Baricitinib (LY3009104) in the Treatment of Cutaneous Lichen Planus

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Study Product: Baricitinib (LY3009104) oral medication

Protocol Number: (IRBe) 21-003075

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Version	Date	Major Changes
1.0		Initial Protocol
1.1	4.30.21	Dose modified (4mg changed to 2mg once daily); patients of childbearing age will receive monthly pregnancy tests (starting at day 0); patients with moderate-to-severe renal impairment will be excluded from study
1.2	11.16.21	Added single-cell RNA sequencing; will require two additional skin biopsies and one additional blood draw at both the week 0 and week 2 visits to obtain tissue; collaboration with University of Michigan for single-cell RNA processing
1.3	2.14.2022	Adding ability for remote visits
1.4	3.17.2022	Adding LPQOL assessment into study visits
1.5	6.07.2022	Removing clinical assessments during remote visits
1.6	6.17.2022	Adding dose escalation and extension for patients and removing CRC visit during remote visits

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
BSA	Body Surface Area
mCAILS	Modified Clinical Assessment Scale of Severity for Index Lesion Signs & Symptoms
CFR	Code of Federal Regulations
CRF	Case Report Form
CXCR3	Chemokine Receptor-3
CXCL9	Chemokines Ligands 9
DEGs	Differentially Expressed Genes
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GVHD	Graft Versus Host Disease
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IL-1	Interleukin-1
IND	Investigational New Drug Application
IFNα	Interferon Alpha
IFNγ	Interferon Gamma
IRB	Institutional Review Board
JAK	Janus Kinase
LP	Lichen Planus
LTR	Lichenoid Tissue Reaction
MDC	Myeloid Dendritic Cells
NRS	Numerical Rating Scale
PDC	Plasmacytoid Dendritic Cells
PGA	Physician Global Assessment
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure

Study Summary

Title	**Baricitinib (**LY3009104) **in the Treatment of Cutaneous Lichen Planus**
Running Title	Baricitinib (LY3009104) in LP
Protocol Number	21-003075
Phase	Phase II
Methodology	Open-Label, Single Arm
Overall Study Duration	21 to 24 weeks
Subject Participation Duration	20 weeks
Single or Multi-Site	Single Site
Objectives	To evaluate the safety and efficacy of Baricitinib (LY3009104) in cutaneous LP as assessed by the change in Physician Global Assessment (PGA) of skin, oral mucosa, and hair, Body Surface Area (BSA), Index Treatment and Control Lesion by Modified Clinical Assessment Scale of Severity for Index Lesion Signs and Symptoms (mCAILS) score, Pruritus Visual Analog Scale (VAS), Verbal Rating Scale (VRS), Pruritus Numerical Rating Scale (NRS), and Skindex-16. To predict responses through the identification of unique biomarkers of LP at week 0 and utilizing RNA sequencing on responsive and non-responsive tissue at week 2.
Number of Subjects	12
Diagnosis and Main Inclusion Criteria	Non-pregnant adults with cutaneous LP
Study Product, Dose, Route, Regimen	Baricitinib (LY3009104) 2 mg orally administrated, once daily.
Duration of Administration	Drug will be administered from Day 0 through Week 16.
Reference therapy	Baricitinib (LY3009104) is currently being used to treat subjects with rheumatoid arthritis and under investigation for atopic dermatitis and psoriasis.
Statistical Methodology	The statistical analysis will provide descriptive summary statistics for categorical and continuous outcomes. Categorical variables will be described by their count and proportion of occurrence while continuous, normally distributed variables will be described by their mean and standard deviation; and continuous, non-normally distributed variables will be described by their median and range

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Baricitinib (LY3009104) is an oral selective inhibitor of the Janus kinase (JAK)

family of protein tyrosine kinases with selectivity for JAK1 and JAK2, and less selectivity for JAK3 with potent activity on the cytokine IFN-γ. IFN-γ is a critical cytokine in the signaling of LP. This study is aimed at evaluating the effects of baricitinib (LY3009104) 2 mg once daily in subjects with cutaneous LP; however, other forms of LP including mucosal and scalp disease may also be present.

Lichenoid tissue reaction (LTR) includes lichen planus (LP), cutaneous lupus, dermatomyositis (DM), and graft versus host disease (GVHD). The pathogenesis of LP is incompletely understood; however, it is clearly T-cell mediated without a known auto-antigen. Lichen Planus (LP) is an inflammatory skin condition characterized by purple, polygonal, pruritic, papules and plaques. LP can affect any ectodermally derived tissues including: the skin (most commonly), nails, and mucous membranes. LP is thought to affect approximately 1-2% of the general population. Most cutaneous LP resolves within one to two years. Disease duration, in ascending order, is generalized cutaneous, non-generalized cutaneous, cutaneous and mucosal, mucosal, hypertrophic, and Lichen Planopilaris (hair LP). LP is the prototypical lichen tissue reaction (LTR). Modern theories of LP encompass three major stages: antigen recognition, lymphocyte activation, and keratinocyte apoptosis. A fourth stage, resolution, is a new and emerging topic. The occurrence of triggering factors in a genetically predisposed individual carrying LP-associated genes, results in disease development. During the initiation phase, damage to keratinocytes results in the release of DNA, RNA, and cathelicidin (LL37). These proteins can stimulate plasmacytoid dendritic cells (PDC) via toll like receptors 7, 9 (TLR7,9) which result in the release of interferon alpha (IFNα). IFNα can have both local and distant effects upon myeloid dendritic cells (MDC) as well as keratinocytes. Stimulated MDC interact with CD4+ T-helper cells and with the correct antigen. The antigen remains unknown but may represent a viral derived peptide. Signaling receptors on MDC will stimulate CD4+ T-helper cells via the release of Tumor necrosis factor alpha (TNFα), Interleukin-1 (IL-1), and -12. In addition, cluster of differentiation- (CD40) and CD40 ligand (CD40L) will result in the co-stimulation of the T-helper/MDC interaction. Stimulated CD4+ T-helper cells then release of interferon gamma (IFNγ) and IL-2. These cytokines stimulate CD8+ T-cytotoxic cells. The stimulated CD8+ cells expressing Chemokine receptor-3 (CXCR3) will migrate to the dermal-epidermal junction following the release of chemokines ligands 9 (CXCL9), -10, -11. These chemokines are released by stressed and stimulated keratinocytes. The stimulated CD8+ cells will interact with the stressed keratinocytes and can induce apoptosis in with the proper and signaling receptors. This antigen also remains unknown but may be a self-antigen released by local stress. The major kill signals are TNFα, granzyme, and perforin. Fas and Fas ligand (FasL) are expressed on both keratinocytes and lymphocytes. Local CXCR3+ DC and T-regulatory cells may also modulate the local lichenoid response.

Based upon the critical role of CD8+ T-cytotoxic cells and IFNα and IFNγ signaling in LP, inhibition with Janus Kinase (JAK) 1, 2 inhibitors have significant therapeutic potential. Fitting with this, recent data has been published showing that IFNγ primed keratinocytes are vulnerable to CD8+ cytotoxic T-cells.[1] This axis is dependent upon JAK inhibitors. Interestingly, this study also showed that the cytotoxic immune response was mediated by JAK2. The use of baricitinib in vitro was able to protect keratinocytes from cell mediated toxicity.

The current topical therapeutic options for LP are limited to topical corticosteroids, calcineurin inhibitors, and retinoids. Topical therapies are effective with limited disease but refractory disease is frequently encountered. Specific variants of LP, such as hypertrophic LP and localized cutaneous disease, are often refractory to all topical therapies and require systemic or skin-directed treatment with oral acitretin, methotrexate, glucocorticoids or light therapy. Long-term therapy with some of these oral medications is less desired due to adverse effects.

Therefore, additional oral and topical therapies would be highly desirable in hypertrophic and refractory localized cutaneous LP. As proof of principle, systemic JAK1, 2 inhibition with ruxolitinib was highly effective in steroid refractory graft versus host disease (GVHD).[2] Additionally, there was a recent case report of an exceptional responder to JAK1, 2 inhibition with ruxolitinib in refractory dermatomyositis (DM).[3] As stated above, DM, GVHD, and LP share a similar histological pattern as well as signaling mechanism and, therefore, we would expect LP to respond similarly with systemic treatment. To test this concept, we would propose a single-center, exploratory, open-label, single-arm design study using systemic JAK1, 2 inhibitor for lesions of LP.

1.2 Investigational Agent

Baricitinib (LY3009104) is an inhibitor of the JAK family of protein tyrosine kinases. Mitogenic and inflammatory cytokines are strongly implicated in the pathogenesis of psoriasis, alopecia areata, atopic dermatitis, and lichenoid tissue reactions of the skin including LP. Baricitinib (LY3009104) inhibits the phosphorylation of STAT proteins and the production of pro-inflammatory factors induced by cytokines such as IL-23 and IFNγ, and has the potential to simultaneously reduce inflammation, cellular activation and proliferation of key immune cells (Investigator's Brochure). IFNγ is a key cytokine in the pathogenesis of LP.[1]

Baricitinib (LY3009104) 2 mg orally administered, once daily in subjects cutaneous LP.

1.3 Preclinical Data

All preclinical data below is referenced from the IB. Please refer to the IB for more details.

Baricitinib represents a selective inhibitor of JAKs with excellent potency and selectivity for JAK2 (half-maximal inhibitory concentration [IC_{50}] = 5.7 nM) and JAK1 (IC_{50} = 5.9 nM), and less potency for JAK3 (IC_{50} = >400 nM), or TYK2 (IC_{50} = 53 nM).[4]
Although baricitinib potently inhibits JAKs, it does not significantly inhibit (<30% inhibition) a broad panel of 26 other kinases when tested at 200 nM (approximately 50 times the average IC_{50} JAK potency of baricitinib). Moreover, baricitinib demonstrates excellent potency in cell-based assays (IC_{50} values of 3 to 30 nM) relevant to the pathogenesis of autoimmune disease such as IL-2 stimulated phosphorylation of JAKs and STATs and IL-2 induced proliferation of T cells. This effect is not due to general cytotoxicity. Baricitinib also potently inhibited the phosphorylation of STAT proteins and the production of proinflammatory factors (IL-17 or monocyte chemotactic protein- [MCP-] 1, for example) induced by other important cytokines such as IL-23 and IL-6 with IC_{50} values in the range of 20 to 60 nM.

To estimate baricitinib potency in blocking JAK activity in hematopoietic cells in vivo where serum protein binding can be a significant factor, a whole blood assay was established that measures STAT3 phosphorylation in response to cytokine stimulation. Baricitinib blocked IL-6-induced STAT3 phosphorylation in human whole blood with an IC_{50} value of 104 ± 14 nM (n = 5). No effects on total STAT3 levels were observed at any concentration tested.

Baricitinib has been administered orally to CD-1 mice, Sprague Dawley rats, beagle dogs, and New Zealand white rabbits. In all toxicology species, exposures generally increased with increasing dose and were largely dose proportional to slightly greater than dose proportional. In general, exposures following repeated dosing were similar to single dose exposures, with some accumulation (approximately 2-fold) occurring in gravid rabbits. Gender differences were minimal.

Following administration of [^{14}C]-baricitinib, minimal metabolism was observed in all species, as parent compound was the primary circulating entity in plasma and the bulk of radioactivity in urine and feces from all species was also attributed to parent compound. Furthermore, the toxicology species used to evaluate baricitinib are exposed to metabolites observed in humans. In mouse, rat, rabbit, dog, and human plasma, baricitinib had moderate protein binding with in vitro values ranging from approximately 45% to 56%.

Regarding multiple-dose toxicokinetics, the plasma toxicokinetics of baricitinib were evaluated in gravid Sprague Dawley rats and New Zealand white rabbits. Gravid rats were given daily oral doses of baricitinib beginning on Gestation Day (GD) 6 continuing through GD17. In a separate fertility and early embryonic development study, the plasma toxicokinetics of baricitinib were also evaluated in gravid Sprague Dawley rats administered daily oral doses of baricitinib for 2 weeks prior to cohabitation (Study Day 14) through GD6. In both studies, the exposures generally increased proportional to dose and no accumulation was observed. Gravid rabbits were administered daily oral doses of baricitinib beginning on GD7 and continuing through GD20. Exposures (C_{max} and AUC) increased in a greater than dose-proportional manner and were

approximately 2-fold higher on GD20 compared to GD7, suggesting some accumulation of compound in rabbits.

Regarding drug distribution, quantitative whole-body autoradiographic techniques were used to determine the tissue distribution of drug-derived radioactivity in male and female pigmented (Long-Evans) and male non-pigmented (Sprague Dawley) rats following a single oral dose of [^{14}C]-baricitinib. Distribution was extensive, with the highest concentrations of radioactivity being found in alimentary canal contents, bile, and urine. Distribution of drug-derived radioactivity was similar in pigmented and non-pigmented rats, with the exception of [^{14}C]-baricitinib distributing to the uveal tract of the eye in pigmented rats, suggesting binding to melanin-containing tissues.

Elimination was nearly complete by 168 hours postdose in non-pigmented rats and 672 hours postdose in pigmented rats, except for low levels of radioactivity detectable in the dorsal caudal nerve, aorta, and uveal tract in pigmented rats. Specifically in the brain, radioactivity was below quantifiable limits (BQL) at all time points in pigmented rats, while in non-pigmented male rats low levels of radioactivity were detected in the brain (cerebrum: 0.189 µg equivalents/g of tissue; medulla: 0.231 µg equivalents/g of tissue) at 2 hours postdose, but were BQL at all other time points out to 168 hours. The low levels of radioactivity detected in the brain were likely from the vascular system and not directly in the brain tissue, thus penetration of baricitinib across the blood brain barrier is unlikely. The predominant routes of elimination were feces (in mice, rats with oral administration,) and urine (in rats with IV administration). Routes of elimination were similar in feces and urine in dogs.

The placental transfer and subsequent fetal exposure following a single oral dose of [^{14}C]-baricitinib was evaluated in pregnant Sprague Dawley rats. [^{14}C]-baricitinib-related radioactivity was widely distributed in fetal tissues at moderate levels through 8 hours postdose. Fetal tissues with the highest concentrations of drug-derived radioactivity were adrenal gland, gastrointestinal tract, myocardium, liver, and lung. Moderate to low levels of [^{14}C]-baricitinib-related radioactivity were measurable in fetal brain and spinal cord through 8 hours postdose. All fetal tissue radioactivity concentrations were BQL by the final sampling time at 24 hours postdose. Lacteal excretion following a single oral administration of [^{14}C]-baricitinib to lactating Sprague Dawley rats was also evaluated. Peak concentrations of [^{14}C]-baricitinib-related radioactivity were observed at 4 hours postdose in milk and declined to low or BQL levels by 24 hours postdose. Exposure to radioactivity was approximately 39- and 18-fold greater in milk than in plasma based on area under the concentration versus time curve from zero to infinity ($AUC_{0-\infty}$) and C_{max} values, respectively. The elimination half-lives of radioactivity in plasma and milk were similar (2.61 and 2.72 hours, respectively).

Following a single oral dose of [^{14}C]-baricitinib, the in vivo metabolism was evaluated in mice, rats, and dogs. Minimal metabolism was observed in all species, as parent compound was the primary circulating entity in plasma and the bulk of radioactivity in urine and feces from all species was also attributed to parent compound. In all species, the major metabolic pathway for these low level (<10% of dose) metabolites was oxidation. A low-level sulfate conjugate and glucuronide conjugate were also identified in mouse and rat feces and mouse and dog urine, respectively. Additionally, 2 to 3 low level unidentified metabolites were observed in various matrices in all species.

The toxicologic and toxicokinetic profiles of baricitinib were characterized in oral studies of up to 6 months in rats and 9 months in dogs. The safety of baricitinib was also characterized in juvenile rats. In the rat study, dose-limiting toxicity was identified at the high-dose level in both sexes. The high dose of 100 mg/kg/day was lowered to 60 mg/kg/day for females due to mortality occurring within the first 3 weeks of dosing that was subsequently determined to have resulted from gavage errors and not baricitinib toxicity. In males, mortality in high-dose (100 mg/kg/day) animals was mainly attributed to cardiomyopathy. This is a common background lesion in aging male rats, and it is possible that repeated dosing with baricitinib exacerbated this lesion. The 100-mg/kg/day dose was associated with plasma drug levels (unbound AUC_{0-24h} 104.7µM*h) approximately 80-fold above those associated with a 4-mg once daily (QD) dose in subjects with

RA. Crystals, degeneration/regeneration, and/or tubular dilatation were observed in the kidney of males at 100 mg/kg/day and females at 100/60 mg/kg/day and considered adverse. Additional findings deemed adverse at ≥25 mg/kg/day included significant but reversible decreases in lymphocytes, generalized lymphoid depletion, and bone marrow hypocellularity, all presumed pharmacological effects of JAK inhibition. The no-observed-adverse-effect level (NOAEL) for QD administration of baricitinib for 26 weeks was 5 mg/kg/day (unbound AUC of 2.04 μM*h). Skeletal malformations (bent limbs and rib anomalies) and an increased incidence of skeletal development variations occurred in rat fetuses. Decreased pup weights were the dose-limiting effect in the rat pre-postnatal study. In juvenile rats, like adults, effects on body weight and the immune system were observed. Bone effects observed in the juvenile study included bacterial osteomyelitis with secondary fracture in one high dose animal, and exacerbation of femoral head and neck degeneration/atrophy.

In a 9-month dog study, administration of doses ≥3 mg/kg/day resulted in baricitinib-related early termination of dogs, suspension of dosing, adverse clinical effects, and anatomic and clinical pathology changes associated with clinical development of demodicosis and pyogranulomatous dermatitis; a secondary effect of the immunomodulatory pharmacology of baricitinib. Liver lesions consisting of minimal to moderate inflammatory cell infiltrates and/or inflammation and minimal to slight biliary hyperplasia, and associated increases in serum liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], gamma-glutamyltransferase [GGT]) were observed in dogs given ≥3 mg/kg/day. However, the relationship of the liver findings to baricitinib is uncertain because of the confounding severe demodectic mange and inflammation that were aggressively treated with Ivermectin and nonsteroidal anti-inflammatory drugs. Based on the adverse nature of the generalized demodicosis in animals given ≥3 mg/kg/day, the NOAEL is 0.5 mg/kg/day (unbound AUC of 0.74 μM*h).

Overall, the major cell types affected by JAK inhibition in the nonclinical safety studies were lymphocytes and eosinophils. Decreases in lymphocytes and eosinophils in dogs were associated with clinical manifestations of immunosuppression including demodectic mange and bacterial, protozoal and/or yeast infections. Significant decreases in mean lymphocyte counts are generally not observed clinically. Given the general lack of correlation between nonclinical and clinical effects such as decreased lymphocyte counts with consequent infections, it seems useful to rely on the clinical safety database for consideration of safety margins, with the understanding that the consequences of immunosuppression may occur.

Regarding developmental toxicity, maternal and embryo-fetal toxicity occurred at the highest doses evaluated. At the high dose of 30 mg/kg in rabbits, maternal effects included mortality and decreased body weight gain, and decreased weight and rib/vertebral anomalies were observed in the fetuses. The NOAEL in rabbits for both maternal and fetal toxicity was 10 mg/kg/day. In the rat, maternal effects were decreased body weight gain and lacrimation at the high dose of 40 mg/kg; skeletal malformations (bent limbs and rib anomalies) and an increased incidence of skeletal development variations occurred in fetuses at the mid and high doses. The maternal NOAEL was 10 mg/kg, and the fetal NOAEL in rats was 2 mg/kg.

Regarding carcinogenicity, administration of baricitinib was well tolerated in both the 2-year rat and 6-month hRAS [001178-T (hemizygous), CByB6F1-Tg(HRAS)2Jic] transgenic mouse studies and did not produce neoplasms at any of the administered doses. Margins of safety based on unbound plasma exposure ranged from approximately 6-66-fold exposure at the maximum projected human dose. In rats, baricitinib administration was associated with increased survival and a decrease in proliferative changes, which included decreased incidences of neoplastic and
hyperplastic lesions in the mammary gland and liver.

In a variety of in vitro binding and kinase assays, baricitinib did not demonstrate cross-reactivity for any of approximately 50 different receptors, channels, and transporters; or against approximately 30 non-JAK family kinases evaluated at 0.1 and 1 μM, and 0.2 μM, respectively. Safety pharmacology studies indicate that, at clinical doses, baricitinib is not expected to produce

effects related to central nervous system (CNS), cardiovascular (including human ether-à-go-go-related gene [hERG]), or respiratory function. At C_{max} exposures approximately 21-(dog) to 162-(rat) fold greater than the 4 mg clinical dose, the following findings were noted: altered autonomic activity, transient decreases in locomotor activity, and single occurrences of lacrimation at 100 mg/kg in a rat CNS evaluation; lower respiratory frequency and minute volume at 100 mg/kg in a rat respiratory evaluation; slight lowering of arterial pressure (2 to 3 hours postdose) and pulse pressure (7 to 18 hours postdose), and slight increase in heart rate (0 to 18 hours postdose) at 3 mg/kg in a dog cardiovascular evaluation; and no prolongation of the QTc interval in dogs. The IC_{50} for baricitinib on the hERG current was 161.5 μM. The exposure margin between expected human C_{max} plasma baricitinib (unbound) concentrations after a 4-mg dose (108 nM) and hERG IC_{50} inhibition is approximately 1400-fold, thus, indicating a low probability of a QT prolongation effect at therapeutically relevant doses.

1.4 Clinical Data to Date

Clinical data to date is referenced from the IB. Please refer to the IB for more details.

As of 13 February 2019, 3 Phase 2 studies and 5 Phase 3 clinical studies have been completed in patients with RA, and an extension study to collect long-term data is ongoing. In addition, Lilly has completed 22 Phase 1 studies (1 in patients with rheumatoid arthritis (RA) and 21 clinical pharmacology studies) and 4 Phase 2 studies (1 in diabetic nephropathy (DN), 1 in psoriasis (Ps), 1 in systemic lupus erythematosus (SLE), and 1 in atopic dermatitis (AD)). Other studies are ongoing, including an expanded access (EA) program for rare autoinflammatory diseases, 7 Phase 3 studies in AD, 3 Phase 3 studies in SLE, 1 Phase 2 study in primary biliary cholangitis (PBC), 2 Phase 3 studies in juvenile idiopathic arthritis (JIA), and 1 Phase 2/3 study and 1 Phase 3 study in alopecia areata (AA). As of this date, approximately 548 healthy volunteers/Phase 1 study participants and 6555 patients have received baricitinib since the start of clinical trials.

Effects on QTc Interval

A thorough QT (TQT) study (JADO) showed that a supratherapeutic single oral dose of 40 mg baricitinib did not prolong the electrocardiogram QT interval corrected for heart rate (QTc) based on ICH-E14 criteria. Single doses up to 40 mg and multiple doses of up to 20 mg daily for 10 days have been administered in clinical trials without dose-limiting toxicity.

Rheumatoid Arthritis

The primary efficacy measure in all completed Phase 3 studies was a 20% improvement in American College of Rheumatology (ACR) response criteria (ACR20). Other efficacy parameters evaluated include the following: ACR50, ACR70;[5] the change in the individual components of the ACR core set (tender joint count, swollen joint count, patient's assessment of pain as measured by Health Assessment Questionnaire-Disability Index [HAQDI], patient's global assessment of disease activity, physician's global assessment of disease activity, health assessment questionnaire, high sensitivity C-reactive protein [CRP]); van der Heijde Modified Total Sharp Score (mTSS);[6] and the Disease Activity Score 28 (DAS28).[7] In addition, the Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), and the Boolean-based definition of remission were evaluated.[8]

The primary efficacy objective (based on ACR20) was met in each completed Phase 3 study, and most major (gated) secondary objectives were also met. Across the completed Phase 3 studies, baricitinib consistently demonstrated significant improvements compared to comparators (placebo, MTX, adalimumab) with respect to relevant domains of efficacy. Across measures, improvements were generally seen with baricitinib from the earliest weeks of treatment (in many instances as early as Week 1) and sustained through the duration of each study.

Baricitinib demonstrated statistically significant inhibition of radiographic progression of structural joint damage (mTSS) in each of the 3 completed studies which incorporated this measure (Studies JADZ, JADV, and JADX).

In Study JADZ, baricitinib 4 mg used as monotherapy demonstrated significantly larger treatment effects across relevant efficacy measures compared to the active comparator, MTX monotherapy. In most respects, the treatment effects observed for baricitinib monotherapy were comparable in magnitude to those associated with the combination of baricitinib plus MTX. Consistent with these findings, in subgroup analyses of Study JADX, treatment effects for baricitinib appeared comparable whether it was used alone, on a background of MTX, or on a background of other cDMARDs.

In Study JADV, all patients received background MTX during the study, a measure introduced to afford the active bDMARD comparator adalimumab the opportunity to exert optimum efficacy. Baricitinib 4 mg demonstrated significantly larger treatment effects across relevant efficacy measures compared to both placebo and to the active comparator adalimumab.

In Studies JADX and JADW, baricitinib 4- and 2-mg doses were evaluated compared to placebo. Study JADW included a substantial proportion of patients who had failed multiple bDMARDs with various mechanisms of action. In each study, both baricitinib dose groups demonstrated treatment effects that were superior to placebo. Treatment effects were more rapid, more consistently statistically significant, and larger in magnitude across important efficacy measures for the baricitinib 4-mg dose than for baricitinib 2 mg. These observations were consistent with findings from completed Phase 2 studies, and were supported by exposure and exposure–response analyses.

In the long-term extension Study JADY, a variety of analyses demonstrated that for patients who had completed 24 to 128 weeks of treatment with baricitinib in an originating study, effectiveness was sustained across measures during an additional 48 weeks of treatment.

Patients who had received other active study drug regimens (MTX, adalimumab, or baricitinib plus MTX) in an originating study and switched study drug to baricitinib upon entering Study JADY did not experience loss of disease control during 48 weeks of treatment. Among patients who had achieved satisfactory and sustained disease control after at least 15 months of treatment with baricitinib 4 mg QD, patients who reduced their dose to 2 mg QD in a randomized, double-blind manner exhibited statistically significant increases in disease activity compared to patients who continued to receive baricitinib 4 mg. However, most patients (in both the groups who continued 4 mg and whose dose was reduced to 2 mg) retained the state of low disease activity or remission that led to their re-randomization.

Safety: In the RA clinical development program, no increased risk for serious adverse events (SAEs) (including serious infections, malignancies, or major adverse cardiac events [MACE]) was observed for either the baricitinib 4-mg or baricitinib 2-mg group compared to placebo control. In baricitinib-treated patients, there were no SAE preferred terms that were reported by >1% of patients. In the baricitinib 2-mg versus 4-mg comparison, there were no differences in the proportion of patients with SAEs through 16 weeks. Deaths have been reported infrequently in patients taking baricitinib and are not considered a risk with baricitinib use. Serious infections were not different from placebo and no differences were noted between doses for serious or opportunistic infections in the placebo-controlled data.

Regarding TEAEs, treatment-emergent infections were more commonly observed in baricitinib-treated patients. The most frequently reported infections were upper respiratory tract infections (URTI), viral URTI, urinary tract infections (UTI), bronchitis, pharyngitis, gastroenteritis, herpes zoster, influenza, sinusitis, and herpes simplex. The majority of the commonly reported AEs were anticipated events in the RA population (for

example, infections including upper respiratory tract infections) or laboratory abnormalities consistent with the pharmacology of JAK inhibitors (for example, increases in creatine phosphokinase [CPK] and lipids including total cholesterol, low density lipoproteincholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C) and triglycerides). Of these AEs, upper respiratory tract infections (including viral upper respiratory tract infections and bronchitis), herpes zoster, lipid increases, and increased CPK were considered adverse drug reactions (ADRs).

Psoriasis

The primary efficacy parameter evaluated were the Psoriasis Area and Severity Index (PASI) 75 (EMEA [WWW]).[9] Additional efficacy parameters evaluated included PASI 50 and PASI 90.

Study JADP: The primary efficacy analysis was to investigate whether at least 1 baricitinib dose group was superior to placebo at Week 12 as measured by the proportion of patients with PASI 75. At 12 weeks, both the 8- and 10-mg groups had significantly greater improvement compared to placebo.

For those patients achieving a PASI 75 response at 12 weeks who stayed on the same dose, this level of efficacy was largely maintained at 24 weeks. For those patients who did not achieve a PASI 75 at 12 weeks, it was possible to achieve additional benefit by increasing the dose, or for partial responders, staying on the same dose for an additional 12 weeks. For the 10-mg group, maximal PASI response was seen at 12 weeks; however, additional benefit was apparent in the 4- and 8-mg groups at 16 weeks. The predicted PASI 75 response at 16 weeks was 42.5% and 48.6% for the 4- and 8-mg groups, respectively.

Safety: In Study JADP, there was a low incidence of SAEs reported during the 4 parts of the study. The SAEs were assessed by the phase of study and if they occurred when switched from a high dose (8 mg or 10 mg) to a low dose (2 mg to 4 mg). In Part A, the incidence of SAEs was the same in all treatment groups, with 1 SAE per group. Events occurring in baricitinib-treated patients included pneumonia, esophageal carcinoma, squamous cell carcinoma of skin, and psoriasis.[10] Three SAEs were reported in Part B, with a gastrointestinal hemorrhage and pulmonary embolism occurring in patients receiving high doses in Parts A and B, and a diabetic foot reported initially in part A in a patient who received placebo and then taking baricitinib 10 mg in Part B. In Part C, an SAE of abdominal pain was reported in a patient receiving a high dose switched to a low dose from Part B to C, and 1 SAE of cellulitis was reported in a patient switched from a high dose to placebo in Part B to C. In Part D, 2 SAEs were reported, arteriosclerosis coronary artery in a patient receiving baricitinib 8 mg and ovarian adenoma in a patient receiving baricitinib 10 mg.

From baseline through the first 12 weeks of treatment, the percentages of patients who experienced at least one TEAE were similar in the placebo, 2- and 4- mg dose groups (44.1%, 50.0% and 47.2%, respectively) but were higher for the 8- and 10-mg dose groups (57.8% and 63.8%, respectively). The most common TEAEs were infestations and infections where the incidence rate was 26.5% for patients treated with placebo and 21.1% for the combined baricitinib groups. The most common occurrence of TEAEs in all groups was nasopharyngitis.

Atopic Dermatitis

Study JAHG was a randomized, double-blind, parallel, placebo-controlled, 16-week Phase 2 study comparing the efficacy and safety of baricitinib to placebo in patients with moderate-to-severe AD. Patients were randomized 4:3:3 to placebo (n=49), baricitinib 2 mg QD (n=37), or baricitinib 4 mg QD (n=38). Background therapy of mid-potency topical corticosteroids (TCS [triamcinolone 0.1% cream]) was used during the 28-day standardization period prior to randomization and continued throughout the study. The study was positive for the primary outcome of the proportion of patients achieving a 50% improvement from baseline in Eczema Area and Severity Index (EASI-50) score in the baricitinib 4-mg QD treatment arm compared to placebo at Week 16. Differences in EASI-50 response compared to placebo were significant in both the 4- and 2-mg groups at Week 4 and remained significant to Week 16 in the 4-mg group

and Week 12 in the 2-mg group. To assess if efficacy was impacted by baseline disease severity, subgroup analysis of response for patients with EASI baseline scores above and below median EASI score at baseline was conducted. This analysis showed that most of the placebo (background TCS) response observed during the trial was observed in the population with lower EASI baseline scores. Given these findings and given that the proposed entry criterion for Phase 3 studies is patients with an EASI score of ≥16, analyses were also performed on the population with EASI scores at baseline ≥16. It is of note that, in general, the overall effect of examining the higher disease severity subgroups (EASI above median, or EASI ≥16) across a range of efficacy measures (particularly more stringent endpoints, e.g., Investigator Global Assessment [IGA] 0,1 and EASI-75) is a lowering of the observed response for the placebo group and to a lesser degree the 2-mg group, whereas the efficacy in the 4-mg groups appears to be largely maintained.

The 4–mg group, and on some analyses to a lesser degree the 2-mg group, was also able to demonstrate significant improvements compared to placebo across a range of other physician and patient-reported outcomes that are clinically relevant to the assessment of AD, for example, Scoring Atopic Dermatitis (SCORAD), Patient Oriented Efficacy Measure (POEM), Dermatology Life Quality Index (DLQI), and also assessments of itch and sleep. A number of these assessments were statistically significant as early as Week 1, and generally reached a maximal effect by Week 4.

There are currently 5 outpatient, multicenter, double-blind, placebo-controlled, Phase 3 studies (I4V-MC-JAHL [JAHL], I4V-MC-JAHM [JAHM], I4V-MC-JAIN [JAIN], I4V-MC-JAIW [JAIW], and I4V-MC-JAIY [JAIY]) and 2 long-term extension studies (I4V-MC-JAHN and I4V-MC-JAIX) evaluating the safety and efficacy of baricitinib in adult patients with moderate to-severe AD who have responded inadequately to or who are intolerant to topical therapy (i.e., TCS or topical calcineurin inhibitors). Based on preliminary results from Phase 3 Studies JAHL and JAHM, baricitinib met the primary endpoint in both studies. In both studies, a statistically significantly larger proportion of patients treated with baricitinib than placebo patients achieved the primary endpoint at Week 16 defined by the Investigator's Global Assessment (IGA) score for AD of clear or almost clear (IGA 0,1).

Safety: In study JAHG, there were 3 treatment-emergent SAEs reported, 2 in the baricitinib 2-mg dose group and 1 in the 4-mg dose group. One SAE occurred in the treatment period in the 4-mg dose group, which was a benign large intestine polyp that was discovered after 21 days of treatment. Two SAEs were reported after treatment discontinuation in patients treated with baricitinib 2 mg. One patient had an uncontrolled flare of AD and the second patient had a case of acute bronchitis in association with underlying alpha-1 antitrypsin deficiency, which was not disclosed at screening.

Treatment-emergent AEs occurring in 4 or more patients in Study JAHG included headache, blood CPK increased, nasopharyngitis, and dermatitis atopic. The events of headache, CPK increased, and nasopharyngitis occurred numerically more often with baricitinib than with placebo. For AEs that have been declared of special interest for baricitinib, there was a numerically higher proportion of patients with an event in the 4-mg group compared to the 2-mg and placebo groups (placebo: 11/49; 22%; baricitinib 2 mg: 10/37; 27%; baricitinib 4 mg: 17/38; 45%). The numerical increase seemed to be driven mostly by an increase in the number of nasopharyngitis and upper respiratory tract infections. One case of herpes zoster was reported for a patient in the placebo group. The percentage of patients discontinuing the study (including the washout, including worsening AD during washout) because of an AE was highest in the 4-mg group (6/38; 16%) compared to the placebo group (5/49; 10%) and the 2-mg group (3/37; 8%).

In preliminary results from Phase 3 Studies I4V-MC-JAHL (JAHL) and I4V-MC-JAHM (JAHM), SAEs were reported by 3%, 4%, 1%, and 1% of patients treated with placebo, 1 mg baricitinib, 2 mg baricitinib, and 4 mg baricitinib, respectively. No serious venous thromboembolic events (VTEs), major adverse cardiovascular events (MACE), or deaths were

reported in the 16-week placebo-controlled period. There were 4 serious events of eczema herpeticum reported in 2 patients receiving placebo and 2 patients receiving baricitinib 1 mg. TEAEs were reported by 55%, 54%, 58% and 56% of patients treated with placebo, 1 mg baricitinib, 2 mg baricitinib, and 4 mg baricitinib, respectively. The most common TEAEs were headache and nasopharyngitis, and nasopharyngitis and upper respiratory tract infections were the most common treatment-emergent infections. No TEAEs of VTEs or MACE were reported in the 16-week placebo-controlled portion of the studies.

Systemic Lupus Erythematosus

Study JAHH was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel, outpatient, 24-week study evaluating the efficacy and safety of baricitinib 4 mg and 2 mg QD in adult patients with SLE receiving standard therapy. A total of 314 patients were randomized to placebo (n=105), baricitinib 2-mg QD (n=105), or baricitinib 4-mg QD (n=104).

The study was positive for the primary efficacy measure, the percentage of patients achieving remission of SLE arthritis and/or rash, as defined by SLE Disease Activity Index 2000 (SLEDAI-2K) at Week 24. A significantly greater percentage of patients treated with baricitinib 4 mg QD (67.3%) achieved remission at Week 24 compared to placebo (53.3%) ($p<0.05$). In contrast, there was no statistically significant effect of baricitinib 2 mg (58.1%) compared to placebo on the percentage of patients achieving remission.

The study was also positive also for the secondary efficacy measures that included SLE Responder Index (SRI-4), occurrence of flare as measured by SLEDAI Flare Index (SFI), and Lupus Low Disease Activity State (LLDAS). The percentage of patients achieving an SRI-4 response at Week 24 was significantly greater for those treated with baricitinib 4-mg QD (64.4%) compared to placebo (47.6%) ($p<0.05$). In contrast, there was no statistically significant effect of baricitinib 2 mg (51.4%) compared to placebo on the percentage of patients achieving SRI-4 response.

The percentage of patients with flare (any severity) during the 24-week treatment period, as assessed with the SFI, was reduced for those treated with baricitinib 4-mg QD (32.7%) compared to placebo (51.4%) ($p<0.05$). The SFI uses the SLEDAI-2K score, disease activity scenarios, treatment changes, and the Physician's Global Assessment (PGA) of Disease Activity to define mild/moderate and severe flares. The index considers the absolute change in total scores, new or worsening symptoms, and increases in medication use or hospitalization due to the disease activity. There was no statistically significant difference between baricitinib 2 mg QD (42.9%) and placebo. A similar dose-associated trend was observed for severe flare but the effect was not statistically significant (11.4% for placebo, 9.5% for baricitinib 2 mg, and 5.8% for baricitinib 4 mg).

There was a statistically significant difference in the percentage of patients treated with baricitinib 4-mg QD who achieved LLDAS at Week 24 compared to placebo ($p<0.05$). In contrast, there was no statistically significant effect of baricitinib 2-mg compared to placebo on the percentage of patients achieving LLDAS.

There are currently 2 ongoing Phase 3, multicenter, randomized, double-blind, placebo-controlled, outpatient clinical trials (I4V-MC-JAHZ and I4V-MC-JAIA) evaluating the safety and efficacy of baricitinib 4 mg and 2 mg in adult patients with SLE receiving standard of care (SOC). The primary objective is to evaluate the effect of baricitinib 4 mg plus SOC compared to placebo plus SOC as measured by the proportion of patients achieving an SRI-4 response at Week 52.

Safety: In study JAHH, the proportions of patients who reported a SAE through a 24-week treatment period and up to 30 days post-treatment were higher in the baricitinib groups (10.5% and 9.6% for baricitinib 2-mg and 4-mg, respectively) compared to placebo (4.8%). Although the numbers were small, infections contributed the most to the imbalance in SAEs, with 6 (5.8%) reported in the baricitinib 4-mg group and 2 (1.9%) in the baricitinib 2-mg group, as compared to 1 (1.0%) in the placebo group. There were no cases of serious herpes zoster or opportunistic infection and no reports of tuberculosis (TB). There were no deaths in the study. There

were no malignancies or MACE reported. One SAE of deep vein thrombosis (DVT) was reported in the baricitinib 4-mg group, in a patient with preexisting antiphospholipid antibodies and pain in the affected limb (right calf) prior to study entry, who was taking a concomitant oral corticosteroid and celecoxib during the study.

The proportion of patients who reported at least 1 TEAE was similar across treatment groups (64.8% for placebo, 71.4% for baricitinib 2 mg QD, and 73.1% for baricitinib 4 mg QD) in the JAHH study during the 24-week treatment period and up to 30 days after treatment. The proportions of patients who reported viral upper respiratory tract infections were higher for baricitinib-treated patients (9.6%) compared to placebo (3.8%) with similar proportions for the baricitinib 2-mg and 4-mg dose groups (9.5% vs. 9.6%, respectively).

Compared to placebo or baricitinib 2-mg, a higher proportion of patients had a treatment interruption due to AE in the baricitinib 4-mg group: 10.5% for placebo, 6.7% for baricitinib 2 mg, and 20.2% for baricitinib 4 mg. Adverse events in the infections and infestations system organ class were the most common reason for treatment interruption in all 3 treatment groups and made the largest contribution among the system organ classes to the difference between baricitinib 4-mg and placebo.

Diabetic Nephropathy

Study I4V-MC-JAGQ was a Phase 2 study in patients with diabetic nephropathy (DN). This study primarily tested the hypothesis that at least 1 baricitinib dose group was superior to placebo in decreasing urinary albumin/creatinine ratio (UACR) from baseline to Week 24. A statistically significant decrease from baseline was observed in the UACR ratio of Week 24 to baseline in the baricitinib 4-mg QD treatment group (least-squares mean difference as a ratio [LSMD]=0.59; p=0.022) when compared with placebo.

Additional analyses of UACR using values obtained from the 24-hour urine collection were supportive of the results observed in the primary and secondary efficacy analyses of UACR that were obtained from the first morning urine (FMU) collection. Statistically significant treatment differences were observed during the treatment period for the decrease from baseline in 24-hour UACR ratio at Week 12 in the baricitinib 1.5-mg QD (LSMD as a ratio=0.71; p=0.040) and baricitinib 4-mg QD (LSMD as a ratio=0.61; p=0.004) treatment groups when compared with placebo, and at Week 24 in the baricitinib 1.5-mg QD treatment group when compared with placebo (LSMD as a ratio=0.67; p=0.031). Analysis of UACR results from both FMU and 24-hour urine collections at Week 28 indicated that the UACR reductions compared with placebo, that were noted at Week 24, were largely maintained after 4 weeks of washout, at Week 28.

No additional efficacy data from ongoing or completed Phase 2 or Phase 3 studies in other inflammatory conditions are currently available.

1.5 Dose Rationale

Balancing the safety risks and efficacy data of varying baricitinib doses from prior studies, our study proposes oral Baricitinib (LY3009104) 2 mg QD dosing for 16 weeks (primary endpoint) in LP study subjects. If the patient opts into the extension portion of the study, the dose will escalate to 4 mg.

1.6 Risks and Benefits

Benefits:

Others with LP may benefit in the future from what we learn in this research study. It is possible their symptoms could also improve while being treated with this study drug

Risks:

The following adverse events were reported as common side effects associated with the use of Baricitinib (LY3009104):

- Very common (occurring in greater than or equal to 10% of subjects), common (occurring in 1-10% of subjects), and rare but serious (occurring in < 1% of subjects) side effects occurring in subjects. As of the clinical data cutoff date, approximately 548 healthy volunteers/Phase 1 study participants and 6555 patients have received baricitinib since the start of clinical trials. The most frequently reported TEAEs in healthy participants and participants with RA, Ps, AD, and SLE receiving 4-mg dose or lower are listed below.

Very Common (affecting more than 10 in every 100 patients)
No adverse event was seen in more than 10% of the rheumatoid arthritis, psoriasis, atopic dermatitis or systemic lupus erythematosus subjects treated with baricitinib (LY3009104).

Common (affecting less than 10 in every 100 patients)
Upper respiratory tract infection / nasopharyngitis (common cold)
Bronchitis / pharyngitis
Urinary tract infection (UTI)
Gastroenteritis (upset stomach)
Herpes zoster / herpes simplex activation (shingles / cold sore, respectively)
Influenza (flu)
Increase in blood chemistry labs (including lipids and CPK)
Headache
Atopic Dermatitis (treatable skin condition)
Thrombocytosis (increased blood platelets)
Nausea

Rare but Serious
Pulmonary embolism (blood clot in lung)
Deep vein thrombosis (blood clot typically in leg)
Cellulitis (severe skin infection)
Anemia

Hematologic and clinical chemistry lab abnormalities:
Baricitinib (LY3009104) taken systemically can inhibit the growth of blood cells. Low blood cells can make subjects more susceptible to infections by bacteria, virus, and fungi. The risk is low with systemic therapy and subjects will be monitored for any signs of inhibition of their blood counts.

Treatment with Baricitinib (LY3009104) has been associated with dose-related increases in CPK and total cholesterol, triglycerides, LDL-cholesterol (C), and HDL-C with stable LDL/HDL ratio. Observed increases have not led serious events or discontinuation of Baricitinib (LY3009104) in prior clinical trial participants. These lipid counts will be monitored throughout the study.

Infection risk:
There is an increased risk of infection with use of Baricitinib (LY3009104). This will be monitored for. Baricitinib (LY3009104) may increase the risk of infections and reactivation of latent infections such as Tuberculosis, Valley Fever or viral infections such as herpes zoster (shingles) or herpes simplex (cold sore). Please seek medical advice if signs or symptoms suggestive of infection occur.

Allergy:
It is possible that some people could have an allergic reaction to Baricitinib (LY3009104).

Venous thromboembolism:
Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in rare occurrences with patients taking Baricitinib (LY3009104). While we do not expect such events to occur, patients should seek medical advice if they experience signs or symptoms of DVT/PE such as significant shortness of breath, bloody cough or lower leg swelling, redness and pain.

Cancer Risk:
Baricitinib (LY3009104) may have the potential to affect the subject's immune system; they may be at increased risk for infections and possibly cancer. Live vaccines should not be given concurrently with Baricitinib (LY3009104).

Pregnancy Risk:
The effect of the study drug on a fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown and may be harmful. Because of these risks, women cannot take part in this study if they are pregnant or breastfeeding.

Skin biopsy:
A skin biopsy is generally a safe procedure, but some potential risks may include local pain, mild local bruising, bleeding, scarring, and an infection at the site where the skin biopsy was performed. If a topical antibiotic is used afterwards, then there is a small risk of an allergic reaction.

Chest X-ray:
Subjects will be exposed to radiation from the chest x-ray. The amount of radiation has a low risk of harmful effects.

ECG:
There may be mild discomfort from the sticky pads and a possibility of the skin being irritated by the adhesive on the sticky pads. Chest hair may need to be shaved prior to the placement of the sticky pads.

Blood draw:
The risks of drawing blood include pain, bruising, lightheadedness, and/or fainting, or rarely, infection at the site of the needle stick.

Other:
As with all research, there is a chance that confidentiality could be compromised; however, we take precautions to minimize this risk.

2 Study Objectives

Primary Objective:
To determine the efficacy of Baricitinib (LY3009104) as measured by PGA of skin overall response at week 16,

Secondary Objective:
To determine the efficacy of Baricitinib (LY3009104) as measured by the change in modified CAILS score of the cutaneous index treatment (weeks 0 and 16) and changes in lesion count (week 0 and 16), the change in Pruritus VAS, VRS, & NRS, (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 0 to 16, weeks 16 to 20 and weeks 0 to 20), change in Skindex-16 (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 0 to 16, weeks 16 to 20 and weeks 0 to 20), change in Physician Global Assessment (PGA) of oral mucosa and

hair (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 0 to 16, weeks 16 to 20 and weeks 0 to 20), change in BSA (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 0 to 16, weeks 16 to 20 and weeks 0 to 20), change in Modified CAILS (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 16 to 20 and weeks 0 to 20), and change in lesion count (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 16 to 20 and weeks 0 to 20).

Exploratory Objectives:
To predict responses and examine the pharmacodynamics of treatment through the identification of unique biomarkers and transcriptomic changes of LP at week 0 and utilizing RNA sequencing on responsive and non-responsive tissue at week 2 to correlate these biomarkers with measures of global response: Modified CAILS, PGA, BSA, and lesion count.

If the patient chooses to participate in the extension, all of the objectives listed above will be observed through to week 32.

3 Study Design

3.1 *General Description*

This is a single center, exploratory, open-label, single-arm design study of 12 patients. Treatment naïve and treatment refractory patients with LP will be treated Baricitinib (LY3009104). Patients who are non-responders to physician choice standard of care will undergo a washout period and will be enrolled in the study.

Multiple safety studies have been conducted with Baricitinib (LY3009104) (see Safety) and a dose of 2 mg QD is deemed safe. (Investigator's Brochure) We propose a single center, exploratory, open-label, single-arm design study of 12 patients. Treatment naïve and treatment refractory patients with LP will be treated with Baricitinib (LY3009104) for 16 weeks.

Individuals with cutaneous LP will be eligible. Individuals must have 4 lesions at baseline; however, a minimum of 8 lesions which are at least 5mm in diameter is ideal. All lesions will be annotated, photographed, and scored. The rationale for a minimum of 8 lesions is based upon the assumption of a 50% response rate at 2 weeks. With 8 lesions, there would be a less than 1% chance that all 8 lesions would resolve spontaneously. Prior treatment will be allowed; however, a washout period of 2 weeks for topical and 4 weeks for systemic agents is required. At the washout period, individuals will undergo evaluation with a PGA and BSA calculation. The indexed lesions will be photographed, measured, scored, and recorded with Modified CAILS scores as well. The Modified CAILS calculations will be used for the determination of responsive and non-responsive lesions. Additional Pruritus measures using the VRS, VAS, NRSSkindex-16, and LPQOL will be collected at that time.

Individuals will then initiate treatment for all lesions of LP once daily and will be evaluated weekly and assessed by PGA of skin, oral mucosa, and hair, BSA, lesion count, Modified CAILS, Pruritus VRS, VAS and NRS scales,Skindex-16, and LPQOL between weeks 0-16 (see Appendix). Week 16 will be the primary endpoint. Therapy will be stopped and the individuals will be evaluated at week 20 after an observation period of 4 weeks and assessed by PGA, BSA, lesion count, mCAILS, Pruritus VRS, VAS and NRS scales,Skindex-16, and LPQOL. Laboratory and safety monitoring will occur at weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, and 32. 3D Photographs will be taken at weeks 0, 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, and 32. Individual lesions will be circled at each visit and the exact area of each lesion will be measured. Up close photos will be taken of the disease.

Tissue will be collected for bulk RNA sequencing and single cell RNA sequencing (for patients who opt in) at week 0 and 2. Blood collection will include the isolation at week 0, 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, and 32. Blood will be drawn into 5mL vials and subsequently separated. The serum and cell pellet will be stored for future analysis. At weeks 0 and 2, an additional 5mL vial of blood will be drawn from patients who agree to provide single-cell RNA sequencing samples. For these samples, the buffy coat (containing peripheral blood mononuclear cells, PBMCs) will be isolated from whole blood, then immediately placed into cryopreservation medium and stored in a -80°C biobank freezer. Up to five skin biopsies will be taken during the study for all patients. At week 0, up to two, 3mm tissue biopsies will be taken from LP lesional skin and one biopsy will be taken from normal appearing skin for bulk RNA sequencing. The initial biopsy of lesional tissue and control will be annotated. At week 2, up to two, 3mm biopsies will be taken – one from normal appearing skin, one from lesional responsive tissue, and/or one from lesional non-responsive tissue. An additional two, 6-8mm biopsies of lesional tissue for single-cell RNA sequencing will be taken– one at week 0 and one at week 2 – from patients who opt in. The week 2 biopsy will be obtained from an annotated lesion, whether responsive or non-responsive. Responsive and non-responsive lesions will be determined by the change in mCAILS between week 0 and 2. Responsive tissue will require at least 50% reduction in mCAILS while non-responsive tissue can have progression, no change, or up to a 50% reduction in mCAILS. The lesions will be chosen utilizing full body photographs taken previously at week 0. Up to 60 of the 3mm biopsy samples will be snap frozen and stored in the tissue biobank. Once completed, RNA sequencing will be performed on the tissue samples and analysis will be performed. Paired analysis of treatment responsive and refractory lesions will be made as well as treated and untreated lesions.

Nucleic Acid Extractions: RNA will be extracted from a total of 50 μm of fresh tissue using the Qiagen FFPE RNeasy Micro extraction Kit according to manufacturer's recommendation.

Bulk RNA Transcriptome Sequencing: RNA transcriptome sequencing will be carried out using commercially available techniques. Briefly, RNA Libraries will be created using up to 100ng of RNA as starting material using the Illumina RNA Exome Library kit according to manufacturer's recommendation. Libraries will undergo quality control for quality and quantity using the Agilent BioAnalyzer High Sensitivity Chip. Pair-End sequencing will then be carried out on the Illumina HiSeq 4000 using 101bp insert fragments.

Single-cell RNA Transcriptome Sequencing: Samples will be prepped and analyzed per single-cell RNA sequencing standard operating procedures of the University of Michigan genomics lab.

Primary and Secondary Measures:

All efficacy assessments will be performed prior to the administration of study treatment at each visit. The recommended order and the overall outline of measurements for the efficacy assessments are described below.

Efficacy measures: PGA, BSA, mCAILS, Pruritus VRS, VAS and NRS,Skindex-16, and LPQOLto determine the efficacy of Baricitinib (LY3009104) as measured by the change in Modified CAILS score of the index lesion (weeks 0 and 16) and changes in lesion count (week 0 and 16).

Secondary Outcome Measures: To determine the efficacy of Baricitinib (LY3009104) as measured by the change in Pruritus VAS, VRS, & NRS, (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 0 to 16, weeks 16 to 20,weeks 0 to 20, weeks 0 to 24, week 20 to 24, week 0 to 28, week 24 to 28, weeks 0 to 32, week 28 to 32), change in Skindex-16 (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 0 to 16, weeks 16 to 20,weeks 0 to 20,weeks 0 to 24, week 20 to 24, week 0 to 28, week 24 to 28, weeks 0 to 32, week 28 to 32), change in LPQOL (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 0 to 16, weeks 16 to 20, weeks 0 to 20,weeks 0 to 24, week 20 to 24, week 0 to 28, week 24 to 28, weeks 0 to 32, week 28 to 32), change in Physician Global Assessment (PGA) of skin, oral mucosa, and hair (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks0 to 12, weeks 12 to 16, weeks 0 to 16, weeks 16 to 20,weeks 0 to 20, weeks 0 to 24, week 20 to 24, week 0 to 28, week 24 to 28, weeks 0 to 32, week 28 to 32), change in BSA (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 0 to 16, weeks 16 to 20,weeks 0 to 20,

weeks 0 to 24, week 20 to 24, week 0 to 28, week 24 to 28, weeks 0 to 32, week 28 to 32), change in Modified CAILS (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 16 to 20,weeks 0 to 20,weeks 0 to 24, week 20 to 24, week 0 to 28, week 24 to 28, weeks 0 to 32, week 28 to 32), and change in lesion count (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 16 to 20,weeks 0 to 20,weeks 0 to 24, week 20 to 24, week 0 to 28, week 24 to 28, weeks 0 to 32, week 28 to 32).

Exploratory Outcome Measures: To predict responses and examine the pharmacodynamics of treatment through the identification of unique biomarkers and trasnscriptomic changes of LP at week 0, and utilizing RNA sequencing on responsive and non-responsive tissue at week 2 to correlate these biomarkers with measures of global response: Modified CAILS, PGA, BSA, and lesion count.

3.2 Number of Subjects

12 subjects will be enrolled in this study.

3.3 Duration of Participation

The study consists of 3 epochs: screening/washout period (at least 1 week and up to 4 weeks), treatment epoch (16 weeks from screen/washout), and follow up epoch (4 weeks). The screening and washout period will allow for treatment naïve/ new diagnosis LP to undergo evaluation and diagnosis and for treatment refractory to undergo a washout. The total duration of the study will be 21-24 weeks, with the option to enroll in a 3 month extension with a dose escalation to 4 mg for patients *who demonstrate response to treatment, but have not yet achieved PGA 0*

Tables:

- **Table-1: Prohibited treatment**

Prohibited treatments[†, ‡]	**Washout period (before Randomization Visit)**
Any concomitant oral or topical JAK inhibitor	Prohibited
Any biologic drug	Stable dose for 3 months
Immunomodulation treatments for LP[§] [e.g., methotrexate, cyclosporine A, corticosteroids (oral, i.v., intramuscular, s.c., intra-articular, transdermal), mycophenolate mofetil, azathioprine]	4 weeks
Topical treatment that is likely to impact signs and symptoms of LP (e.g., pimecrolimus, tacrolimus)	2 weeks
Non-immunosuppressive agents (tetracycline antibiotics & niacinamide)	2 weeks
Prohibited regimen of Topical Corticosteroids (TCS)	
TCS on any location on body (including face, scalp and/or genitoanal area)	2 weeks

[†]If the prohibited treatment is being used during the study for any indication, the subject must discontinue use of the prohibited treatment if he/she wishes to continue in the study.

[‡] In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator/qualified site staff. If the subject received a live virus vaccination during the study, the subject must discontinue study treatment.

[§]Inhalative CS with only a topical effect (e.g., to treat asthma) are not considered "systemic immunomodulation treatments" and are therefore acceptable as co-medication. Immunosuppressive medication for conditions other than LP will be allowed.

Table 2: Washout Periods for Monoclonal Antibodies (Biologic Drugs)

Brand Name	Generic Name	Recommended Minimum Washout (approximately 5 half-lives)
ACTEMRA	Tocilizumab	8 weeks
CIMZIA	Certolizumab pegol	10 weeks
COSENTYX	Secukinumab	16 weeks
DUPIXENT	Dupilumab	12 weeks
ENBREL	Etanercept	4 weeks
HUMIRA	Adalimumab	8 weeks
KEVZARA	Sarilumab	7 weeks
ORENCIA	Abatacept	8 weeks
REMICADE	Infliximab	6 weeks
RITUXIN	Rituximab	6 months
SIMPONI	Golumimab	10 weeks
STELARA	Ustekinumab	16 weeks
TALTZ	Ixekizumab	10 weeks
TREMFYA	Guselkumab	12 weeks
XOLAIR	Omalizumab	16 weeks

Table-3: Screening and Visits (+/- 3-day window)

	Screening	Day 0	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32
Baricitinib (LY3009104)		X	X	X	X	X	X	X	X	X	X		
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray	X												
Assessments: PGA, BSA, lesion number, mCAILS, Skindex-16, Pruritus VAS, VRS & NRS, LPQOL		X	X	X	X	X	X	X	X	X	X	X	X
Photographer		X	X	X	X	X	X	X	X	X	X	X	X
Skin Biopsy (tissue/serum bank)		X		X									
ECG	X					X							
Urine Pregnancy Test	X	X				X	X	X	X	X	X	X	X
Venipuncture	X	X	X	X	X	X	X	X	X	X	X	X	X
Biomarker/RNAseq blood (tissue/serum bank)		X	x	X	x	X	x	x	X	x	X	X	X
CMP	X		X	X	X	X	X	X	X	X	X	X	X
Lipid Panel	X		X	X	X	X	X	X	X	X	X	X	X
CPK	X		X	X	X	X	X	X	X	X	X	X	X
CBC	X		X	X	X	X	X	X	X	X	X	X	X
Quantiferon Gold	X												
Hepatitis B	X												
Hepatitis C	X												

HIV	X												
Coccidioidomycosis	X												

3.4 Primary Study Endpoints

Overall response by PGA of skin at week 16.

3.5 Secondary Study Endpoints

Change in modified CAILS of index treatment lesion (week 0 and 16) and change in lesion count (week 0 and week 16). Change in Pruritus VAS, VRS, & NRS, (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 0 to 16, weeks 16 to 20,weeks 0 to 20, weeks 0 to 24, week 20 to 24, week 0 to 28, week 24 to 28, weeks 0 to 32, week 28 to 32), change in Skindex-16 (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 0 to 16, weeks 16 to 20,weeks 0 to 20, weeks 0 to 24, week 20 to 24, week 0 to 28, week 24 to 28, weeks 0 to 32, week 28 to 32), change in LPQOL (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 0 to 16, weeks 16 to 20, weeks 0 to 20, weeks 0 to 24, week 20 to 24, week 0 to 28, week 24 to 28, weeks 0 to 32, week 28 to 32), change in Physician Global Assessment (PGA)of oral mucosa, and hair (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 0 to 16, weeks 16 to 20,weeks 0 to 20, weeks 0 to 24, week 20 to 24, week 0 to 28, week 24 to 28, weeks 0 to 32, week 28 to 32), change in BSA (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 0 to 16, weeks 16 to 20, weeks 0 to 20, weeks 0 to 24, week 20 to 24, week 0 to 28, week 24 to 28, weeks 0 to 32, week 28 to 32), change in Modified CAILS (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 16 to 20,weeks 0 to 20, weeks 0 to 24, week 20 to 24, week 0 to 28, week 24 to 28, weeks 0 to 32, week 28 to 32), and change in lesion count (week 0 to week 2, weeks 0 to 4, weeks 4 to 8, weeks 0 to 8, weeks 8 to 12, weeks 0 to 12, weeks 12 to 16, weeks 16 to 20 and weeks 0 to 20, weeks 0 to 24, week 20 to 24, week 0 to 28, week 24 to 28, weeks 0 to 32, week 28 to 32).

3.6 Primary Safety Endpoints

A thorough baseline screening will be followed for all patients and is outlined in Table-2. A detailed list of the methods in which baseline screening will be performed is outlined in Supplemental 2. All blood draws and safety assessments must be performed prior to study treatment administration. Appropriate safety assessments (e.g., evaluation of AEs and SAEs) should be repeated after dosing with study treatment. A physical examination, including general appearance and vital signs, will be performed as indicated in Table-2. If indicated, based on medical history and/or symptoms, additional exams will be performed at the discretion of the investigator. If possible, the same member of the study site staff throughout the study will perform assessments for an individual subject. Information for all physical examinations will be included in the source documentation at the study site. Significant findings that are present prior to the subject signing informed consent will be included in the Medical History. Significant findings made after the signing of the informed consent, which meet the definition of an AE, must be recorded as an AE. Vital signs (blood pressure, pulse, height, weight) will be assessed at each physical examination as indicated in Table-2 (see Supplemental 2 for details on how to acquire vital signs). Whether action needs to be taken to address notable vital signs will be decided by the investigator, considering the overall status of the subject. Laboratory studies will be drawn as indicated in Table-2. Whether action needs to be taken to address notable laboratory values will be decided by the investigator, considering the overall status of the subject. Hematology assessments will be measured at all scheduled study visits specified in Table-2. Serum chemistry will be a comprehensive metabolic and lipid panels that will be measured at all scheduled study visits specified in Table-2.

If the prohibited treatment is being used during the study for any indication, the subject must discontinue use of the prohibited treatment if he/she wishes to continue in the study. In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator/qualified site staff. If the subject received a live virus vaccination during the study, the subject must discontinue study treatment.

3.7 Identification of Source Data

All data in the study will be captured in the case report forms including:

- Safety measures
- Efficacy measures
- Laboratory studies
- Vital Signs
- Exploratory measures

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

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

- Subjects must be able to understand and comply with the requirements of the study and communicate with the investigator. Subjects must give written, signed, and dated informed consent before any study related activity is performed. When appropriate, a legal representative will sign the informed consent according to local laws and regulation
- Both men and women must be at least 18 years of age at the time of screening
- Subjects must have clinical and histological features of LP
- LP requiring systemic treatment
- Subjects must have treatment naïve cutaneous LP or treatment refractory disease, as defined by failure of at least one established treatment for LP
    - Failure of prior therapy
        - Topical treatment
        - Systemic immunosuppressant
        - Oral metronidazole
        - Oral sulfasalazine
        - Oral retinoid

4.2 Exclusion Criteria

Subjects fulfilling **any** of the following criteria are not eligible for inclusion in this study. To ensure the recruitment of a representative sample of all eligible subjects, the investigator may apply no additional exclusions.

- On excluded therapies, not on a stable dose of a therapy, or incompletely washed out for a therapy (Table-1.)
- Known hypersensitivity or other adverse reaction to Baricitinib (LY3009104)
- Variants of LP deemed by the investigators to be inappropriate for Baricitinib (LY3009104) including but not limited to:
    - Drug-induced LP
    - Predominant non-cutaneous variants of LP, note that individuals can have disease in non-cutaneous areas; however, they must also have cutaneous disease.
        - Lichen Planopilaris
        - Oral Lichen planus
- Pregnant or nursing (lactating) women (pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test)
- Women of childbearing potential [Post-menopausal or not of child-bearing potential is defined by 1 year of natural (spontaneous) amenorrhea or surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks ago. Oophorectomy alone must be confirmed by follow up hormone level assessment to be considered not of child-bearing potential, defined as all women

physiologically capable of becoming pregnant, unless they are using basic methods of contraception which includes:

  - Total abstinence (Periodic abstinence and withdrawal are not acceptable methods of contraception)
  - Female sterilization (bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least 6 weeks before taking study treatment. Oophorectomy alone requires follow up hormone level assessment for fertility.
  - Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject.
  - Barrier methods of contraception: condom or occlusive cap.
  - Use of oral, injected or implanted hormonal methods of contraception or other forms or hormonal contraception that have complete efficacy (failure <1%). (The dose of the contraceptive should be stable for 3 months)

- Active ongoing inflammatory diseases of the skin other than LP that might confound the evaluation of the benefit of Baricitinib (LY3009104)
- Underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions) which, in the opinion of the investigator, significantly immunocompromises the subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy
- Moderate-to-severe renal impairment including patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2
- Active systemic infections during the 2 weeks prior to randomization (common cold viruses excluded) or any infection that reoccurs on a regular basis.
- Current severe progressive or uncontrolled disease which the investigator renders the subject unsuitable for the trial or puts the subject at increased risk
- Have had any major surgery within 8 weeks prior to screening or will require major surgery during the study that, in the opinion of the investigator would pose an unacceptable risk to the patient.
- Have experienced any of the following within 12 weeks of screening: VTE (DVT/pulmonary embolism [PE]), myocardial infarction (MI), unstable ischemic heart disease, stroke, or New York Heart Association Stage III/IV heart failure.
- Have a history of recurrent (≥ 2) VTE (DVT/PE).
- Have a history of lymphoproliferative disease; have signs or symptoms suggestive of possible lymphoproliferative disease, including lymphadenopathy or splenomegaly; have active primary or recurrent malignant disease; or have been in remission from clinically significant malignancy for <5 years prior to randomization.
- Have had symptomatic herpes zoster infection within 12 weeks prior to randomization.
- Have a history of disseminated/complicated herpes zoster (for example, ophthalmic zoster or CNS involvement).
- ALT or AST >2 x upper limits of normal (ULN); alkaline phosphatase (ALP) ≥2 x ULN; total bilirubin ≥1.5 x ULN; hemoglobin <10 g/dL (100.0 g/L); total white blood cell count <3000 cells/μL (<3.00 x 103/μL or <3.00 billion/L); neutropenia (absolute neutrophil count [ANC] <1500 cells/□L) (<1.50 x 103/□L or <1.50 billion/L); lymphopenia (lymphocyte count <1000 cells/μL) (<1.00 x 103/μL or <1.00 bilion/L); thrombocytopenia (platelets <100,000 cells/μL) (<100 x 103/μL or <100 billion/L)
- Have a positive test for hepatitis B virus (HBV) defined as:

  a. positive for hepatitis B surface antigen (HBsAg), or

  b. positive for hepatitis B core antibody (HBcAb) and positive for hepatitis B virus deoxyribonucleic acid (HBV DNA)

  Note: Patients who are HBcAb-positive and HBV DNA-negative may be enrolled in the study but will require additional HBV DNA monitoring during the study.
- Have hepatitis C virus (HCV) infection (hepatitis C antibody-positive and HCV ribonucleic acid [RNA]-positive).

  Note: Patients who have documented anti-HCV treatment for a past HCV infection AND are HCV RNA-negative may be enrolled in the study.
- Have evidence of HIV infection and/or positive HIV antibodies.

- Have had household contact with a person with active TB and did not receive appropriate and documented prophylaxis for TB.
- Have evidence of active TB or latent TB
- Have evidence of active TB, defined in this study as the following:
    - Positive purified protein derivative (PPD) test (≥5 mm induration between approximately 2 and 3 days after application, regardless of vaccination history), medical history, clinical features, and abnormal chest x-ray at screening.
    - QuantiFERON®-TB Gold test or T-SPOT®.TB test (as available and if compliant with local TB guidelines) may be used instead of the PPD test. Patients are excluded from the study if the test is not negative and there is clinical evidence of active TB.

  Exception: patients with a history of active TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, have no clinical features of active TB, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria met. Such patients would not be required to undergo the protocol-specific TB testing for PPD, QuantiFERON®-TB Gold test, or T-SPOT®.TB test but must have a chest x-ray at screening (i.e., chest imaging performed within the past 6 months will not be accepted).
- Have evidence of untreated/inadequately or inappropriately treated latent TB, defined in this study as the following:
    - Positive PPD test, no clinical features consistent with active TB, and a chest x-ray with no evidence of active TB at screening; or
    - If the PPD test is positive and the patient has no medical history or chest x-ray findings consistent with active TB, the patient may have a QuantiFERON®-TB Gold test or T-SPOT®.TB test (as available and if compliant with local TB guidelines). If the test results are not negative, the patient will be considered to have latent TB (for purposes of this study); or
    - QuantiFERON®-TB Gold test or T- SPOT®.TB test (as available and if compliant with local TB guidelines) may be used instead of the PPD test. If the test results are positive, the patient will be considered to have latent TB. If the test is not negative, the test may be repeated once within approximately 2 weeks of the initial value. If the repeat test results are again not negative, the patient will be considered to have latent TB (for purposes of this study).
- Have been exposed to a live vaccine within 12 weeks of randomization or are expected to need/receive a live vaccine during the course of the study (with the exception of herpes zoster vaccination).
- Have donated more than a single unit of blood within 4 weeks prior to screening or intend to donate blood during the course of the study.
- Have a history of intravenous drug abuse, other illicit drug abuse, or chronic alcohol abuse within the 2 years prior to screening or are concurrently using, or expected to use during the study, illicit drugs (including marijuana).

4.3 Subject Recruitment, Enrollment and Screening

- From the Principal Investigator or Co-Investigator clinical practices
- Screening requirements or qualifying lab values
- Evaluation and documentation of inclusion/exclusion criteria

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

- Subject safety issues
- Failure of subject to adhere to protocol requirements
- Disease progression
- Subject decision to withdraw from the study (withdrawal of consent)

Subjects who withdraw from the study for any reason will have their information recorded at the time of withdrawal. At the time of withdrawal, the subject will be considered at the final treatment date and will move into the treatment observation phase (4 weeks). Subjects will not be replaced. Follow up for subjects will continue to follow the normal follow up (Table-2)

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

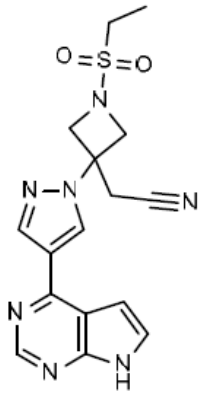
At the time of withdrawal, the reason for withdrawal will be recorded in the CRF. Individuals who withdraw will go into the observation phase for 4 weeks. If a subject withdraws consent, attempts will be made to obtain permissions to collect follow up information.

5 Study Drug

5.1 Description (Investigator's Brochure)

The chemical name of Baricitinib (LY3009104) is 2-(3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile (Figure 1). Baricitinib (LY3009104) has a molecular formula of $C_{16}H_{17}N_7O_2S$ and a molecular weight of 371.42.

Baricitinib (LY3009104) Structural Formula



Baricitinib (LY3009104) drug substance is a white to practically white to light pink powder. Baricitinib (LY3009104) has been formulated in 3 strengths (1 mg, 2 mg, or 4 mg) that are actively being investigated.

Baricitinib (LY3009104) is an oral formulation of an investigational product under development for the treatment of patients with rheumatoid arthritis, alopecia areata, atopic dermatitis, psoriasis, systemic lupus erythematosus and other potential autoimmune diseases of the skin. Baricitinib (LY3009104) is an oral selective inhibitor of the Janus kinase (JAK) family of protein tyrosine kinases with selectivity for JAK1 and JAK2, and less selectivity for JAK3 with potent activity on the cytokine IFN-γ. JAK1 and JAK2 mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Mitogenic and inflammatory cytokines are strongly implicated in the pathogenesis of psoriasis, alopecia areata, atopic dermatitis, and other potential autoimmune diseases of the skin. Inhibition of specific cytokine function using antibodies directed against the common p40 subunit of interleukin (IL)-12 and IL-23 has demonstrated proof-of-concept validating cytokine signaling as a therapeutic target for the treatment of psoriasis.

Pharmacodynamics:
The decrease in the cytokine-stimulated pSTAT3 formation in response to single- and multiple dose baricitinib was measured in 3 clinical pharmacology studies. Data showed a dose dependent
inhibition of pSTAT3 formation in response to cytokine stimulation in the single dose range of 1-mg to 20-mg (Study JADF) and multiple once-daily doses of 2-mg to 20-mg for
10 days (Study JADE). Similar levels of inhibition were observed using either IL-6 or TPO as

the stimulus. Maximal inhibition of pSTAT3 formation occurred approximately 1 to 2 hours post-dose, coincident with t_{max}. The pSTAT3 levels returned approximately to baseline levels by 24 hours for all dose groups following single and multiple doses. Based on the results from Study JADF and Study JADE, a PK/PD relationship was established for baricitinib-induced inhibition of IL-6 stimulated pSTAT3 formation. The calculated IC_{50} value was 75 nM (27.9 ng/mL) from Study JADF and 100 nM (37.1 ng/mL) from Study JADE (for a combined value of 90 nM (33.3ng/mL). These results are similar to the IC_{50} value of 104 nM (38.6 ng/mL) estimated from in vitro data. These data suggest that QD dosing of 4-mg, but not 2-mg, results in a period of time when the baricitinib concentration in the central compartment is above the ex vivo IC_{50} for IL-6-stimulated pSTAT3 formation.

Pharmacokinetics:
Baricitinib is rapidly absorbed with a median time of maximum observed drug concentration (t_{max}) of 1 hour (range: 0.5 to 3 hours). Over a single-dose range of 1 mg to 30 mg in healthy subjects, mean estimates of baricitinib C_{max} and $AUC_{(0-\infty)}$ increased approximately proportionally to dose. Baricitinib PK after multiple doses were predictable from single dose data. Accumulation during QD dosing was minimal, with an accumulation ratio of 1.11- and 1.15-fold for C_{max} and AUC, respectively. Steady state was typically reached between the second and third doses.

Renal elimination of parent is the principal clearance mechanism for baricitinib, and baricitinib apparent clearance (CL/F) is directly related to baseline glomerular filtration rate (GFR). The differences in CL/F between populations are likely due to differences in renal function, which affects apparent renal clearance (CL_r/F). Pharmacokinetic parameter estimates are
also available for patients with atopic dermatitis based on Phase 2 Study I4V-MC-JAHG (JAHG), although a different PK model was applied. The estimated values of CL/F and apparent total volume of distribution were 12.3 L/h and 105 L, respectively for this patient population.

The mean absolute bioavailability of baricitinib was 79%. The protein binding of baricitinib was 50 ± 2% in plasma and 55 ± 3% in serum. Mean volume of distribution following IV administration was 75.7 L (21% coefficient of variation [CV]), suggesting distribution of baricitinib into tissues. About 75% of the baricitinib dose is excreted in the urine predominately as parent, and about 20% of the dose is excreted in the feces.

Bioequivalence was demonstrated between the baricitinib 4-mg commercial oral tablet and a 4-mg dose (2 mL of 2 mg/mL suspension) of a pediatric suspension in Study I4V-MC-JAGU. There was no statistically significant difference in exposure to baricitinib based on AUC and C_{max} between the tablet and suspension formulation when administered in the fasted state. When the suspension was administered with a high-fat, high-calorie meal, the C_{max} of baricitinib was reduced by 32.5% compared to the fasted state. The median t_{max} of baricitinib was also delayed by 2 hours in the fed compared to the fasted state; however, the overall exposure based on AUC was similar in the fed and fasted states.

<u>Potential for Baricitinib (LY3009104) to Affect Other Drugs:</u>
Cytochrome P450 Enzymes: In vitro, baricitinib did not significantly inhibit nor induce the activity of CYP enzymes (CYPs 3A, 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6). In clinical pharmacology studies, coadministration of baricitinib with the CYP3A substrates simvastatin, ethinyl estradiol, or levonorgestrel resulted in no clinically meaningful changes to these drugs.

Transporters: In vitro, baricitinib did not inhibit the transporters Pgp or OATP 1B1. In vitro, baricitinib does inhibit OAT1, OAT2, OAT3, OCT1, OCT2, OATP1B3, BCRP, MATE1, and MATE2-K, but clinically meaningful changes to drugs that are substrates for these transporters are unlikely. In clinical pharmacology studies, there were no clinically meaningful effects when baricitinib was coadministered with digoxin (Pgp substrate) or MTX (substrate of several transporters).

Potential for Other Drugs to Affect Baricitinib:
Cytochrome P450 Enzymes: In vitro, baricitinib is a CYP3A4 substrate. In clinical pharmacology studies, coadministration of baricitinib with ketoconazole (CYP3A inhibitor) resulted in no clinically meaningful effect. Coadministration of baricitinib with fluconazole (CYP3A/CYP2C19/CYP2C9 inhibitor) or rifampin (CYP3A inducer) resulted in no clinically meaningful changes to baricitinib.

Transporters: In vitro, baricitinib is a substrate for OAT3, Pgp, BCRP, and MATE2-K. In a clinical pharmacology study, probenecid (OAT3 inhibitor with strong inhibition potential) dosing resulted in approximately a 2-fold increase in AUC(0-∞) with no change in Cmax of baricitinib. Simulations with diclofenac and ibuprofen (OAT3 inhibitors with less inhibition potential) predicted minimal effect on baricitinib. Coadministration of baricitinib with cyclosporine (Pgp/BCRP inhibitor) or MTX (substrate of several transporters) resulted in no clinically meaningful effects on baricitinib exposure.

5.2 Treatment Regimen

Subjects will administer Baricitinib (LY3009104) 2 mg tablet once daily on an empty stomach. Treatment will take place from Day 0 to Week 16.

5.3 Preparation and Administration of Study Drug

The study drug will be supplied by Eli Lilly to the Mayo Clinic Pharmacy, attn. Todd Luckritz, Pharm D, R.Ph. 13400 E Shea BLVD, Scottsdale, AZ 85259. The study drug will be stored in the Mayo Clinic Pharmacy. The study drug will be labelled in the Mayo Clinic Pharmacy and will be dispensed to the subjects. The subjects will be given sufficient quantity of tablets at each visit for use between subsequent study visits. Instructions on proper use will be provided to each subject.

5.4 Subject Compliance Monitoring

Compliance will be assessed through direct questioning of subjects as well as through drug use diaries.

5.5 Prior and Concomitant Therapy

Individuals on stable doses of medications for chronic illnesses will be allowed. Individuals on immunosuppressive agents for LP will not be allowed; however, individuals on stable doses of immunosuppressant for other conditions will be allowed if deemed to be safe by the treating physicians. Additional exclusionary drugs are included in Table-1.

Individuals using Baricitinib (LY3009104) should use topical broad-spectrum sunscreens with a minimum of SPF30, avoid excess sunlight, and wear sun protective clothing.

5.6 Packaging

The drug will be packaged in bottles with 30 tablets of Baricitinib (LY3009104) 2 mg per bottle. The entire quantity needed for the study will be provided in one shipment. The study drug bottles will be labeled with a diaper label that fully surrounds the bottle. All applicable US FDA required text will be included on the label, included Caution: Limited by U.S. Law to Investigational Use.

5.7 Receiving, Storage, Dispensing and Return

5.7.1 Receipt of Drug Supplies

The drug will be obtained or delivered from Eli Lilly and Company to the pharmacy at each investigative site.

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipping invoice. Any discrepancies, damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The sponsor-investigator must be notified immediately of any discrepancies, damaged or unusable products that are received.

5.7.2 Storage

The Baricitinib (LY3009104) drug product should be stored between 15°C and 30°C (59°F and 86°F). The supplies will be stored in the Mayo Clinic Pharmacy.

5.7.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form and signed and dated by the study team. A three month extension and dose excalation to 4mg will be available to all patients *who demonstrate response to treatment, but have not yet achieved PGA 0*

5.7.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be documented and investigated, prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

6.1 Visit 1

<u>Screening visit:</u>

During this visit, we will do some tests and procedures to see if subjects are eligible to take part in this research study. The study staff will review the results of these tests and procedures. If subjects aren't eligible, the Principal Investigator will tell them why. At this visit we will:

- Patients will have the ability to conduct this visit remotely. If done remotely, vitals and a physical exam will not be conducted. The patient will need to do the blood sample, chest x-ray and electrocardiogram at their local laboratory and send the results to the PI prior to their Day 0 visit. The patient will give the receipts for the tests to the CRC who will process the reimbursements.
- Ask about medical history
- Perform a physical exam, including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates)
- Perform a chest x-ray
- Perform an electrocardiogram (ECG)
- Draw a blood sample
- We may take swabs to test for certain fungal and bacterial infections

- Test urine for pregnancy if female subject is able to become pregnant

If it isn't known if subject has HIV, Hepatitis B or C, blood tests will need to be done.

6.2 Visit 2

Day 0 Visit we will:

- Perform a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes
- Take photographs of skin lesions to document any changes
- Draw blood sample(s)
- Perform skin biopsies (up to three, 3mm and up to one, 6-8mm tissue samples will be taken)
- Dispense study drug
- Test urine for pregnancy if female subject is able to become pregnant

6.3 Visit 3

Week 1 Visit we will:

- Patients will have the ability to conduct this visit via video visit with the provider. If being conducted remotely, vitals, physical exam, skin lesion assessments, and labs will not be conducted. The patient will need to send photos and the PI will conduct the IGA assessment via video visit.
- Perform a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes
- Take photographs of skin lesions to document any changes
- Draw a blood sample
- Dispense study drug

7.4 Visit 4

Week 2 Visit we will:

- Perform a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes
- Take photographs of skin lesions to document any changes
- Draw blood sample(s)
- Perform skin biopsies (up to two, 3mm and up to one, 6-8mm tissue samples will be taken)
- Dispense study drug

7.5 Visit 5

Week 3 Visit we will:

- Patients will have the ability to conduct this visit via video visit with the provider. If being conducted remotely, vitals, physical exam, skin lesion assessments, and labs will not be conducted. The patient will need to send photos and the PI will conduct the IGA assessment via video visit.
- Give subject a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes

- Take photographs of skin lesions to document any changes
- Draw a blood sample
- Dispense study drug

7.6 Visit 6

Week 4 Visit we will:

- Perform a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes
- Take photographs of skin lesions to document any changes
- Draw a blood sample
- Perform an ECG
- Dispense study drug
- Test urine for pregnancy if female subject is able to become pregnant

7.7 Visit 7

Week 8 Visit we will:

- Perform a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes
- Take photographs of skin lesions to document any changes
- Draw a blood sample
- Dispense study drug
- Test urine for pregnancy if female subject is able to become pregnant

7.8 Visit 8

Week 12 Visit we will:

- Perform a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes
- Take photographs of skin lesions to document any changes
- Draw a blood sample
- Dispense study drug
- Test urine for pregnancy if female subject is able to become pregnant

7.9 Visit 9

Week 16 Visit we will:

- Perform a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes
- Take photographs of skin lesions to document any changes
- Draw a blood sample
- Dispense study drug
- Test urine for pregnancy if female subject is able to become pregnant

7.10 Visit 10

Week 20 Visit we will:

- Perform a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes
- Take photographs of skin lesions to document any changes
- Draw a blood sample
- Dispense study drug
- Test urine for pregnancy if female subject is able to become pregnant

7.11 Visit 11

Week 24 Visit we will:

- Perform a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes
- Take photographs of skin lesions to document any changes
- Draw a blood sample
- Dispense study drug
- Test urine for pregnancy if female subject is able to become pregnant

7.12 Visit 12

Week 28 Visit we will:

- Perform a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes
- Take photographs of skin lesions to document any changes
- Draw a blood sample
- Test urine for pregnancy if female subject is able to become pregnant

7.13 Visit 13

Week 32 Visit we will:

- Perform a physical exam, check vital signs and ask about side effects or health problems since last visit
- Exam skin lesions to note any changes
- Take photographs of skin lesions to document any changes
- Draw a blood sample
- Test urine for pregnancy if female subject is able to become pregnant

7 Statistical Plan

7.1 Sample Size Determination

Data analysis: Assuming a medium effect size (0.3) and a target power of 80%, a two-armed study would need about 108 subjects and a single arm about 88 subjects. Due to the costs associated with a study, we propose a single armed study of 12 subjects with corollary science including RNA sequencing. This will reduce costs and provide biomarkers predictive of response. Effect sizes will be estimated for the appropriate statistical tests that will be used for group comparisons in future studies. This will enable more accurate power and sample size estimates moving forward.

7.2 Statistical Methods

Descriptive Statistics

Sample Size Computation and Power Analysis:
The sample size for this pilot study is set at 12 subjects for logistical and financial reasons. This is similar in size to other exploratory studies and will provide adequate data for estimation purposes for planning future studies. With 12 subjects, the study is intended to be for estimation purposes only.

Statistical Analysis Plan:
Data Analysis - The statistical analysis will provide descriptive summary statistics for categorical and continuous outcomes. Categorical variables will be described by their count and proportion of occurrence while continuous, normally distributed variables will be described by their mean and standard deviation; and continuous, non-normally distributed variables will be described by their median and range. The paired or unpaired Wilcoxon tests will be used to quantify differences in numerical outcomes while the Fisher's exact test and the McNemar's or Bowker's tests will be used to quantify changes in categorical variables.
If missingness occurs at random a mixed model will be utilized to assess the change in the lesion over time. A sensitivity analysis will be performed using the last observation carried forward and the results will be compared to that of the mixed model.
Effect sizes will be estimated for the appropriate statistical tests that will be used for group comparisons in future studies. This will enable more accurate power and sample size estimates moving forward.

Bioinformatic Analysis:
Bulk RNA-seq analysis: We will use our recently developed LinNorm program (https://www.bioconductor.org/packages/release/bioc/html/Linnorm.html) to process RNA-seq data and detect differentially expressed genes (DEGs) by comparing the RNA-seq profiles. We will first find DEG between responsive and non-responsive samples from the same individual by using paired or unpaired Wilcoxon rank-sum test (depending on how the samples are collected). We will then rank each gene in the DEGs based on the occurrence frequencies in all 12 subjects to find common DEGs for responsiveness (use permutation test to determine the p value). For the top ranked genes (common DEGs), we will use DAVID[11] and GSEA[12] software to find enriched inflammatory pathways and GO terms for the DEGs. By comparing the normal tissue with the pathogenic tissue (responsive + non-responsible) using the above approach, we will detect a common DEGs for LP pathogenesis. Hierarchical clustering[13] and Principal Component Analysis (PCA)[14] will be applied to samples for their hierarchical relationship and clustering properties. Ideally normal, responsive and non-responsible tissues should form three distinct groups. The PCA analysis will provide us a set of gene signatures that can distinguish these three types of tissues. The common DEGs for responsiveness and pathogenesis, as well as gene signature from PCA will be used for our pathogenesis or survival prediction. We will perform structure variants calling from RNA-seq data with SNPiR,[15] and reconstruct gene co-expression networks with ARACHNE.[16] Additionally, we will perform de-convolutional analysis, to compare the immune profiles of responsive and non-responsive tissue and to correlate immune profiles. Predictive biomarkers will be correlated with lesional and global responses.

Single-cell RNA Seq analysis: will be performed according to standard operating procedures of University of Michigan genomics lab and bioinformatics

7.3 Subject Population(s) for Analysis

- All-completed population: All subjects that receive at least one dose will be considered for analysis.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event
An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event
Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant disability or incapacity
- birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

For this study, the study treatment follow-up period is defined as 30 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

A thorough baseline screening will be followed for all subjects and is outlined in Table-2. A detailed list of the methods in which baseline screening will be performed is outlined in Supplemental 2. All blood draws and safety assessments must be performed **prior** to study treatment administration. Appropriate safety assessments (e.g., evaluation of AEs and SAEs) should be repeated after dosing with study treatment. A physical examination, including general appearance and vital signs, will be performed as indicated in Table-2. If indicated, based on medical history and/or symptoms, additional exams will be performed at the discretion of the investigator. If possible, the same member of the study site staff throughout the study will perform assessments for an individual subject. Information for all physical examinations will be included in the source documentation at the study site. Significant findings that are present prior to the subject signing informed consent will be included in the Medical History. Significant findings made after the signing of the informed consent, which meet the definition of an AE, must be recorded as an AE. Vital signs (blood pressure, pulse, height, weight) will be assessed at each physical examination as indicated in Table-2 (see Supplemental 2 for details on how to acquire vital signs). Whether action needs to be taken to address notable vital signs will be decided by the investigator, considering the overall status of the subject.

Temporary Interruption of Investigational Product: In some circumstances, patients may need to temporarily interrupt treatment as a result of AEs or abnormal laboratory values that may have an unclear relationship to investigational product. For the abnormal laboratory findings and clinical events (regardless of relatedness), specific guidance is provided for temporarily interrupting treatment and when treatment may be restarted. Retest frequency and timing of follow up laboratory tests to monitor the abnormal finding is at the discretion of the investigator. Investigational product that was temporarily interrupted because of an AE or abnormal laboratory value may be restarted at the discretion of the investigator.

- Absolute Neutrophil Count (ANC): Treatment should be interrupted if ANC < 1 x 109 cells/L and may be restarted once ANC return above this value
- Absolute Lymphocyte Count (ALC): Treatment should be interrupted if ALC < 0.5 x 109 cells/L and may be restarted once ALC return above this value
- Hemoglobin (Hb): Treatment should be interrupted if Hb < 8 g/dL and may be restarted once Hb return above this value
- Hepatic transaminases: Treatment should be temporarily interrupted if drug-induced liver injury is suspected

Permanent Discontinuation from Investigational Product: Investigational product must be permanently discontinued if the patient or the patient's designee requests to discontinue investigational product. Discontinuation of the investigational product for abnormal liver tests should be considered by the investigator when a patient meets 1 of the following conditions:

- ALT or AST >8 x ULN
- ALT or AST >5 x ULN for more than 2 weeks after temporary interruption of investigational product
- ALT or AST >3 x ULN and total bilirubin level (TBL) >2 x ULN or international normalized ratio (INR) >1.5
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3 x ULN that is deemed to be of liver origin and drug-related
- ALP >2.5 x ULN and TBL >2 x ULN
- ALP >2.5 x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Investigational product should be permanently discontinued if any of the following laboratory abnormalities are observed:
- White blood cell count <1000 cells/□L (1.00 x 103/□L or 1.00 billion/L)

- ANC <500 cells/□L (0.50 x 103/□L or 0.50 billion/L)
- Lymphocyte count <200 cells/□L (0.20 x 103/□L or 0.20 billion/L)
- Hemoglobin <6.5 g/dL (<65.0 g/L)

Hepatitis B virus DNA testing will be performed in enrolled patients who tested positive for HBcAb at screening. Patients who are HBcAb-positive and HBV DNA-negative (undetectable) at Visit 1 will require HBV DNA monitoring every 3 months and at the patient's last visit, regardless of their hepatitis B surface antibody (HBsAb) status. The following actions should be taken in response to HBV DNA test results:

- If a single result is obtained with a value "below limit of quantitation," the test should be repeated within approximately 2 weeks.
- If the repeat test result is "target not detected," monitoring may resume according to the study schedule.
- If the patient has 2 or more test results with a value "below limit of quantitation" during the study, HBV DNA testing should be performed approximately once per month for the remainder of the study and referral to a hepatologist is recommended.
- If a result is obtained with a value above limit of quantitation at any time during the study, the patient will be permanently discontinued from investigational product and should be referred to a hepatology specialist immediately

Supplemental 1: Appropriateness of Measures

Skin Scoring:

There are no validated skin scoring systems for LP. Therefore, we will use simple measures of BSA which is objective and PGA which is well validated in other inflammatory skin conditions. Additionally, we will simply annotate the number of lesions on the individual as a marker of total disease burden. The latter measure, mCAILS was devised for evaluation of cutaneous T-cell lymphoma lesions for trial purposes. This system provides accurate measurements of CTCL patches, plaques, and tumors. This scoring system captures lesion redness, size, texture, pigmentation and elevation characteristics. We will use a Modified CAILS scoring system that discards pigmentation scoring as resolving LP lesion inherently leave behind hyperpigmented skin changes which may confound active lesion scoring. This will provide a composite analysis of the index lesions as well as the general body involvement of the individual. The Modified CAILS system is advantageous over the PASI or EASI system in that in allows for more accurate calculation of surface area and incorporates that into the final score.

In cases where some or all of the affected body regions contain such extensive LP disease that make counting individual LP lesions unfeasible, the lesion count in these areas will be estimated. The palmar surface of the hand equates to approximately 1% BSA. To estimate the lesion count in a body region of extensive disease, the number of lesions counted within an area equivalent to area the palmar surface of the hand within that extensively diseased body region will be multiplied by the representative BSA of that body region to determine the estimated lesion count contained in that body region. Representative BSAs of body regions are defined as follows: head (7%), neck (2%), anterior trunk (13%), arms (8%), forearms (6%), hands (5%), posterior trunk (13%), buttocks (5%), thighs (19%), legs (14%), feet (7%) and groin (1%).

Itch Scoring:

The VAS, VRS, NRS and Skindex-16 are all well validated measure of itch. The VAS, VRS and NRS scores focus on a gestalt of itch. The Skindex-16 scoring system focuses on itch and its impact upon quality of life.

Supplemental 2: Safety Measures

Baseline Screening:

A serum β-hCG test will be performed in all pre-menopausal women as indicated. All pre-menopausal women who are not sterile at screening will also have a urine pregnancy test performed locally as indicated. Any woman with a confirmed positive pregnancy test during screening is not eligible for the study. A positive urine pregnancy test during the treatment periods of the study requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If the serum β-hCG test is positive, study treatment must be definitively discontinued.

Blood Pressure and Pulse:

Height and Weight:
Height and body weight will be measured in indoor clothing, but without shoes. If possible, body weight assessments should be performed by the same study site staff member and using the same scale throughout the study.

Blood Draws:
Subjects should avoid smoking within the hour preceding the blood draws. All laboratory studies will be conducted within the Mayo Clinic Health Systems (Mayo Clinic Arizona and Mayo Clinic Rochester). Details on the collections, shipment of samples and reporting of results will follow Mayo Clinic's current protocols. For the identification of notable values, the Mayo Clinic reference laboratory should be consulted.

Supplemental 3: Safety Monitoring

Infection monitoring:
Study subjects will be evaluated at each visit for signs or symptoms of infection.

- Vitals signs as well as constitutional symptoms will be assessed.
- Assessment for common infections such as cellulitis as well as oral, vaginal, and cutaneous candidiasis will be performed

Post-study Adverse Event
All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if

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

Laboratory studies will be drawn as indicated in Table-2. Whether action needs to be taken to address notable laboratory values will be decided by the investigator, considering the overall status of the subject. Hematology assessments will be measured at all scheduled study visits specified in Table-2. Serum chemistry will be a comprehensive metabolic panel will be measured at all scheduled study visits specified in Table-2.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

8.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriate action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

Relationship of adverse events to study drug

For all AEs, the investigator will assess the causal relationship between the study drug and the AE using his/her clinical expertise and judgment according to the following algorithm that best fits the circumstances of the AE. The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies. A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device and/or study procedure and the AE. The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

8.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

Action taken regarding treatment

AE Action:

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

- No action taken (i.e. further observation only)
- [study/investigational] treatment dosage adjusted/temporarily interrupted
- [study/investigational] treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given

- patient hospitalized/patient's hospitalization prolonged

AE Outcome:
- All AE outcomes should be recorded (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Serious Adverse Events (SAE)
An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria (Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.):
- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

SAE Reporting:

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30-days after the subject stopped study participation must be reported to Eli Lilly and Company as soon as possible but no later than 5 days from learning of its occurrence according to the Mayo Clinic IRB policy. Any SAEs experienced after the 30-days period should only be reported to Eli Lilly and Company and the Mayo Clinic IRB if the investigator suspects a causal relationship to study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted as soon as possible but no later than 5 days from the investigator receiving the follow-up information. SAE should be followed up until resolution or until it is judged to be permanent. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information collected on the adverse event worksheet (*and entered in the research database)*:
- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention*):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5**)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

AE Reporting:
Its relationship to the:

- Study treatment (no/yes), or
- Investigational treatment (no/yes), or
- The other study treatment (non-investigational) (no/yes), or
- Both or indistinguishable

The relationship will be categorized as follows:

- Unrelated- Clearly due only to extraneous causes and does not meet criteria listed under possible or probable.
- Unlikely- Does not follow a reasonable temporal sequence from administration. May have been produced by the patient's clinical state or by environmental factors or other therapies administered.
- Possible- Follows a reasonable temporal sequence from administration but may have been also produced by the patient's clinical state, environmental factors or other therapies administered.
- Probable- Clear-cut temporal association with administration with improvement on cessation of investigational medicinal product or reduction in dose. Reappears upon rechallenge. Follows a known pattern of response to the investigational medicinal product.

Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
Whether it constitutes a serious adverse event (SAE)

Adverse Events (AE):
The severity grade/Common Toxicity Criteria (CTC) AE Version 5.0 grade

- Mild: usually transient in nature and generally not interfering with normal activities
- Moderate: sufficiently discomforting to interfere with normal activities
- Severe: prevents normal activities

If CTCAE grading does not exist for an adverse event, use
1=mild, 2=moderate, 3=severe, 4=life-threatening, CTCAE Grade 5 (death) is not used, but is collected in other CRFs (Study Completion, Death/Survival).

8.3.2 Sponsor-Investigator reporting: Notifying the FDA and Funding Sponsor

The sponsor-investigator will report to the FDA all unexpected, serious suspected adverse reactions according to the required IND Safety Reporting timelines, formats and requirements.

Unexpected fatal or life threatening suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 7 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Other unexpected serious suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Any clinically important increase in the rate of serious suspected adverse reactions over those listed in the protocol or product insert will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Findings from other studies in human or animals that suggest a significant risk in humans exposed to the drug will be reported. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigators initial receipt of the information about the event.

SAE Reporting to the Sponsor (Eli Lilly and Company)

All Serious Adverse Events ("SAE") required to be reported pursuant to the Protocol shall be provided to Eli Lilly and Company and its representatives by Institution or Principal Investigator within twenty-four (24) hours of learning of the event as well as provide any additional reports agreed upon by the Institution or Principal Investigator and Eli Lilly and Company's contact below. SAE Reports will be sent to the email address provided below. By sending to this e-mail address, the Eli Lilly and Company Pharmacovigilance group and the Eli Lilly and Company clinical operations project manager will receive copies of the reports. This process will be tested and established before the first patient is enrolled in the trial. Notwithstanding anything to the contrary herein, Institution or Principal Investigator will have the primary responsibility of reporting adverse events ("AE") to regulatory authorities.

Copies of IND safety reports submitted to the FDA by the Institution will be shared with the contact below so that these reports can be evaluated and included in investigator brochure or Incyte IND safety submissions as required to ensure safety of other patients who are receiving the product from Eli Lilly and Company for sponsored trials.

Eli Lilly and Company contact for e-mail transmission of individual SAE reports.:

Safety Contacts:

Procedure for Reporting of Pregnancy and Lactation to the Sponsor (Eli Lilly and Company)

Data on fetal outcome are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

8.4 Stopping Rules

The stopping rules specified below are based on the knowledge available at study development. The stopping rule applies to the overall study. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy the following:

• If 2 or more patients in the first 6 treated patients (or 30% after the first 6 treated patients have been accrued) experience a grade 3 or higher non-hematologic adverse event.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

8.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

The occurrence of adverse events will be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when the patient volunteers them during or between visits or through physical examination, laboratory test, or other assessments. Please see Supplemental 3 for a detailed description of safety monitoring. Clinically significant abnormal laboratory values or test results will be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for labs and other test abnormalities are included determined by the Mayo Clinic Arizona and Mayo Medical Laboratory. Adverse events will be recorded in the Adverse Events Case Report Form (CRF) under the signs, symptoms or diagnosis associated with them, and severity. All adverse events will be treated appropriately. Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome (see Supplemental 3). Information about common side effects already known about the investigational drug can be found in the package insert. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. The investigator will also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE. To ensure patient safety, every SAE (see Supplemental 3 for definition), regardless of suspected causality, occurring after the patient has provided informed consent and after the patient begins taking study drug and until 30 days after the patient has stopped study participation will be recorded and reported to Incyte. Any SAEs experienced after this 30-day period should only be reported to Incyte if the investigator suspects a causal relationship to the study drug. All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met. Medical and scientific judgment will be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the outcomes listed in SAE. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction. All AEs (serious and non-serious) are captured and recorded, SAEs also require individual reporting (see Supplemental 3). To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to the sponsor-investigator within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment. Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information

The rights of a research subject to revoke their authorization for use of their PHI. *(This information is contained within the Mayo IRB Informed Consent Template Section).* Study data will be securely stored on a password protected computer that only the research study team will have access to. Any study related paper documents will be stored in a locked cabinet that only the research study team will have access to.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

Data Security and Confidentiality

All study data will be collected by the research team, reviewed by the PI, and stored in secure, locked files and/or databases in order to protect it from inadvertent loss or improper access. All laboratory specimens, evaluation forms, reports, and other records will be identified by coded number only to maintain subject confidentiality. Information gained from this study that can be linked to the subject's identity will not be released to anyone other than the investigators, the subject and the subject's physician. All the information obtained in connection with these studies will remain confidential as far as possible within state and federal law. The results of these studies will be published in scientific journals without identifying the subjects by name.

Data Quality Assurance

Source document verification will be performed to ensure that the database accurately reflects data on the CRFs.

Data Clarification Process

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents. These will include subject case histories and regulatory documents. There will be a subject code master list that will be stored so as to protect subjects' confidentiality. Case Report Forms will be coded. There will be no subject names or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes.

The sponsor-investigator will retain the specified records and reports for;

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717

Whichever is longer

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

Eli Lilly and Company is funding this research study.

12.2 Subject Stipends or Payments

Subjects will receive $50 for each biopsy visit they complete (Day 0 and Week 2). They will receive $25 for all other visits that they complete. If they complete all study visits they will receive a total of $300.

13 Publication Plan

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

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15 Attachments

Appendix:

Physician Global Assessment: [17, 18]
Grade 0 Completely clear: no evidence of disease (100% improvement) CCR
Grade 1 Almost clear: very significant clearance (≥90% to <100%) PR
Grade 2 Marked Improvement: significant improvement (≥75% to <90%) PR
Grade 3 Moderate improvement: intermediate between slight and marked (≥50% to <75%) PR
Grade 4 Slight improvement: some improvement (≥25% to <50%); however, significant evidence of disease remains SD
Grade 5 No change; disease has not changed from baseline condition (+/-<25%) SD
Grade 6 Worse, disease is worse than at baseline evaluation by (≥25%) or more PD

CCR- Complete clinical response
PR- Partial response
SD- Stable disease
PD- Progressive Disease

Modified CAILS-
Clinical Assessment Scale of Severity for Index Lesion Signs and Symptoms (mCAILS) [17, 18]

Scale	Grade
0	No evidence of sign or symptom
1	Intermediate interval
2	Mild: less than average presentation of sign or symptom
3	Intermediate interval
4	Moderate: average disease presentation of sign or symptom
5	Intermediate interval
6	Severe: greater than 25% worse than average severity of sign or symptom
7	Intermediate interval
8	Very severe: the near worst severity sign or symptom

A scale of 0 to 18 was used to grade lesion size by square centimeter (0, 0 [no measurable area]; 1, >0 and ≤4; 2, >4 and ≤10; 3, >10 and ≤16; 4, >16 and ≤25; 5, >25 and ≤35; 6, >35 and ≤45; 7, >45 and ≤55; 8, >55 and ≤70; 9, >70 and ≤90; 10, >90 and ≤110; 11, >110 and ≤130; 12, >130 and ≤155; 13, >155 and ≤180; 14, >180 and ≤210; 15, >210 and ≤240; 16, >240 and ≤270; 17, >270 and ≤300; and 18, >300). The area of the lesion will be measured with digital planimetry. [17-19]

mCAILS index lesion score:

1. Erythema (0-8)
2. Scaling (0-8)
3. Plaque elevation (0-8)
4. Size (0-18)

- Trained clinical evaluators assessed the same patients throughout the study.
- The CA (the ratio of summation (Σ) of all clinical signs for these index lesion at each visit compared with baseline) included cutaneous tumors and all extra cutaneous manifestations of disease.
- Complete clinical remission (CCR) required a CA ratio of 0 with no evidence of disease
- Partial remission (PR) was defined as a CA ratio of 0.5 or lower
- Progressive disease was defined as a 25% or higher increase in CA ratio

(Olsen et al., 2011b, Duvic et al., 2001b)

Itch-
Numerical Rating Scale (NRS) (bottom)- [20, 21]

0- No itch
1-4 Mild itch
4-7 Moderate itch
7-9 Severe itch
10- Very severe itch

Pruritus Verbal Rating Scale (VRS)

On average, please rate your itch over the past 24 hours:

□ 0 (None)
□ 1 (Mild)
□ 2 (Moderate)
□ 3 (Severe)

At its worst, please rate your itch in the last 24 hours:

□ 0 (None)
□ 1 (Mild)
□ 2 (Moderate)
□ 3 (Severe)

Pruritus Visual Analogue Scale

Please rate your **average** itch level over the past day by placing a vertical mark on the line below.

No Itch ——————————————— Worst Imaginable Itch

_____._____cm

Please rate your **worst** itch level over the past day by placing a vertical mark on the line below.

No Itch ——————————————— Worst Imaginable Itch

_____._____cm

VAS score interpretation:

VAS 0 = No itch
VAS <3 = Mild itch
VAS ≥3 <7 = Moderate itch
VAS ≥7 <9 = Severe itch
VAS ≥9 = Very severe itch

Skindex-16-

Skindex 16 [22, 23]-

Scoring (0=never bothered to 6=always bothered), Total 0 to 96

Symptom Subscale
1. Skin itching
2. Skin burning or stinging
3. Skin hurting
4. Skin irritated

Emotional Subscale
5. Persistence or recurrence of condition
6. Worry about condition
7. Appearance of skin
8. Frustration about skin
9. Embarrassment about skin
10. Annoyed about skin
11. Feeling depressed

Functional Subscale
12. Effect of skin on interaction with others
13. Effect of skin on desire to be with people
14. Skin making it hard to show affection
15. Effect of skin on daily activity
16. Skin making it hard to work/have enjoyment

MAYO CLINIC

16 LICHEN PLANUS QUALITY OF LIFE QUESTIONNAIRE (LPQoL) v2.0

MRN: ……

……

Date: ……

Score: ……

Name:
……
……

17 This questionnaire aims to measure how much your lichen planus has affected your life over the LAST MONTH. Please check one box for each question.

1. How much has your lichen planus affected your sleep?

Very much ☐ A lot ☐ A little ☐ Not at all ☐

2. How much has your lichen planus affected your work or study?

Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

3. How much has your lichen planus affected your hobbies and interests?
Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

4. How much have you felt self-conscious because of your lichen planus? Very much ☐ A lot ☐ A little ☐ Not at all ☐

5. Have you felt lower in mood due to your lichen planus?
Very much ☐ A lot ☐ A little ☐ Not at all ☐

6. Have you felt more irritable with other people due to your lichen planus? Very much ☐ A lot ☐ A little ☐ Not at all ☐

7. How much has applying the treatment for your lichen planus been troublesome? Very much ☐ A lot ☐ A little ☐ Not at all ☐

8. Have you felt unsupported for your lichen planus?
Very much ☐ A lot ☐ A little ☐ Not at all ☐

18 Please answer the following questions if your lichen planus affects your SKIN. If it does not, please skip to the next section.

9. How sore has your skin been?
Very much ☐ A lot ☐ A little ☐ Not at all ☐

10. How itchy has your skin been?
Very much ☐ A lot ☐ A little ☐ Not at all ☐

19 Please answer the following questions if your lichen planus affects your MOUTH or THROAT. If it does not, please skip to the next section.

11. How much has your oral lichen planus stopped you from eating certain foods? Very much ☐ A lot ☐ A little ☐ Not at all ☐

12. How much has your oral lichen planus affected your taste?

Very much ☐ A lot ☐ A little ☐ Not at all ☐

13. How much has your oral lichen planus affected your ability to carry out dental hygiene e.g. brushing your teeth?

Very much ☐ A lot ☐ A little ☐ Not at all ☐

14. How much has your mouth been sore or burning?

Very much ☐ A lot ☐ A little ☐ Not at all ☐

20 Please answer the following questions if your lichen planus affects your GENITALIA (private parts). If it does not, please skip to the next section.

15. How much has your genital lichen planus caused any sexual difficulties?

Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant ☐

16. How much has your genital area been sore or burning?

Very much ☐ A lot ☐ A little ☐ Not at all ☐

17. How much has your genital area been itchy?

Very much ☐ A lot ☐ A little ☐ Not at all ☐

21 Please answer the following questions if your lichen planus affects your SCALP/HAIR (lichen planopilaris). If it does not, please skip to the next section.

18. How sore or itchy has your scalp been due to your lichen planus? Very much ☐ A lot ☐ A little ☐ Not at all ☐

19. How much has the appearance of your scalp lichen planus e.g. hair loss bothered you? Very much ☐ A lot ☐ A little ☐ Not at all ☐

22 Please answer the following questions if your lichen planus affects your NAILS. If it does not, please skip to the next section.

20. How sore has your nail lichen planus been?

Very much ☐ A lot ☐ A little ☐ Not at all ☐

21. How much has your nail lichen planus caused difficulty handling objects? Very much ☐ A lot ☐ A little ☐ Not at all ☐

22. Have any these areas been actively affected for you in the last month? Please circle [3 points for each affected]: Eyes Ears Nose Esophagus Larynx Perianal and Buttock Bladder

23. Are there any other ways that lichen planus affects your quality of life that we have not addressed?

……
……..

Thank you for your time. Scoring (0-84): Very much = 3 A lot = 2 A little = 1 Not at all = 0 The LPQoL is calculated by the sum of all the scores for each question.