment 1 (issue date 23 August 2016) to OLE Protocol Amendment 2 (issue date 22 November 2016) – applies to Netherlands, Hungary, and U.S.

Subjects who first enroll in OLE protocol LYC-30937-2002 Amendment 1, designed with a 4-week treatment period, may continue OLE study drug treatment in OLE protocol Amendment 2, which allows continued treatment up to 44 weeks. When these subjects complete Visit 3/Week 4 of Amendment 1, they will then sign the revised informed consent for

Amendment 2 and will be dispensed study drug through IWRS and will proceed participating under Amendment 2 starting at Visit 4/Week 6.

If OLE Protocol Amendment 2 has not yet received regulatory and/or EC/IRB approval at the time a subject completes Visit 3/Week 4 of Amendment 1, they should follow Amendment 1 visit schedule and return and complete the follow-up Visit 4/Week 6. Once the necessary regulatory and/or EC/IRB approvals are received the subject may re-start OLE study drug at Amendment 2 Visit 5/Week 8.

6.2.2 Visits 2, 3, 4, 5, 6, 7 (Weeks 2, 4, 6, 8, 20, 32)

All subjects returning for these visits will complete the following procedures:

- Obtain vital signs after sitting quietly for at least 5 minutes (includes SBP, DBP, HR, T, RR)
- Measure weight
- Conduct a PE
- Perform 12-lead ECG (Visit 4/Week 6 only)
- Collect stool frequency and rectal bleeding information from diary
- Collect a serum sample for chemistry and hematology laboratory analysis
- Collect a serum sample for coagulation laboratory analysis (Visit 3/Week 4 only)
- Collect urine for urinalysis (Visit 3/Week 4 only)
- Obtain urine sample for urine pregnancy test (women of childbearing potential only)
- Review concomitant medication use
- Query for AEs
- Dispense paper diary for collection of stool and rectal bleeding information
- Review compliance to OLE medication
- Register visit in IWRS and dispense study drug and remind subjects to take 1 capsule per day in the morning upon waking (fasting overnight) and to wait for approximately 1 hour before eating (registration in IWRS and drug dispensing are not done at Visit 4/Week 6)
- Remind the subject to report any increases in body temperature and/or AEs

6.2.3 Visit 8 or Early Termination (Week 44)

All subjects returning for this visit will complete the following procedures:

- Obtain vital signs after sitting quietly for at least 5 minutes (includes SBP, DBP, HR, T, RR)
- Measure weight
- Conduct a PE
- Perform a 12-lead ECG
- Collect stool frequency and rectal bleeding information from diary
- Collect a serum sample for chemistry, hematology, coagulation laboratory analysis and a urine sample for urinalysis
- Obtain urine sample for urine pregnancy test (women of childbearing potential only)
- Review concomitant medication use
- Query for AEs
- Review compliance to OLE medication

6.2.4 Visit 9 Follow-Up (Week 46)

All subjects returning for Visit 9 will complete the following procedures:

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

6.2.5 Unplanned Visits

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

6.3 Subject Diary

Subjects will use a diary to record their stools and rectal bleeding information. Subjects will be requested to record this information daily on each of the 5 days prior to the clinic visits. Site personnel will contact subjects approximately 7 days prior to the specified study visits to remind them to collect this diary information. This diary information will be recorded in the CRF (except at Visit 4/Week 6, when this information will only be collected in the subject source documents).

6.4 Safety Assessments Performed

6.4.1 Physical Examinations

A PE will be conducted at the time points indicated in the schedule of events (Table 1).

Standard PE 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.

6.4.2 Vital Signs Measurements

Vital signs will be measured at the time points indicated in the schedule of events (Table 1).

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 blood pressure (BP) and HR is acceptable. If done manually, HR must be measured in the brachial/radial artery following the site's standard procedures. Clinically significant changes from the subject's baseline should be recorded as AEs.
- 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 should be at the same height (at the level of the heart) during each BP measurement.

6.4.3 12-Lead Electrocardiogram

A 12-lead ECG will be conducted at the time points indicated in the schedule of events (Table 1).

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: HR, PR-interval, QRS-duration, QT-interval, QT interval corrected for heart rate according to Fredericia's formula (QTcF)-interval and the investigator's assessment of the ECG profile. Clinically significant changes from baseline should be recorded as AEs.

6.4.4 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 1). 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, alanine aminotransferase (ALT), aspartate aminotransferase (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, white blood cells (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), international normalized ratio (INR) and fibrinogen.

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

Urine pregnancy tests will be performed in women of childbearing potential (as established in study LYC-30937-2001) at the time points designated in the Table 1.

6.4.5 Body Temperature Monitoring

Subjects are to take their body temperature at the time points indicated in the schedule of events (Table 1) (ie, approximately 4 and 8 hours after taking the study drug during the first week of treatment). Subjects will record these temperatures and the time study drug is taken each day in a log and they'll bring this completed log to study Visit 2.

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

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.

6.4.6 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. [Because UC subjects experience these symptoms as part of their disease, it is very important to understand and document at screening the "normal" severity and frequency of these symptoms for each 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.

Elevated Lactate and Liver Function:

If a subject exhibits any of the following elevations, study drug should be withheld and the subject should be evaluated for cause:

- ALT or AST > 8 x upper limit of normal (ULN)
- ALT or AST > 5 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 repeat lab and neither dehydration nor 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 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.

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 21 CFR 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. For example: 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

AEs, both serious and non-serious, 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. AEs should be recorded on CRFs from the time the subject takes their first dose of OL drug.

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. The diagnosis should be recorded on the CRF, rather than recording individual signs and symptoms. For example, congestive heart failure should be recorded rather than low ejection fraction, pedal edema, rales

and dyspnea. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom not part of the diagnosis should be recorded separately, for example: congestive heart failure and conjunctivitis should recorded as separate AEs.

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 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 non-leading questions: "How are you feeling?" All AEs (serious and non-serious) 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 (NCI) Common Terminology for Adverse Events (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 sub-investigator. The initial SAE report form should be completed and sent 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 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 a 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. A serious adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed. A serious adverse reaction is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed. Non-SUSAR SAEs will be reported to country regulatory authorities 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 46 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, should be reported to Lycera or designee.

7.7 Exposure in Utero (EIU)

For IP within clinical trials, an EIU occurs if:

- A female becomes, or is found to be, pregnant after receiving the IP.

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, however such events should be considered as SAEs and the investigator should follow the procedures for reporting SAEs.

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 non-serious). The causality assessment is the determination of whether there exists a reasonable possibility that the study drug itself (eg, LYC-30937-EC) 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 IP", this should be clearly documented on study records and will be categorized as "not related to study drug" for reporting purposes.

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. For analysis purposes "Suspected [Possible or Probable]" events are considered "Related."

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, PE 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, PA USA
Office: +1-484-243-6222
Mobile: +1-610-457-5095
Facsimile: +1-734-207-3178

7.11 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 4.03) AE of special interest – see Section 6.4.6 for list of AEs of special interest.

ECGs are scheduled to be performed at Week 6 and Week 44 (end of treatment). 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.

7.11.1 Suspension of Study

The study will be suspended if any subject experiences a study drug-related AE that meets Grade 4 or 5 CTCAE criteria or if 2 or more subjects experience a study drug-related Grade 3 adverse event of the same type. The unblinded medical reviewer will review these cases to determine treatment assignment. 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 unblinded medical reviewer will review these cases to determine treatment assignment.

8.0 STATISTICAL AND ANALYTICAL PLAN

8.1 Analysis Populations

8.1.1 Safety Set

The Safety Set is defined as all subjects who sign the OLE consent and received at least 1 dose of study drug in the extension study. All safety analyses will be performed on the Safety Set.

8.2 General Statistical Considerations

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 statistical analysis plan (SAP).

8.3 Demographic and Subject Characteristics

Demographic information and subject characteristics such as gender, race, age, baseline weight, baseline Mayo stool frequency and rectal bleeding subscores, treatment group in the double-blind study, and whether or not the subject achieved clinical remission at Visit 6/Week 8 of the LYC-30937-2001 study will be listed and summarized.

8.4 Safety Analysis

AE collection begins after the subject signs the ICD and continues until completion of post-treatment follow-up Visit 9/Week 46. Open-label TEAEs are defined as AEs that start after OL study drug administration (LYC-30937-EC) and include worsening of conditions that existed prior to study drug administration.

AEs, SAEs and AEs that led to discontinuation of treatment will be listed and summarized by system organ class, by severity, and by relationship. SAEs resulting in death will be listed and summarized separately. TEAEs and TESAEs will also be summarized by system organ class, by severity, and by relationship.

Other safety data, such as physical examinations, vital signs, ECGs, clinical laboratory data, and body temperature will be listed and summarized by study visit.

Concomitant medications will be listed and summarized.

8.5 Exploratory Efficacy Analysis

The Mayo stool frequency and rectal bleeding subscores will be listed and summarized by study visit. Baseline stool frequency and rectal bleeding subscores will be those subscores obtained at Visit 6/Week 8 of double-blind study LYC-30937-2001.

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, ICDs, 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 ICD, the Regulatory binder, and IP 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

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

FDA/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 ICDs, 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 purposes 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.

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13.0 APPENDICES

13.1 Appendix A: 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				
Hematology	8	3	24*	Central Lab
Chemistry	8	4	32*	Central Lab
Coagulation	2	3	6	Central Lab
TOTAL			**62***	

* Subjects who start the OLE study more than 3 weeks after completing double-blind Visit 7/Week 10 will have additional hematology and chemistry assessments performed and therefore will have an additional approximately 7 mL of blood collected giving an approximate total of 69 mL for the OLE study.

14.0 DOCUMENT HISTORY

Document	Version Date	Summary of Changes	
		Description of Change	**Rationale**
Original Protocol	09 May 2016	N/A	N/A
Amendment 1	23 August 2016	• Section 2.3.3: information consolidated; • Section 2.4: added Phase 1b study data and consolidated information; • Section 4.4.1: Inclusion criteria 4 revised to require that women of child bearing potential use two highly effective forms of contraception; • Section 6.2: added activity for site to telephone subjects to remind them to complete diary; • Sections 6.2 and 6.3 revised to define days at which subjects should record stool frequency and rectal bleeding in their diary; • Section 6.3.6 revised to state that study drug will be withheld in subjects who exhibit any of the listed clinical lab elevations; • Section 7.4: AE severity assessment revised to use NCI CTCAE grading; • Section 7.5 revised to add sponsor medical monitor contact information and SAE reporting email and fax numbers;	• Section 2.3.3: Text revised for conciseness. IB contains additional detail; • Section 2.4: Text consolidated for conciseness. IB contains additional detail. Phase 1b preliminary information added for completeness; • Section 4.4.1: Inclusion criteria 4 revised to align with FDA guidance related to women of childbearing potential using two highly effective forms of contraception; • Section 6.2: Telephone reminders to subjects added to reinforce dosing and diary compliance; • Sections 6.2 and 6.3: Revised to provide detail on exploratory diary data collection; • Section 6.3.6: Revised for consistency based on FDA feedback on associated double-blind protocol; • Section 7.4: AE severity collection revised for consistency based on FDA input on associated double-blind protocol; • Section 7.5: revised to add detail on SAE reporting and to added sponsor medical monitor contact information added for completeness;

Document	Version Date	Summary of Changes	
		Description of Change	**Rationale**
		• Section 7.11 revised to add individual stopping criteria based on abnormal ECG findings of prolonged QT/QTc interval; • Section 11.1 revised to remove statement that subjects will be identified by their initials. Subject initials are not being collected and therefore won't be used for subject identification.	• Section 7.11: Revised to be consistent with FDA request on associated double-blind protocol; • Section 11.1: Revised to be consistent with associated double-blind protocol.
Amendment 2	22 November 2016	• Sections 1.0, 2.1, 2.2, 2.4 updated to include information on the Phase 1 study in patients with UC who received LYC-30937-EC at single doses of 25 mg and 100 mg; • Sections 1.0, 3.1.2, 3.2.2, 4.1, 4.5, 5.2, 6.1 – 6.2.4, 7.6, and 8.4 revised due to extension of the OLE treatment period up to 44 weeks, including the addition of study visits at Weeks 8, 20, 32, 44, and 46; • Section 1.0 revised to add participating countries • Section 1.0 revised to include the approximate last subject last visit timing date; • Section 2.3.3 updated to include chronic toxicology information from rat and monkey studies; • Section 4.4.1 Inclusion Criteria #2 revised to clarify that highly effective forms of contraception include hormonal contraceptives which include the following forms: oral, patch, long acting injectable and implants;	• Sections 1.0, 2.1, 2.2, 2.4 updated because the referenced Phase 1 study information was newly obtained and relevant to include in this protocol amendment. • The primary purpose of this Amendment 2 is to extend the OLE treatment period up to 44 weeks; Sections 1.0, 3.1.2, 3.2.2, 4.1, 4.5, 5.2, 6.1 – 6.2.4, 7.6, 7.11, and 8.4 were revised in accordance with this treatment extension; • Added for completeness; • Section 1.0 updated with approximate last subject last visit to provide estimated end of study timing; • Section 2.3.3 updated with chronic toxicology, which supports extension of OLE treatment period up to 44 weeks; • Section 4.4.1 Inclusion Criteria #2 was revised to clarify that the various forms of hormonal contraception are considered effective forms of contraception in this trial;

Document	Version Date	Summary of Changes	
		Description of Change	**Rationale**
		• Section 4.5 revised to clarify that subjects who withdraw should complete Visits 8 and 9;	• Revised for clarity;
		• Section 5.3.3 revised to clarify that drug receipt is be acknowledged in IWRS upon receipt of drug;	• Revised for completeness;
		• Sections 6.2 (Table 1 footnote), 6.2.1, 6.4.5 updated to include body temperature log ;	• A body temperature log is being included to allow subjects to document their temperatures taken at home during the first week of OLE treatment;
		• Section 6.4.6 direction added to understand underlying baseline UC symptoms of abdominal pain and vomiting;	• Added for clarification to ensure baseline assessment of underlying UC symptoms;
		• Appendix A: revised the approximate blood volume collected.	• Appendix A was updated with the approximate volume of blood collected at the additional study visits necessary for the extended treatment period.