LYC-30937
Clinical Protocol LYC-30937-2003
Issue Date: 30 August 2016

A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO ASSESS THE EFFICACY AND SAFETY OF LYC-30937-EC IN SUBJECTS WITH MODERATE CHRONIC PLAQUE-TYPE PSORIASIS

PROTOCOL NUMBER: LYC-30937-2003

STUDY PHASE: 2A

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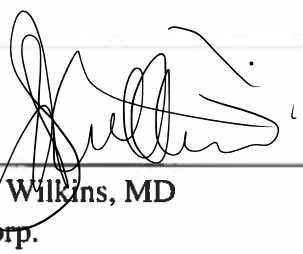

30 Aug 2016

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

Date

Confidentiality Statement:

INVESTIGATOR STATEMENT

I have read and understand the protocol and agree to conduct this study as detailed herein, in compliance with current Good Clinical Practice (GCP) and the applicable regulatory requirements, and will make every reasonable effort to complete the study within the time designated.

I will provide adequate protocol training to my associates, colleagues, and employees assisting in the conduct of the study. The protocol and all relevant information on the study drug relating to pre-clinical and prior clinical experience, which was furnished by the sponsor, will be made available to all physicians, nurses and other personnel who participate in the conduct of this study. I will discuss this material with them to assure that they are fully informed regarding the drug(s) and the conduct of the study.

I will obtain approval from, the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the protocol and Informed Consent Document (ICD) before enrollment of subjects in the study. I understand that any modifications to the protocol made during the course of the study must first be approved by the IRB except when such modification is made to remove an immediate hazard to the patient.

I will ensure that a fully executed ICD is obtained from each patient before initiation of any study procedures.

I will report any serious adverse event (SAE) that occurs during the course of the study in accordance with the procedures described in Section 7.5 of the protocol.

I will allow the sponsor, Lycera Corp. (Lycera) and its agents, as well as the United States Food and Drug Administration (US FDA) and other regulatory agencies, to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, ensuring patient confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify Lycera as soon as possible thereafter.

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Signature of principal investigator:

_____ _____

ADD NAME
ADD AFFILIATION

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LIST OF ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transferase
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
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
C_{ave}	average concentration
CFR	Code of Federal Regulation
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CYP	cytochrome P450 enzyme
EC	enteric coated
EC_{50}	effective concentration 50% (concentration at which 50% maximal response occurs)
ECG	electrocardiogram
EIU	exposure in utero
FAS	Full Analysis Set
FDA	Food and Drug Administration
FE	food effect
FSH	follicle stimulating hormone
GCP	good clinical practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
HEENT	head, eyes, ears, nose, and throat

HIV	human immunodeficiency virus
HPMC	hydroxyl-propyl-methyl-cellulose
HR	heart rate
hsCRP	high sensitivity C-reactive protein
IB	investigator's brochure
IC_{50}	50% inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonization
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IL	interleukin
IRB	institutional review board
IRT	interactive response technologies
LDH	lactate dehydrogenase
LDL	low density lipoprotein
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
NCI CTCAE	National Cancer Institute common terminology criteria for adverse events
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PE	physical examination
PI	principal investigator
PK	pharmacokinetics
PT	prothrombin time
q.d.	*quaque die*, once daily
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RBC	red blood cell
ROS	reactive oxygen species
RR	respiratory rate
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan

SI	international system units
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TNBS	trinitrobenzene sulfonic acid
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
UV	ultraviolet
WBC	white blood cell

1.0 PROTOCOL SUMMARY

Indication

Chronic Plaque-type Psoriasis

Study Rationale

Chronic plaque-type psoriasis is an autoimmune disorder that manifests as a chronic inflammatory skin disease. The features of the underlying inflammation are erythema of the skin with associated induration, scaling, and plaque formation, often in the extensor surfaces. It affects 1–3% of the world's population and can result in significant morbidity and diminished quality of life of individuals with the disease.[1]

Pathologic chronically activated T lymphocytes are crucial in the development of chronic plaque-type psoriasis.[2], [3] These abnormal lymphocytes cause chronic inflammation and the resultant clinical manifestations of the disease. There is increasing evidence that these chronically activated lymphocytes traffic to skin from highly immune-rich areas of the body – "immune hubs" – like the intestines.[4], [5] This is further supported by evidence of correlation of systemic autoimmune diseases and bacterial presence in the gut [6], [7], [8] and the detection of upregulated gut-tropic CCR9+ immune cells in inflamed end organs.[9]

LYC-30937-enteric coated (EC) is an allosteric modulator of F_1F_0 adenosine triphosphate synthase enzyme (F_1F_0-ATPase) that acts on chronically activated lymphocytes locally in the lumen of the gut due to limited systemic absorption. The mechanism of LYC-30937-EC is to induce apoptosis of chronically activated lymphocytes such as those thought to drive the pathogenesis of plaque-type psoriasis. In preclinical experiments, LYC-30937 has been shown to differentially affect chronically activated lymphocytes versus normal lymphocytes because of the metabolic differences between the cells. LYC-30937 has demonstrated efficacy in animal models of psoriasis and other models of systemic inflammation like collagen-induced arthritis despite very low systemic exposure. It has also been studied in healthy subjects up to a 300 mg daily dose and 200 mg daily dose over 7 days with very low systemic absorption and a very low incidence of adverse events (AEs).

With the low systemic exposure of LYC-30937-EC, the good tolerability demonstrated in healthy subjects, the growing scientific support that chronically activated lymphocytes traffic from immune-rich areas of the body to chronically inflamed tissue, and the efficacy of gut-directed F_1F_0-ATPase modulators demonstrated in systemic autoimmune models (psoriasis and collagen-induced arthritis) despite very low systemic exposures, it is proposed that LYC-30937-

EC may provide a favorable benefit to risk profile in patients with moderate chronic plaque-type psoriasis .

Study Objectives

The objective of this study is to assess the efficacy, safety, and tolerability of LYC-30937-EC compared to placebo in subjects with chronic plaque-type psoriasis.

Primary Objective

The primary objective will be to assess the efficacy of LYC-30937-EC in inducing a reduction from baseline in Psoriasis Area and Severity Index (PASI) compared with placebo in subjects with chronic plaque-type psoriasis over the treatment duration of 12 weeks.

Secondary Objectives

The secondary objectives will be to evaluate the overall efficacy, safety and tolerability of LYC-30937-EC compared with placebo in subjects with chronic plaque-type psoriasis.

Exploratory Objectives

The exploratory objectives will be to assess concentration of LYC-30937 in plasma and in skin tissue. Skin biopsies are optional and will be collected in a subset of approximately 6 consenting study subjects to assess LYC-30937 concentrations in skin.

Endpoints

Primary Efficacy Endpoint

The primary endpoint of the study will be the mean percent change from baseline to Week 12 in PASI.

Secondary Efficacy Endpoint

The secondary efficacy endpoints of the study will be:

- The proportion of subjects who achieve a ≥ 75% reduction from baseline in PASI at Week 12.
- The mean percent change from baseline to Week 12 in body surface area (BSA).

- The proportion of subjects who achieve "cleared" (score = 0) or "minimal" (score = 1) on the static Investigator's Global Assessment (IGA) at Week 12.

- The proportion of subjects who achieve a 2 step reduction on the static IGA at Week 12.

Secondary Safety Endpoint

The secondary safety endpoint of the study will include AEs and their causality assessments by investigators, physical examinations (PE), vital signs measurements, 12-lead electrocardiogram (ECG), and laboratory assessments.

Exploratory Endpoint

Concentration of LYC-30937 will measured in plasma and in skin as an exploratory endpoint.

Study Population

This study will include adult males and non-pregnant, non-lactating females with moderate chronic plaque-type psoriasis.

Study Design

This is a phase 2a multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy, safety and tolerability of LYC-30937-EC treatment in subjects with chronic plaque-type psoriasis.

All subjects who meet the eligibility criteria will be randomized 2:1 into the LYC-30937-EC or placebo group.

Assessments

Efficacy Assessments

The following efficacy assessments will be performed in this study:

- PASI

- Static IGA

Safety Assessments

All subjects who are randomized will be monitored for AEs until they leave the study.

Additional safety assessments include:

- PE
- vital sign measurements including systolic and diastolic blood pressure (BP), heart rate (HR), respiratory rate (RR), and body temperature
- 12-lead ECG
- laboratory assessments including chemistry, hematology, and urinalysis

Anticipated Number of Subjects

Approximately 30 subjects will be enrolled into the study and dosed in a 2:1 ratio of LYC-30937-EC or placebo.

Anticipated Number of Sites

Approximately 6 sites are planned to be included in the study.

First Subject Screened

The study is planned to start in the 4th quarter of 2016.

Study Countries

United States

2.0 INTRODUCTION

2.1 Disease Background

Psoriasis is an autoimmune disorder, manifesting in the skin, joints, or both.[10] The disease is characterized by inflammation accompanied by hyperkeratosis resulting in inflamed, raised plaques, usually on the extensor surfaces of the body. Psoriasis provides many challenges including high prevalence, chronicity, disfiguration, disability, and associated comorbidities

(such as arthritis, depression, inflammatory bowel disease, and cardiovascular diseases).[10], [11], [12]

The prevalence of psoriasis in the US was estimated to be 7.4 million in 2013. The estimated total financial burden of psoriasis was estimated as 35.2 billion dollars.[13]

The current treatment options for psoriasis are determined by the severity of the disease. For patients with severe disease that affects a large percentage of BSA, there has been robust efficacy demonstrated by biologics that block the effect of key cytokines that drive the inflammation like anti-tumor necrosis factor (TNF) α, anti-interleukin (IL) 12/23 and anti-IL-17.[14] Patients with moderate plaque psoriasis are either treated with topical agents (eg, corticosteroids, retinoids, vitamin D analogs), for minimal BSA involvement, ultraviolet (UV) light (with or without psoralen), or oral drugs that aim to reduce inflammation through systemic effects on the immune system (eg, methotrexate and apremilast). These treatments are limited in demonstrating robust efficacy or have safety issues through local effects on the skin or systemic effects on the immune system. The current study with LYC-30937-enteric coated (EC) aims to assess the efficacy and safety of an agent that works locally in the gut with limited systemic exposure to address this continued unmet medical need.

2.2 Product Background

LYC-30937-EC is an orally administered small molecule modulator of the mitochondrial F_1F_0-ATPase, being developed for the treatment of inflammatory diseases such as ulcerative colitis (UC) and chronic plaque-type psoriasis. It is formulated with an enteric coating that allows for drug delivery beyond the stomach at a pH of 5.8 – 6.8. The properties of the study drug are such that systemic absorption is low as demonstrated in a healthy volunteer trial where LYC-30937-EC was administered up to a 300 mg single dose and 200 mg daily dose over one week. In the multiple ascending dose (MAD) trial in which 200 mg capsules were dosed once daily for one week, the maximum concentration (C_{max}) seen was 21.4 ng/mL (mean 10.3 ng/mL) and the maximum area under the curve (AUC) seen was 306 ng·h/mL (mean 173 ng·h/mL).

The LYC-30937-EC mechanism of action is the selective induction of apoptosis in metabolically sensitive lymphocytes such as those chronically activated by skin antigens and thought to drive the inflammation of chronic plaque-type psoriasis. Gut-directed ATPase modulators have demonstrated efficacy in animal models of autoimmune disease like psoriasis and collagen induced arthritis despite very low systemic exposure. These data support the hypothesis that delivering drug to the immune-rich bowel may have an effect on active skin inflammation thus supporting study of the compound in humans with chronic plaque-type psoriasis.

Based on its mechanism of action and distribution profile, LYC-30937-EC is anticipated to demonstrate clinical efficacy free from generalized immune suppression in subjects with chronic plaque-type psoriasis.

2.3 Nonclinical Studies

2.3.1 Nonclinical Pharmacology

LYC-30937 is an orally administered small molecule that functions as an allosteric modulator of the mitochondrial ATPase, 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 of a lymphocyte cell line.

Recent literature on autoimmune disease pathogenesis proposes that chronically activated lymphocytes traffic through immune-rich hubs, such as the gut, prior to infiltrating distal inflamed tissues like the skin. Because LYC-30937 and related molecules have significantly higher exposure in the gut then in plasma, this may allow local targeting of pathogenic cells in the gut. In support of this hypothesis, LYC-30937 and other ATPase modulator compounds are efficacious in rodent models of systemic autoimmune disease despite very low systemic exposures. For instance, efficacy was demonstrated by LYC-30937 in a collagen induced arthritis model at an average concentration (C_{ave}) of 0.9 ng/mL (2nM) and an area under the plasma (concentration-time) curve from time 0 to 24 hours ($AUC_{0\text{-}24h}$) of 22 ng·h/mL which is below the effective concentration to achieve 50% of the maximal response (EC_{50}) based on biochemical (27 nM) and cellular assays (59 nM). Another ATPase modulator in the chemical series, LYC-51661, demonstrated efficacy in the imiquimod-induced ear swelling rodent model. It demonstrated this efficacy at 30 mg/kg which is comparable to exposures above as LYC-51661 is approximately 100-fold less potent than LYC-30937. LYC-30937 was selected for advancement based on its *in vitro* potency, *in vivo* immunomodulatory activity, and a pharmacokinetic (PK) profile characterized by high local tissue concentrations in the gastrointestinal tract.

In rodent inflammatory bowel disease 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. It is in the gut where it is

hypothesized that chronically activated lymphocytes traffic prior to infiltrating distal inflamed areas like the skin.

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%). When administered as a powder blend in an EC capsule (the intended clinical formulation) to monkeys, the $AUC_{0\text{-}24}$ of LYC-30937-EC is approximately 10% of that achieved using a lipid-based formulation. In mouse, rat, and monkey, LYC-30937 exhibits low to moderate plasma clearance, low to moderate volume of distribution, and a long terminal elimination half-life. Plasma protein binding is moderate in all species (13-18% free).

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

2.3.3 Safety Pharmacology and Toxicology

LYC-30937 is not genotoxic and does not produce adverse central nervous system (CNS), 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 $\geq$ 5800 ng·h/mL was associated with sporadic instances of mortality. The NOAEL was 2 mg/kg/day with plasma AUC values of 1690 ng·h/mL in male rats and 1040 ng·h/mL in female rats. In the rat 91-day GLP toxicology study, the no observed adverse event level (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.

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.

2.4 Previous Human Experience

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

The Phase 1a study was comprised of a single ascending dose (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.

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 (64-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 open-label, SAD study to evaluate the PK profile, safety and tolerability in subjects with UC. A total of 6 subjects received LYC-30937-EC treatment at either 25 mg (3 subjects) or 100 mg (3 subjects). No AEs were reported for the study.

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 Investigator's Brochure (IB) and in Addendum #1.

2.5 Dose Selection Rationale

The proposed dose to be studied in this Phase 2a study is 25 mg once daily (q.d.) oral dose. The rationale for this is based on the exposures required to demonstrate efficacy in models of autoimmune disease, and the safety margins for the both the fasted and fed states.

From the SAD study, a dose of 25 mg was associated with a C_{max} of 1.7 ng/mL and an AUC_{0-72} of 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 collagen-induced arthritis model where C_{ave} was 0.9 ng/mL (2nM) and AUC was 22 ng·h/mL. Exposures were comparable in an imiquimod-induced ear swelling model when those exposures are extrapolated for the 100-fold less potent ATPase modulator. 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 trafficking in the gut.

The 25 mg dose is also to ensure safety. Subjects in this study 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

The rationale for the clinical study is that current systemic therapies for tissue-specific autoimmune diseases are often associated with immune suppression. The selective action of LYC-30937-EC, on metabolically sensitive, chronically activated lymphocytes coupled with the minimal systemic exposure suggest a possible benefit to patients of an efficacious drug without immunosuppression and systemic adverse events. The benefit of LYC-30937-EC is that it intended to fulfill the existing unmet needs in the treatment of chronic plaque-type psoriasis.

Based on the results from the first-in-human study described in Section 2.4, single doses of up to 300 mg were shown to be safe and well tolerated (in the SAD component of the study) and single dose exposures in the 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. In the Phase 1 study in healthy subjects and in the Phase 1b study in subjects with active UC, no safety signals were detected. There were no clinically significant laboratory abnormalities and the subjects tolerated the drug well.

In Phase 2, the subjects will have an active autoimmune disease (chronic plaque-type psoriasis) and therefore will be a different study population. These subjects will be administered study drug once daily for 12 weeks and will be closely monitored for any AE or other safety parameters during the course of the study. Because a high fat meal increased absorption 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 efficacy of LYC-30937-EC in subjects with chronic plaque-type psoriasis is being evaluated in this study, therefore any benefit is theoretical at this time. This is the first study to evaluate efficacy in this population.

3.0 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

The objective of this study is to assess the efficacy, safety, and tolerability of LYC-30937-EC compared to placebo in subjects with chronic plaque-type psoriasis.

- **Primary Study Objective**

  The primary objective will be to assess the efficacy of LYC-30937-EC in inducing a reduction from baseline in PASI compared with placebo in subjects with chronic plaque-type psoriasis over the treatment duration of 12 weeks.

- **Secondary Study Objectives**

  The secondary objectives will be to evaluate the overall efficacy, safety and tolerability of LYC-30937-EC compared with placebo in subjects with chronic plaque-type psoriasis.

- **Exploratory Objectives**

  The exploratory objectives will be to assess concentration of LYC-30937 in plasma and in skin tissue. Skin biopsies are optional and will be collected in a subset of approximately 6 consenting study subjects to assess LYC-30937 concentrations in skin.

3.2 Endpoints

- **Primary Endpoints (Efficacy)**

  The primary efficacy endpoint of the study will be the mean percent change from baseline to Week 12 in PASI.

- **Secondary Endpoints (Efficacy)**

  The secondary efficacy endpoints of the study will be:

  – The proportion of subjects who achieve a ≥ 75% reduction from baseline in PASI at Week 12.

  – The mean percent change from baseline to Week 12 in BSA.

- The proportion of subjects who achieve "cleared" (score = 0) or "minimal" (score = 1) on the static IGA at Week 12.

- The proportion of subjects who achieve a 2 step reduction on the static IGA at Week 12.

- **Secondary Safety Endpoint**

  The secondary safety endpoint of the study will include AEs, PE, vital sign measurements, 12-lead ECG, and laboratory assessments.

- **Exploratory Endpoint**

  Concentration of LYC-30937 will measured in plasma and in skin as an exploratory endpoint.

4.0 STUDY DESIGN

4.1 Design Overview

This is a phase 2a multi-center, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy, safety and tolerability of LYC-30937-EC treatment in subjects with chronic plaque-type psoriasis.

After signing an informed consent, all eligible subjects will be followed for approximately 16 weeks, which includes up to 2 weeks between screening and Study Day 1 (first dose of treatment), 12 weeks for treatment, and 2 week for follow-up.

There are 3 distinct phases of this study outlined below:

Screening: The screening visit will take place up to 2 weeks prior to randomization and subject's first dose of LYC-30937-EC (or matching placebo). Subjects who meet all eligibility requirements will return for the next phase of the study.

Treatment Period: Subjects meeting all entry criteria will be randomized in a 2:1 ratio to active treatment (LYC-30937-EC 25 mg q.d.) or matching placebo. Subjects will receive their first dose of study drug at the investigational site after randomization has occurred. Subjects will return to the investigational site at Weeks 2, 4, 8, and 12 for efficacy assessments, safety monitoring, and study drug receipt (at Weeks 2, 4, 8).

Follow-Up: There will be 1 follow-up visit performed at Week 14 for final safety monitoring purposes.

After completion of all follow-up visits, the study database will be locked to allow for the analysis of data collected up through Week 14.

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

4.2 Number of Subjects and Sites

A total of approximately 30 subjects will be randomized into the study and treated at approximately 6 sites (refer to Section 8.1 Sample Size Calculation).

4.3 Assignment of Subject Numbers

Subjects will be assigned a 6-digit unique identification number sequentially as they sign the informed consent document and agree to participate in the study. The first 3 numbers will identify the site number (e.g., 200, 201, 202) and the next 3 numbers will be assigned consecutively starting with "001" then "002." Subject identification numbers will be captured on the 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.

Each subject meeting entry criteria will be assigned a randomization number. The treatment assignment for the subject will be linked to the randomization number. Before enrollment begins, the randomization numbers list will be generated. The subject identification number and randomization number will be assigned by an interactive response technologies (IRT) system.

Rescreening of subjects who previously failed screening may be allowed depending on the reason for the screen fail and after consultation and approval by the study Sponsor. Depending on the timing of the rescreening, the subject may need to repeat certain screening assessments to confirm eligibility into the study and this determination will be made through discussion with the Sponsor on a case-by-case basis.

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

Subjects must meet the following inclusion criteria to participate in the study.

1. Consenting adult aged 18 – 75 years at screening.

2. Have a diagnosis of plaque-type psoriasis for ≥ 6 months prior to screening.

3. Must have chronic plaque-type psoriasis of moderate severity confirmed at both Screening and Baseline visits. Moderate severity is defined as:
    - PASI > 7 with BSA involvement of 5 – 15% inclusive, and
    - overall lesion severity of moderate or marked, where:
        - moderate = moderate plaque elevation (= 0.75mm); moderate red coloration; coarse scale predominates;
        - marked = moderate plaque elevation (= 1mm); bright red coloration; thick, non-tenacious scale predominates.

4. Female subjects of childbearing potential must use two 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 contraception (oral, patch, injectable, implant) or double-barrier method (condom or diaphragm with spermicide). This contraception must be continued during the study and for 30 days after taking the last dose of study drug. (Post-menopausal defined as lack of menses for ≥ 6 months prior to screening confirmed with serum follicle stimulating hormone (FSH) > 25 mIU/mL at screening.)

5. Male subjects with partners of childbearing potential must take appropriate precautions to avoid fathering a child while participating in the study and use appropriate barrier contraception or abstinence during the study and for 30 days after their last dose of study drug.

6. Agree to avoid prolonged sun exposure and avoid tanning booths or UV light sources during the study.

7. Ability to provide written informed consent and to be compliant with the schedule of events.

4.4.2 Exclusion Criteria

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

1. Non-plaque-type psoriasis (eg, pustular, erythrodermic, and guttate psoriasis).

2. Drug-induced psoriasis (ie, new onset or current exacerbation from beta-blockers, calcium channel blockers, or lithium).

3. Spontaneously improving or rapidly deteriorating plaque psoriasis.

4. Comorbid psoriatic arthritis not amenable to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs).

5. Treatment with any biologic agent for plaque psoriasis.

6. Failed 2 or more systemic treatments for plaque psoriasis.

7. Received phototherapy or prolonged sun exposure or use of tanning booth or other ultraviolet light source within 4 weeks prior to initiating screening procedures.

8. Received systemic drug therapy (non-biologic) for plaque psoriasis or any other systemic medications that could affect psoriasis or its evaluation (PASI or static IGA), including but not limited to oral or injectable corticosteroids, retinoids, sulfasalazine, within 4 weeks of initiating screening procedures.

9. Received topical medication that could affect psoriasis or its evaluation (PASI or static IGA), including but not limited to corticosteroids, retinoids, topical vitamin D derivatives, pimecrolimus, tacrolimus, calcipotriene, within 2 weeks of initiating screening procedures.

10. Received immunosuppressant agents (eg, cyclosporine, azathioprine, methotrexate) within 8 weeks of initiating screening procedures.

11. Known mitochondrial disorder.

12. Any of the following laboratory abnormalities:

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

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

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

    d white blood cell (WBC) count < 3000/mm^3 (SI: < 3.0 x 10^9/L)

    e platelets < 80000/ mm^3 (SI: 80 x 10^9/L)

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

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

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

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

    Note that recurring urinary tract infections are allowed.

16. History of cancer, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin that have been adequately treated with no re-occurrence for at least 1 year prior to screening).

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

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

19. History of treatment with an investigational agent within 30 days prior to initiating screening procedures.

20. In the opinion of the investigator, the subject is not a suitable candidate for this study. For example, a medical condition that may put the subject at increased risk, likely not to be cooperative with study procedures or with completion of the study, or the inability to communicate reliably with the investigator.

4.5 Subject Withdrawals

All subjects have the right to withdraw at any point during the study without prejudice. Lycera must be notified immediately if a randomized subject is withdrawn from the study, and every effort should be made to inform Lycera prior to withdrawing the subject. Subjects who are withdrawn may be replaced at the discretion of Lycera on a case-by-case basis.

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

- screen failure: subject does not meet entry criteria and was not randomized
- occurrence of any AE (if the subject withdraws due to an AE the investigator should follow the subject until the AE resolves or stabilizes), concurrent illness, or laboratory abnormality 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, or regulatory authority(ies) for safety, behavioral, or administrative reasons

- subject lost to follow-up (If a subject does not return for a scheduled visit, every effort should be made to contact the subject and/or the subject's family; this effort must be clearly documented)

- other (eg, subject moved)

The subject will be asked to undergo final visit procedures (Visit 6/Week 12) in order to document subject outcome, if possible. The investigator or site staff should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved AEs.

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: chronic plaque-type psoriasis

- strength: 25 mg

- dosage form: oral, delayed release, EC hydroxyl-propyl-methyl-cellulose (HPMC) capsule

- inactive placebo: matching oral, EC HPMC capsule containing the same inactive excipients as the LYC-30937-EC active treatment capsules

- manufacturer: QS Pharma (Boothwyn, US)

5.2 Treatment Regimen

The treatment (LYC-30937-EC or placebo) will be administered orally q.d. from Study Day 1 through the end of the double-blind treatment phase (Visit 6/Week 12) for a total of 84 days of treatment. The capsules must be administered in the morning upon awaking after fasting

overnight. Subject should not eat for approximately 1 hour (or more) after taking study drug. The exception to this is the Visit 2/randomization visit when the first dose of study drug is administered in the clinic. Subjects may have eaten their morning meal prior to coming for this visit. They should note the time they ate their last meal prior to this clinic visit and study drug should not be administered until at least 2 hours after that meal.

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

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

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

5.3 Randomization

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

5.4 Maintaining and Breaking the Blind

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

To minimize the potential for bias, treatment information will be kept confidential and will not be available for release to the investigator, site staff and Lycera until after database lock at the end of the study (Visit 7/Week 14).

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

5.5 Drug Supplies

5.5.1 Packaging and Labeling

All study drug will be supplied in bottles.

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

The study drug is to be dispensed according to the protocol. The distribution will only occur after all required documentation is obtained including study approval by the Competent Authorities and the IRB.

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

5.5.2 Product Accountability, Storage, Dispensing, and Return

Upon receipt of the study medication, the principal investigator (PI) or authorized designee will inspect and count the study drug. All study drug supplies for the study will be stored in a locked and secure location accessible only to those authorized by the PI to dispense the study drug. The study drug supply is to be stored under controlled room temperature conditions (15-25°C). A detailed inventory log will be maintained by the PI or authorized designee.

The first dose of study drug will be taken in the clinic under medical supervision. Subsequent dosing will take place at the subject's home including on the days of study clinic visits. Subjects are to take their study drug dose in the morning upon awaking after fasting overnight and they should not eat for approximately 1 hour after taking study drug. The subject will receive a new medication supply containing sufficient study drug for the period until the visits specified in Table 1.

Lycera (or designee) will retrieve all partially used or unused treatments. A detailed log of the returned study drug will be established. The PI will not destroy unused study drug unless Lycera provides written authorization.

5.5.3 Treatment Compliance

Subject compliance with taking the treatment will be assessed by counting the number of returned capsules at each visit. 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 of study drug should be discussed to try to ascertain the reason(s). Every effort should be made to ensure proper subject dosing.

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

5.6 Concomitant Medications

Subjects will not use biologics intended for treatment for plaque psoriasis during the study. They will not use immunomodulatory medications during the study.

Other limitations of concomitant medications during the study are:

- No topical therapy for psoriasis
- No new systemic therapy for psoriasis
- No use of phototherapy, tanning booths, prolonged sun exposure or other ultraviolet (UV) light sources
- No use of any investigational drug
- Patients may use Eucerin cream for excessively dry skin, but these should not be used with 24 hours of study visits. No oil-based gels are to be used
- No topical or oral corticosteroids are permitted; patients may use inhaled corticosteroids or nasal corticosteroids

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 procedures is 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 defined as Study Day 1. The timing of all study visits are based on Study Day 1.

- Study visit timing and windows are as follows:

  – Screening (Visit 1) – approximately Study Day -14 to Day -1

  – Randomization/treatment (Visit 2) – Study Day 1

  – Visit 3 (Week 2 – Study Day 15) – window ± 2 days

  – Visit 4 (Week 4 – Study Day 29) – window ± 2 days

  – Visit 5 (Week 8 – Study Day 57) – window ± 3 days

  – Visit 6 (Week 12 – Study Day 85) – window ± 3 days

  – Follow-up (Visit 7) (Week 14 - Study Day 99) – window ± 3 days

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

6.2 Schedule of Events

Table 1: Schedule of Events

Protocol Activity	Screening	Randomization and Dosing	Treatment				Follow-up
			Week 2	Week 4	Week 8	Week 12/ ET	Week 14
Study Day	-14 to -1	1	15 ± 2 days	29 ± 2 days	57 ± 3 days	85 ± 3 days	99 ± 3 days
Visit Number	1	2	3	4	5	6	7
Informed consent	X						
Demography [a]	X						
Medical/surgical history	X						
Serology [b]	X						
Prior psoriasis treatments	X						
Serum pregnancy test (pre-menopausal female subjects)	X						
FSH (post-menopausal female subjects) [c]	X						
Vital signs [d]	X	X	X	X	X	X	X
Assess protocol eligibility [l]	X	X					
Randomization		X					
Dispense study drug		X	X	X	X		
Administer study drug at the clinic		X					
Telephone reminder to subject regarding taking study drug after fasting overnight		X [m]					
Review study drug compliance			X	X	X	X	
PASI and % BSA	X	X		X	X	X	
Static IGA	X	X		X	X	X	
Photographs [j]		X				X	

Table 1: Schedule of Events

Protocol Activity	Screening	Randomization and Dosing	Treatment				Follow-up
			Week 2	Week 4	Week 8	Week 12/ ET	Week 14
Study Day	-14 to -1	1	15 ± 2 days	29 ± 2 days	57 ± 3 days	85 ± 3 days	99 ± 3 days
Visit Number	1	2	3	4	5	6	7
Skin biopsy [k]					X		
Urine pregnancy test (female subjects of childbearing potential)		X	X	X	X	X	X
Height	X						
Weight	X		X	X	X	X	
Physical examination	X		X	X	X	X	
12-Lead ECG	X					X	
Chemistry panel [e]	X		X	X	X	X	X
Hematology panel [f]	X		X	X	X	X	X
Urinalysis [g]	X					X	
Plasma PK sample collection[h]					X		
Concomitant medications	X	X	X	X	X	X	X
Assess AEs [i]	X	X	X	X	X	X	X

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; CRP = C-reactive protein; ECG = electrocardiogram; FSH = follicle stimulating hormone; HbsAG = hepatitis B surface antigen; HCV = hepatitis C virus; HDL = high density lipoprotein; HIV = human immunodeficiency virus; hsCRP = high sensitivity C-reactive protein; IGA = Investigator's Global Assessment; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean cell hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PASI = Psoriasis Area and Severity Index; PD = pharmacodynamics; PK = pharmacokinetics; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell

[a] Demography includes smoking status, drug and alcohol consumption, and date of chronic plaque-type psoriasis diagnosis.
[b] HbsAG, HCV antibodies, and HIV-1/2 antibodies.
[c] Post-menopausal is defined as having no menses for ≥ 6 months prior to screening and a serum FSH level > 25 mIU/mL at screening.
[d] Vital signs will be collected after the subject has been sitting quietly for ≥ 5 minutes and include blood pressure (systolic and diastolic), heart rate, respiratory rate, and temperature.
[e] 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.

[f] Hematology Panel includes: platelets, WBCs with differential if abnormal (% and absolute counts), hematocrit, RBCs, hemoglobin, MCV, MCHC, and MCH.
[g] Urinalysis (dipstick) 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 nitrate.
[h] All subjects will have one blood sample collected at Week 8 (any time post study drug dose) to measure plasma LYC-30937 concentration.
[i] AEs will be assessed after the informed consent is signed.
[j] Photographs will be taken at randomization (pre-dosing) and at Week 12 in a subset of subjects.
[k] Optional skin biopsy will be collected at Week 8 in a subset of approximately 6 consenting subjects. Biopsy collection instructions will be included in a separate document. This tissue will be assayed for concentration of LYC-30937.
[l] Note that confirmation of moderate plaque-type psoriasis is determined at both Screening and Visit 2 (baseline, prior to first dose).
[m] Site will telephone subjects the day after randomization visit to remind them to take study drug in the morning after fasting overnight and to wait approximately 1 hour before eating a meal.

6.2.1 Visit Procedure Guidelines

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

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

Re-screening of subjects initially not meeting all selection criteria may be allowed once after consultation with the sponsor.

6.3 Efficacy Assessments Performed

6.3.1 Psoriasis Area and Severity Index (PASI) and Body Surface Area (BSA)

The PASI[17], a widely used index to express the severity of chronic plaque-type psoriasis, will be assessed at the time points indicated in the schedule of events (Table 1). The PASI is a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance.

The index combines the assessment of severity of the lesions (erythema, induration/thickness, and desquamation/scaling) and percentage of affected area into a single score ranging from 0 (no disease) to 72 (maximal disease).

The index is calculated as follows (also see Appendix A):

- The subject's body is divided into 4 regions (head, upper extremities, trunk, and lower extremities). Each of these 4 regions is first scored by itself and then all 4 scores are combined into the final PASI.

- For each region, the percent of area of skin involved (0 to 100% BSA), is estimated using the palm (including fingers) and % BSA is totaled for the whole body. Additionally the % BSA in each of the 4 body regions is transformed into a grade from 0 (0%) to 6 (90-100%) for the PASI calculation.

- Within each of the 4 body regions, the severity of chronic plaque-type psoriasis is estimated by the evaluation of 3 clinical signs: erythema (redness), induration (thickness), and desquamation (scaling). Severity parameters are measured on a scale of 0 (none) to 4 (very severe).

- The sum of all 3 severity parameters for each region of skin is then multiplied by the area score for that area and multiplied by a different factor for each region (0.1 for head, 0.2 for upper extremities, 0.3 for trunk and 0.4 for lower extremities).

The investigator will collect the components necessary to calculate the PASI and these components will be entered into the CRF where the PASI score will be calculated. To be eligible for study participation, the subject must have a PASI score of greater than 7 at both the screening visit and the randomization visit, with total BSA involvement of 5-15%, inclusive.

The PASI scoring system is described further in Appendix A.

6.3.2 Static Investigator's Global Assessment (static IGA)

The static IGA[15] is used to measure psoriasis severity in clinical trials. The static IGA used in this trial will be a 6-point scale and will be evaluated at the time points indicated in the schedule of events (Table 1). The scoring is based on response to treatment measured by lesion erythema, induration, and scale. The static IGA scoring and descriptors are as follows:

Score	Short Descriptor	Detailed descriptor
0	Cleared	No plaque elevation, erythema or scaling; hyperpigmentation may be present
1	Minimal	Minimal plaque elevation (=0.25mm); faint erythema; minimal scaling, with occasional fine scale over < 5% of lesion
2	Mild	Mild plaque elevation (=0.5mm); light red coloration; fine scale predominates
3	Moderate	Moderate plaque elevation (=0.75mm); moderate red coloration; coarse scale predominates
4	Marked	Moderate plaque elevation (=1mm); bright red coloration; thick, non-tenacious scale predominates
5	Severe	Severe plaque elevation (≥1.25mm); dusky to deep red coloration; very thick, tenacious scale predominates

6.4 Safety Assessments Performed

6.4.1 Physical Examinations (PE)

A standard PE will be performed by the PI or by an appropriately trained individual at the time points indicated in the schedule of events (Table 1) 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 PE 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 measurements will be performed at the time points indicated in the schedule of assessments (Table 1) and will consist of BP (systolic and diastolic), HR, RR, and temperature. Subjects should sit quietly with feet flat on the floor or be supine (lying down) for at least 5 minutes prior to measurements.

- Subject must remain seated or lying down for the entire measurement.
- The use of automated devices for measuring BP and HR is acceptable. If done manually, HR must be measured in the brachial/radial artery as per site standard procedures.
- Blood pressure 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. Clinically significant changes from baseline should be recorded as AEs.

6.4.3 12-Lead ECG

A standard 12-Lead ECG will be performed after 5 minutes of rest in the supine position using a standardized automated device at the time points indicated in the schedule of assessments (Table 1). The following ECG parameters will be recorded: HR, PR-interval, QRS-duration, QT-interval, QT interval corrected for HR according to Fridericia's formula (QTcF)-interval and the PI's assessment of the ECG profile. Clinically significant changes from screening should be recorded as AEs.

6.4.4 Laboratory Assessments

Laboratory assessments will be performed at the time points indicated in the schedule of assessments (Table 1) and will be evaluated by a central laboratory.

The PI 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 PI should be repeated. Confirmed, clinically significant laboratory abnormalities should be further evaluated by the PI 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, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), reflexive bilirubin (total, direct, indirect), alkaline phosphatase (ALP), cholesterol, triglycerides, creatine phosphokinase (CPK), high sensitivity C-reactive protein (hsCRP), high density lipoprotein (HDL), and low density lipoprotein (LDL).

Hematology Panel Sample

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

Urine Sample (Dipstick)

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

Childbearing Potential Evaluation and Pregnancy Tests

Serum FSH in postmenopausal female subjects and a serum hCG (pregnancy test) in premenopausal females will be evaluated at the central lab at screening.

Urine pregnancy tests for female subjects of childbearing potential will be performed at the time points indicated in the schedule of assessments (Table 1).

6.4.5 Body Temperature monitoring

Subjects' body temperature will be measured at clinic visits (Table 1). Use the same type thermometer throughout the study (eg, oral, axillary, etc.)

If the temperature reading is > 101°F (or 38.3°C), the subject is to 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, the study drug is to be withheld and the subject should be evaluated for other sources of increased temperature as medically indicated. Study drug may be re-started if it has not been interrupted for 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 study drug for more than 3 days the investigator should withdraw the subject from the trial.

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 they must contact their investigator. They should present to the clinic as soon as possible to be evaluated for potential source of the symptom and liver function testing should be performed. The study medical monitor should be contacted. If a source is not readily identified then study drug should be withheld and the subject should continue to be evaluated for the source and managed as medically indicated. Study drug may be re-started if it has been interrupted for no more than 3 days and the source of the vomiting or abdominal pain is determined, or if these symptoms resolve, and in the clinical judgement of the investigator and study medical monitor it is safe for the subject to continue study drug. If the subject is off drug for more than 3 days the investigator should withdraw the subject from the study.

Monitoring Lactate and Liver Function:

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

- ALT or AST > 8 x ULN
- ALT or AST > 5 x ULN for more than 2 weeks
- ALT or AST > 3 x ULN and total bilirubin > 2 x ULN
- 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 the 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 case. 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, international normalized ratio, 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 on Harmonization (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 PE findings
- hypersensitivity
- progression/worsening of underlying disease

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

7.2 Serious Adverse Events Definition

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

- death
- life-threatening (ie, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does NOT include an event, that had it occurred in a more severe form, might have caused death.)
- in-subject hospitalization or prolongation of existing hospitalization
- persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- congenital anomaly/birth defect
- other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (eg, an allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency)

7.3 Adverse Event Reporting

Adverse events, both serious and 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. For all enrolled/randomized subjects, AEs should be recorded on CRFs from the time the subject has signed informed consent. For subjects not randomized, only SAEs and AEs leading to screen failure will be collected on the CRFs from the time the subject has signed informed consent.

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

AEs should be reported using concise medical terminology on the CRFs. 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 blinded physician will assess subjects at each visit for the occurrence of AEs. In order to avoid bias in eliciting AEs, subjects should be asked the following 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 Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.

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

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

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

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

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE

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

7.5 Serious Adverse Event Reporting

All observed or volunteered SAEs regardless of treatment group or suspected causal relationship to the study drug will be reported as described below. If an SAE occurs, Lycera or designee is to be notified within 24 hours of awareness of the event by the investigator or designee.

All SAEs and follow-up information must be reported to Lycera or designee within 1 business day or 24 hours of awareness of the event as required by your local requirements by emailing a completed SAE report form to following email address:

SAE Email: **LyceraDrugSafety@mmsholdings.com**

In particular, if the SAE is fatal or life threatening, notification to Lycera or designee 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 Lycera or designee 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 study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and the document the time of his/her first awareness of the SAE.

The study sponsor medical monitor will perform final medical review of SAEs. Full details of the SAE processing and review procedures will be documented in a safety management plan and medical monitoring plan. Serious adverse events, including any deemed as suspected unexpected serious adverse reactions (SUSAR) will be reported to U.S. FDA within 15 calendar days of 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's not listed in the LYC-30937 IB or is not listed at the specificity or severity that has been observed. Non-SUSAR SAEs will be reported annually as per regulatory guidance.

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

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

7.6 Post-Week 14 Reporting of Serious Adverse Events

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

7.7 Exposure in Utero

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

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

If any study subject becomes pregnant during their participation in the study, the subject will stop study drug and withdraw from the study. The investigator must submit this information to Lycera or designee on the 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 or placebo) caused or contributed to an AE.

If the final determination of causality is unknown and the investigator does not know whether the study drug caused the event, then the event will be handled as "related to study drug" for reporting purposes. If the investigator's causality assessment is "unknown, but not related to study drug", this should be clearly documented on study records 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, other illness, other, 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 categorized as "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 Study Hold or Stopping Criteria

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

ECGs are scheduled to be performed at Week 12 (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 drug-related adverse event that meets grade 4 or 5 CTCAE severity criteria or if 2 or more subjects experience the same type of grade

2 study drug-related adverse event and/or meets the serious criteria as defined in Section 7.2. 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.

8.0 STATISTICAL AND ANALYTICAL PLAN

8.1 Sample Size Calculation

A total of approximately 30 subjects will be randomized into the study and using a 2:1 randomization ratio of LYC-30937-EC 25 mg or placebo daily.

A sample size of 30 subjects (20 LYC-30937-EC and 10 placebo) will achieve approximately an 80% power to detect difference in the mean percent change from baseline in PASI at Week 12 in the LYC-30937 treatment group compared to the placebo treatment group. The mean percent change from baseline in PASI at Week 12 in the placebo treatment group is assumed to be 16.7% with SD=32.0.[16] The power was computed assuming the mean percent change from baseline in PASI at Week 12 in the LYC-30937-EC treatment group is at least 52.7% (SD=32.0) for a mean difference of at least 36.0%. The test statistic used is the two-sided t-test. The alpha level of the test was targeted at 0.05.

8.2 Analysis Populations

8.2.1 Full Analysis Set

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

8.2.2 Safety Set

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

8.3 Demographic and Subject Characteristics

Demographic information and subject characteristics such as gender, race, age, and baseline vital signs, baseline PASI score, baseline % total BSA involvement, and baseline static IGA will be summarized by treatment group and overall.

8.4 General Statistical Considerations

For safety and efficacy endpoints, baseline will be defined as the last observation prior to dosing.

Continuous safety and efficacy endpoints will be summarized using mean, standard deviation, median, minimum, and maximum. Discrete safety and efficacy endpoints will be summarized by the number and percent of subjects in each category. Continuous efficacy endpoints will be analyzed using an analysis of covariance model with treatment as a factor and baseline value as a covariate. Discrete variables will be analyzed using a chi-square test. There will be no adjustments for multiplicity. Additional details of the statistical analyses will be described in the statistical analysis plan (SAP).

8.5 Efficacy Analysis

8.5.1 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is the mean percent change from baseline in PASI score at Week 12. The endpoint will be calculated by taking the Week 12 PASI score and subtracting the baseline PASI score then dividing by the baseline PASI score and multiplying by 100 to get the percentage. The mean percent change from baseline in PASI scores will be compared between the LYC-30937-EC treatment group and placebo using analysis of covariance with treatment as a factor and baseline as a covariate to assess the null hypothesis that the LYC-30937-EC arm mean percent change equals the placebo arm mean percent change The mean difference (LYC-30937-EC versus placebo) will also be estimated along with the 95% confidence interval of the difference. If the confidence interval does not contain 0 the null hypothesis will be rejected and the mean percent change from baseline in PASI score at Week 12 will be considered different due to treatment arm.

8.5.2 Secondary Efficacy Endpoint Analyses

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

- The proportion of subjects who achieve a ≥ 75% reduction from baseline in PASI at Week 12 will be calculated by taking the number of subjects who achieve a ≥ 75% reduction from baseline in PASI at Week 12 divided by the total number of subjects in each treatment arm. The proportion of subjects in each treatment arm will be compared using a chi-square test.

- The mean percent change from baseline to Week 12 in the BSA will be calculated by taking the Week 12 BSA and subtracting the baseline percent BSA then dividing by the baseline percent BSA and multiplying by 100 to get the percentage of baseline. The mean percent change in each treatment arm will be compared using the same methodology for the primary efficacy endpoint.

- The proportion of subjects who achieve "cleared" (score = 0) or "minimal" (score = 1) on the static IGA at Week 12 will be calculated by taking the number of subjects who achieve "cleared" (score = 0) or "minimal" (score = 1) on the static IGA at Week 12 divided by the total number of subjects in each treatment arm. The proportion of subjects in each treatment arm will be compared using a chi-square test.

- The proportion of subjects who achieve at least a 2 step reduction on the static IGA at Week 12 will be calculated by taking the number of subjects who achieve at least a 2 step reduction on the static IGA at Week 12 (ie, a score of 5 at baseline to a score of 3 or less at Week 12) divided by the total number of subjects in each treatment arm. The proportion of subjects in each treatment are will be compared between treatment arms using a chi-square test.

8.6 Safety Analysis

Adverse event collection begins after the subject signs the informed consent document and continues until Week 14. For all randomized subjects, AEs should be recorded on CRFs from the time the subject has signed informed consent through Week 14. For subjects not randomized, only SAEs and AEs leading to screen failure will be collected from the time the subject has signed informed consent through screen failure. Treatment-emergent AEs are defined as AEs that start after study drug administration (LYC-30937-EC or placebo) and include worsening of conditions that existed prior to study drug administration. Adverse events

that occur in subjects who screen fail will only be listed if they were the reason the subject was a screen failure.

Adverse events and SAEs will be summarized by system organ class, by severity, and by relationship; this will be done by treatment group and overall. Serious adverse events resulting in death will be listed and summarized separately.

Other safety data, such as vital signs and clinical laboratory data will be summarized by study visit and treatment group. Where appropriate, change from baseline in safety data will also be summarized for each study visit, for end of treatment visit, and for "worse value" by treatment group.

9.0 ETHICAL CONSIDERATIONS

9.1 Basic Principles

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

9.2 Institutional Review Board/Independent Ethics Committee

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

9.3 Informed Consent

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

9.4 Study Termination

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

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

10.0 DATA HANDLING AND RECORD KEEPING

10.1 Study Monitoring

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

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

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

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

10.2 Study Documentation

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 study, the CRFs are an electronic data record. The completed original CRFs are the sole property of Lycera and should not be made available in any form to third parties, except for authorized representatives of Lycera or appropriate regulatory authorities, without written permission from Lycera.

It is ultimately the investigator's responsibility to ensure completion and to review and approve all CRFs. Individual CRFs may be signed by the investigator or by an authorized staff member (and may be an electronic signature). A final CRF must be signed by the investigator to attest

that the information contained on the CRF is true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs. Subject source documents are the investigator's subject records maintained at the study site. In most cases, the source documents will be the hospital's or the investigator's chart. In cases where the source documents are the hospital or the investigator's chart, the information collected on the CRFs must match those charts.

The CRF for questionnaires may serve as the source document.

10.3 Record Retention

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

FDA/ICH

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

ICH

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

To enable evaluations and/or audits from regulatory authorities or Lycera, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent [documents], 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 initials and number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated in this study are to be available for inspection on request by the FDA or other government regulatory agency inspectors, and the IRB/IEC but should otherwise remain confidential.

11.2 Publication of Data and Protection of Intellectual Property

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

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

12.0 REFERENCES

[1] Jacobson CC, Kumar S, Kimball AB. Latitude and psoriasis prevalence. J Am Acad Dermatol. 2011;65(4):870-3.

[2] Sa SM, Valdez PA, Wu J, Jung K, Zhong F, Hall L, et al. The effects of IL-20 subfamily cytokines on reconstituted human epidermis suggest potential roles in cutaneous innate defense and pathogenic adaptive immunity in psoriasis. J Immunol. 2007;178(4):2229-40.

[3] Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. Nature 2007;445(7130):866-73.

[4] Steinman L. Weighing in on autoimmune disease: 'Hub-and-spoke' T cell traffic in autoimmunity. Nat Med. 2013;19(2):139-41.

[5] Odoardi F, Sie C, Streyl K, Ulaganathan VK, Schläger C, Lodygin D, et al. T cells become licensed in the lung to enter the central nervous system. Nature 2012;488(7413):675-9.

[6] Scher JU, Sczesnak A, Longman RS, Segata N, Ubeda C, Bielski C, et al. Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis. Elife 2013;2:e01202

[7] Vaahtovuo J, Munukka E, Korkeamäki M, Luukkainen R, Toivanen P. Fecal microbiota in early rheumatoid arthritis. J Rheumatol. 2008;35(8):1500-5.

[8] Wu HJ, Ivanov II, Darce J, Hattori K, SHima T, Umesaki Y, et al. Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells. Immunity 2010;32(6):815-27.

[9] Morton AM, Sefik E, Upadhyay R, Weissleder R, Benoist C, Mathis D. Endoscopic photoconversion reveals unexpectedly broad leukocyte trafficking to and from the gut. Proc Natl Acad Sci U S A 2014;111(18):6696-701.

[10] Boehncke WH, Schön MP. Psoriasis. Lancet 2015;386(9997):983-94.

[11] Oliveira Mde F, Rocha Bde O, Duarte GV. Psoriasis:classical and emerging comorbidities. An Bras Dermatol 2015;90(1):9-20.

[12] Torres T, Bettencourt N. Psoriasis: the visible killer. Rev Port Cardiol. 2014;33(2):95-9.

[13] Vanderpuye-Orgle J, Zhao Y, Lu J, Shrestha A, Sexton A, Seabury S, et al. Evaluating the economic burden of psoriasis in the United States. J Am Acad Dermatol. 2015;72(6):961-7.

[14] Papp KA, Langley RG, Sigurgeirsson B, Abe M, Baker DR, Konno P, et al. Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis; a randomized double-blind, placebo-controlled phase II dose-ranging study. Br J Dermatol. 2013;168(2):412-21.

[15] Langley RGB, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) scale: a modified tool for evaluating plaque psoriasis severity in clinical trials. J Dermatological Treatment 2015;26(1):23-31.

[16] Papp K, Reich K, Leonardi CI, Kircik L, Chimenti S, Langley RGB, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). J Am Acad Dermatol. 2015;73(1):37-49.

[17] Fredriksson T and Pettersson U. Severe psoriasis – oral therapy with a new retinoid. Dermatologica 1978;157:138-244

13.0 APPENDICES

13.1 The PASI Scoring System

Body Region	**Erythema (E)**	**Thickness (I)** (plaque elevation, induration)	**Scaling (S)** (desquamation)	**Area score % (A)** [4]
Head (H) [1]	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=0% 1=1-9% 2=10-29% 3=30-49% 4=50-69% 5=70-89% 6=90-100%
Trunk (T) [2]	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=0% 1=1-9% 2=10-29% 3=30-49% 4=50-69% 5=70-89% 6=90-100%
Upper extremities (U)	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=0% 1=1-9% 2=10-29% 3=30-49% 4=50-69% 5=70-89% 6=90-100%

Lower extremities (L) [3]	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=0% 1=1-9% 2=10-29% 3=30-49% 4=50-69% 5=70-89% 6=90-100%

[1] Neck is evaluated as part of the head (H).

[2] Axillae and groin are evaluated as part of the Trunk (T).

[3] Buttocks are evaluated as part of the Lower extremities (L).

[4] Degree of involvement as a percentage for each body region affected.

In the PASI the body is divided into 4 regions: head (H), trunk (T), upper extremities (U) and lower extremities (L). Each region is considered to account for the following % of total BSA, head = 10% (0.1), trunk = 30% (0.3), upper extremities = 20% (0.2) and lower extremities = 40% (0.4).

Estimation of the % body area affected by psoriatic plaque in each region is done by the trained clinician using the palm (fingers included) and then converted the corresponding numeric score (0 to 6) as indicated in column 5 in the above table.

Each region is also evaluated separately for signs of disease (erythema (E), thickening (I), and scaling (D), which are rated and given a score (0 to 4), as indicated in the above table.

The PASI generates a numeric score that can range from 0 (no signs of psoriasis) to 72.

Scores from the 4 regions are combined to get the PASI score using the PASI formula:
$PASI = 0.1(E_H + IH = S_H)A_H + 0.3(E_T + I_T + S_T)A_T + 0.2(E_U + I_U + S_U)A_U + 0.4(E_L + I_L + S_L)A_L$

The investigator will be responsible for collecting the components (E, I, S) and the total regional area. These components will be entered into the CRF and calculation of the PASI score will done in the CRF.

SAMPLE: PASI Scoring Worksheet

Plaque Characteristics	Lesion Score	Head	Upper extremities	Trunk	Lower Extremities
Erythema (E)	0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe				
Induration/Thickness (I)					
Scaling (S)					
Add together each of the 3 scores for each body region to give 4 separate sums (A)					
Lesion Score Sum (A)					

Percentage body surface area affected	Area Score	Head	Upper extremities	Trunk	Lower Extremities
Area Score (B) *Degree of involvement as a percentage for each body region affected (each region given a score of 0 to 6)*	0 = 0% 1 = 1 - 9% 2 = 10 - 29% 3 = 30 - 49% 4 = 50 - 69% 5 = 70 - 89% 6 = 90 - 100%				
Multiply each Lesion Score Sum (A) by Area Score (B), for each body region, to give the 4 individual subtotals					
Subtotals (C)					
Multiply each of the Subtotals (C) by amount of body surface area represented by that region, i.e., x 0.1 for head, x 0.2 for upper extremities, x 0.3 for trunk, and x 0.4 for lower extremities.					
Body Surface Area		**x 0.1**	**x 0.2**	**x 0.3**	**x 0.4**
Totals (D)					
Add together each of the scores for each body region to give the total PASI Score.					

Total PASI Score = _____

14.0 DOCUMENT HISTORY

Summary of Changes			
Document	**Version Date**	**Description of Change**	**Rationale**
Original Protocol	30AUG 2016	NA	NA