Protocol J1P-MC-KFAD(d)
A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Multiple-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Subcutaneous LY3471851 in Patients with Atopic Dermatitis

LY3471851

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Protocol Amendment (d) Electronically Signed and Approved by Lilly on date provided below

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1. Protocol Synopsis

Title of Study:

A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Multiple-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Subcutaneous LY3471851 in Patients with Atopic Dermatitis

Rationale :

Study J1P-MC-KFAD is a Phase 1 study designed to evaluate the safety, tolerability, and pharmacokinetics (PK) of multiple subcutaneous (SC) doses of LY3471851 (also known as NKTR-358) in patients with atopic dermatitis (AD).

LY3471851 is recombinant human interleukin 2 (rhIL-2) with stable covalently attached polyethylene glycol (PEG) moieties. IL-2 has pleiotropic immunoregulatory functions and has a role in the control of the proliferation and survival of regulatory T (Treg) cells, which are impaired in various autoimmune diseases and inflammatory skin diseases, including AD.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary • To evaluate the safety and tolerability of multiple SC doses of LY3471851 administered to patients with AD	Incidence of adverse events, treatment-emergent adverse events, and serious adverse events
Secondary • To quantify LY3471851 plasma concentrations following multiple SC doses in patients with AD	C_{max}, T_{max}, and AUC after the first dose and trough concentrations after repeated dosing

Abbreviations: AD = atopic dermatitis; AUC = area under the plasma concentration versus time curve; C_{max} = maximum observed plasma concentration; SC = subcutaneous; T_{max} = time to maximum observed plasma concentration.

Summary of Study Design:

This is a double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability, PK, and PD effects of multiple doses of LY3471851 in up to 2 cohorts of patients with AD involving ≥10% body surface area in the affected skin and an Eczema Area and Severity Index (EASI) score of ≥16 at screening.

Treatment Arms and Planned Duration for an Individual Patient:

LY3471851 will be provided as a sterile solution for SC injection in a C -mL vial containing C mg LY3471851. Dosing solutions will be prepared at the clinical study sites by a pharmacist and loaded into SC dosing syringes. In each of up to 2 cohorts, patients will receive SC injection(s) of LY3471851 (n=16) or placebo (n=4).

Patients will receive either LY3471851 or placebo every 2 weeks over a treatment period of 12 weeks. Cohort 1 started with a dose of 10 µg/kg in CCI but was paused due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in CCI . Based on safety and efficacy results of interim data from Cohort 2, Cohort 1 may be restarted in Q1/Q2 2021 at the original dose of 10 µg/kg or at a dose lower than the Cohort 2 dose of 24 µg/kg. The restart of Cohort 1 enrollment could potentially be delayed due to a worsening of the SARS-CoV-2 situation.

Enrollment of Cohort 2 started in CCI with a dose of 24 µg/kg every 2 weeks. The initiation of Cohort 2 is supported by emerging safety, PK, and PD data from the MAD study at the highest dose level of 24 µg/kg (Study J1P-MC-KFAB) and longer-term toxicology studies.

The last safety follow-up will be 50 days after the last dose, with additional visits up to Week 48 for EASI 50 (patient's EASI score reduced by at least 50% relative to their baseline score) responders at Week 19.

Number of Patients:
Approximately 50 patients with AD will be enrolled from approximately 20 study sites within the United States and possibly Canada and the European Union. Patients can be replaced if they discontinue before last treatment visit at Day 85.

Statistical Analysis:
The safety population will consist of all patients who receive at least 1 dose of study drug according to the randomization.

The PK population will consist of all randomized patients who receive LY3471851 and have adequate PK data to permit a meaningful analysis.

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities system organ class and preferred term and will be summarized by treatment. Other safety data including vital signs, and clinical laboratory tests will be summarized by treatment.

Pharmacokinetic parameters will be calculated from plasma concentration-time data after the first dose using standard noncompartmental methods of analysis, and summarized using descriptive statistics.

Data listings and summary statistics will be provided for safety by treatment group over time. For continuous variables, summary statistics will include the mean, standard deviation, minimum, maximum, median, and number of observations. For categorical variables, frequency counts and percentages will be provided.

2. Schedule of Activities

Study Schedule Protocol J1P-MC-KFAD: Treatment and Initial Follow-up

Assessment Period	Screen	Treatment												Follow-up			ED
Study Week Completed					1		2		4	6	8	10	12	14	16	19	
Study Day	-28 to -2	1[a]	3	5	8 ±1	11 ±1	15[a]	22 ±3	29[a] ±3	43[a] ±3	57[a] ±3	71[a] ±3	85[a,b] ±3	99 ±3	113 ±3	134[c] ±3	
Patient Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Informed consent	X																
Inclusion/exclusion criteria	X	X															
Demographics	X																
Physical examination[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical history	X	X															
C-SSRS "Baseline/Screening"	X																
C-SSRS "Since Last Visit"		X			X		X		X		X		X		X	X	X
Self-Harm Supplement Form and Follow-up Form[e]	X	X			X		X		X		X		X		X	X	X
TB test[f]	X																
Vital signs (HR, RR, BP, T) (supine)[g,h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X	X[i]					X		X	X	X	X	X				X[j]
Height	X																
HIV, HBV (surface antigen and core antibody), and HCV screening	X																
12-lead single ECG (supine)[h]	X	X[k]		X									X[l]				
Clinical laboratory tests[m]	X	X			X[n]		X	X[n]	X	X	X	X	X	X		X	X
Serum/urine pregnancy test[o]	X	X					X		X	X	X	X	X	X		X	X
Urine drug screen[p]	X																
Randomization		X															
IP administration		X					X		X	X	X	X	X				
PK blood sample		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD blood collection (flow cytometry)		X		X	X		X	X	X		X		X	X			X[j]
Immunogenicity sample (serum)		X					X		X		X		X			X	X

Assessment Period	Screen	Treatment												Follow-up			ED
Study Week Completed					1		2		4	6	8	10	12	14	16	19	
Study Day	-28 to -2	1[a]	3	5	8 ±1	11 ±1	15[a]	22 ±3	29[a] ±3	43[a] ±3	57[a] ±3	71[a] ±3	85[a,b] ±3	99 ±3	113 ±3	134[c] ±3	
Patient Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Cytokine blood sample		X		X	X		X	X	X		X		X	X			X
IL-19 sample (serum)		X		X	X		X	X	X		X		X	X	X	X	X
Blood for DNA pharmacogenetics		X															
Stored samples for exploratory biomarkers (plasma and serum)		X		X	X		X	X	X		X	X	X		X		X
Stored samples for exploratory mRNA expression and DNA epigenetics (whole blood)		X		X	X		X	X	X		X		X		X		X
Epigenetic marker immunomonitoring assays (T-cell subsets)		X		X	X		X	X	X		X		X	X			X
PBMC isolation		X					X		X				X				
Injection-site assessments[q]		X	X	X	X	X	X	X	X	X	X	X	X	X			X
CCI		CCI															
CCI																	
Lesional skin biopsy x 2		X						X					X				
Nonlesional skin biopsy x 1		X											X				
Clinical photography		X									X		X				
IGA	X	X					X	X	X	X	X	X	X	X	X	X	X
EASI[t]	X	X					X	X	X	X	X	X	X	X	X	X	X
BSA	X	X					X	X	X	X	X	X	X	X	X	X	X
DLQI		X					X	X	X	X	X	X	X	X	X	X	X
POEM		X					X	X	X	X	X	X	X	X	X	X	X
Itch NRS		X					X	X	X	X	X	X	X	X	X	X	X
Concomitant medications recording	X	◄															►
Adverse events recording	X	◄															►

Note: If multiple procedures take place at the same time point, the following order of the procedures should be used: ECG, vital signs, and venipuncture.

Abbreviations: BP = blood pressure; BSA = body surface area; C-SSRS = Columbia Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; EASI = Eczema Area and Severity Index; EASI 50 = patient's EASI score reduced by at least 50% relative to their baseline score; ECG = electrocardiogram; ED = early discontinuation; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = heart rate; IGA = Investigator's Global Assessment; IL = interleukin; IP = investigational product; mRNA = messenger ribonucleic acid; NRS = Numeric Rating Scale; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamics; POEM = Patient-Oriented Eczema Measure; PK = pharmacokinetics; RR = respiratory rate; T = temperature; TB = tuberculosis; VAS = visual analog scale.

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Study Schedule Protocol J1P-MC-KFAD: Clinical Response Follow-up for EASI 50 Responders at Week 19 Safety Follow-up

Assessment Period	Response Follow-up Period							ED
Study Week Completed	24	28	32	36	40	44	48	
Study Day	169 ± 3	197 ± 3	225 ± 3	253 ± 3	281 ± 3	309 ± 3	337 ± 3	
Patient Visit	17	18	19	20	21	22	23	
Vital signs (HR, BP) (supine)	X	X	X	X	X	X	X	X
C-SSRS "Since Last Visit"	X	X	X	X	X	X	X	X
PK blood sample	X			X			X	X
IGA	X	X	X	X	X	X	X	X
EASI	X	X	X	X	X	X	X	X
BSA	X	X	X	X	X	X	X	X
DLQI	X	X	X	X	X	X	X	X
POEM	X	X	X	X	X	X	X	X
Itch NRS	X	X	X	X	X	X	X	X
Lesional skin biopsy x 2							X	X
PD blood collection (flow cytometry)	X						X	X
Concomitant medications recording	←	—	—	—	—	—	—	→
Adverse events recording	←	—	—	—	—	—	—	→

Abbreviations: BP = blood pressure; BSA = body surface area; C-SSRS = Columbia Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ED = early discontinuation; HR = heart rate; IGA = Investigator's Global Assessment; NRS = Numeric Rating Scale; PD = pharmacodynamics; POEM = Patient-Oriented Eczema Measure; PK = pharmacokinetics.

3. Introduction

3.1. Study Rationale

Study J1P-MC-KFAD is a Phase 1 study designed to evaluate the safety, tolerability, and pharmacokinetics (PK) of multiple subcutaneous (SC) doses of LY3471851 in patients with atopic dermatitis (AD).

3.2. Background

Eli Lilly and Company (Lilly) is developing LY3471851 in partnership with Nektar Therapeutics (Nektar). LY3471851 was referred to as NKTR-358 under Nektar-sponsored studies and regulatory submissions. Hereafter in this protocol, this study drug will only be referred to as LY3471851.

LY3471851 is recombinant human interleukin 2 (rhIL-2) with stable covalently attached polyethylene glycol (PEG) moieties. IL-2 has pleiotropic immunoregulatory functions and has a role in the control of the proliferation and survival of regulatory T (Treg) cells, which are impaired in various autoimmune diseases and inflammatory skin diseases, including AD (reviewed in Nedoszytko et al. 2017; Abbas et al. 2018; Sharabi et al. 2018).

3.2.1. *Cell-Subset Abbreviations and Definitions*

Several different cell subsets as defined by markers are referenced in this document, and for simplicity, are abbreviated with naming conventions. These naming conventions and their associated marker definitions are shown in Table KFAD.1.

Table KFAD.1. Cell-Subset Abbreviations Defined by Associated Markers

Abbreviation	Definition by Cell Markers
Tcon cells[a]	*Tcon-Cell Subsets* 1. CD3+ CD4+ CD8- CD25+ FoxP3- 2. CD3+ CD4+ CD8- CD25- FoxP3+ 3. CD3+ CD4+ CD8- CD25- FoxP3- 4. CD3+ CD4- CD8+
Total Treg cells	CD3+ CD4+ CD8- CD25+ FoxP3+
$CD25^{bright}$ Treg cells[b]	CD3+ CD4+ CD8- $CD25^{bright}$ FoxP3+
NK cells[c]	CD3- CD16+ CD56+
Proliferating cells	Ki67+

Abbreviations: CD = cluster of differentiation; FoxP3 = forkhead box P3; NK = natural killer; Tcon = conventional T; Treg = regulatory T.

[a] Tcon cells refers to all 4 subsets.

[b] $CD25^{bright}$ is defined by an established gate in the flow cytometry analysis, selecting the 0.5% (at baseline) highest expressing total Treg cells. The gate established at baseline as 0.5% is carried over the time course.

[c] Only the CD56+ NK cells were measured in LY3471851 Studies 16-358-01 and 17-358-02.

3.2.2. *LY3471851, Treg Cells, and Atopic Dermatitis*

Analysis of skin lesions from patients with AD has shown either a decrease in Treg cell numbers or a reduction in immunosuppressive functions of Treg cells (Nedoszytko et al. 2017). Moreover, filaggrin null mutations correlate with altered circulating Tregs in patients with AD (Moosbrugger-Martinz et al. 2018). The proliferative and functional deficit of Treg cells is hypothesized to contribute to the pathogenesis of AD and other skin-related inflammatory diseases, and treatment with a low-dose IL-2 conjugate therapy (LY3471851) offers a potential path to overcome the imbalance between conventional T (Tcon) cells and Treg cells. The goal of the LY3471851 therapy is to increase Treg cell number and function with minimal effect on Tcon cells in patients with inflammatory diseases such as AD, which could translate to a beneficial clinical outcome.

3.2.3. *IL-2 Biology*

IL-2 is a fundamental T-cell growth factor that is responsible for the survival, proliferation, and differentiation of various T-cell subsets (Boyman et al. 2012). In response to infection, increased expression of IL-2 is essential for the generation of host defense responses involving natural killer (NK) and effector T cells; and by the same mechanism of action therapeutic administration of IL-2 has demonstrated antitumor activity in some patients with certain cancers. In addition, IL-2 plays a crucial role in promoting the development of Treg cells (Malek and Castro 2010). Treg cells are capable of downmodulating the function of Tcon-cell and effector T-cell responses, maintaining immunologic homeostasis, and preventing autoimmunity. Impaired IL-2 production and dysfunctions in Treg cell biology have been identified as key immunological defects leading to the breakdown of immune self-tolerance, a causative mechanism implicated in multiple inflammatory diseases, including AD (Klatzmann and Abbas 2015). This apparent paradoxical effect of IL-2 on T-cell subsets with opposing mechanisms of action can be explained by the difference in IL-2 receptor biology between Treg and Tcon cells. Treg cells are activated at low concentrations of IL-2 due to constitutive cell-surface expression of the high-affinity trimeric IL-2αβγ receptor complex and enhanced downstream signaling associated with this trimeric IL-2 receptor complex, while Tcon cells require higher concentrations of IL-2 for stimulation, as naïve Tcon cells express only the moderate-affinity dimeric IL-2βγ receptor complex and activated Tcon cells express the IL-2αβγ receptor transiently (Klatzmann and Abbas 2015).

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3.2.5. *IL-2 Dosage in Clinical Studies*

IL-2 variants have been administered to patients and healthy subjects in a range of dosages, generally described as high dose and low dose.

High-dose IL-2 is administered to patients with certain cancers to produce expansion, and thereby activity, of the cytotoxic lymphocytes that can have antitumor activity. In approved cancer indications, the recommended treatment regimen for IL-2 (aldesleukin) is 600,000 International Units/kg (0.037 mg/kg), administered through intravenous (IV) infusion every 8 hours for a maximum of 14 doses (Proleukin® package insert, 2015). However, high-dose IL-2 therapy can cause severe adverse events (AEs) such as hypotension, vascular leak syndrome, pulmonary edema, heart toxicities (Sim and Radyanyi 2014) and other toxicities

(Proleukin package insert, 2015). In addition, high-dose IL-2 therapy may decrease the normal suppressive activity of Treg cells on effector T cells (Moon et al. 2015), potentially disrupting immune homeostasis.

Low-dose IL-2 is administered to patients with chronic graft-versus-host disease or inflammatory diseases for the expansion, and thereby activity, of Treg cells that maintain immunologic homeostasis (Mizui 2019), and the low-dose IL-2 therapy might reduce the risk of AEs that are associated with high-dose IL-2, which needs to be shown in future longer-term studies. These observations support IL-2 in the form of LY3471851 as a therapeutic strategy to provide the desired PD effects at doses with potentially favorable benefit to risk ratios for patients with AD.

Recombinant IL-2 (aldesleukin) is an IL-2 analog with similar biological activity as endogenous human IL-2. Aldesleukin has an elimination half-life of approximately 85 minutes, necessitating dosing every 8 hours during cancer treatments (Proleukin package insert, 2015).

The IL-2 component of LY3471851 has the identical sequence as aldesleukin. LY3471851 binds to the high-affinity IL-2 receptor, composed of the receptor α, β, and γ components. When compared with IL-2, the PEG conjugation decreases the affinity of the molecule for the IL-2 receptor components, thus favoring binding to the high-affinity receptor. The PEG conjugation also results in a markedly prolonged half-life (approximately 10 days) compared to IL-2.

Thus, LY3471851 avidly stimulates cells that express the high-affinity IL-2 receptor, especially CD4+ Tregs.

In contrast, LY3471851 poorly stimulates conventional T cells, like effector CD8 CTLs, that express predominantly the components of the IL-2βγ receptor.

The result is relatively greater stimulation of Tregs.

3.2.6. *LY3471851 First-in-Human Study*

The first-in-human, single-ascending dose (SAD) study of LY3471851 (Study 16-358-01) was a Phase 1, double-blind, randomized, placebo-controlled study evaluating the safety, tolerability, PK, and PD of single-ascending low SC doses of LY3471851 in 100 healthy subjects. Eight planned cohorts completed dosing with 0.3, 1.0, 3.0, 6.0, 9.0, 13.5, 20.0, and 28.0 μg/kg of LY3471851, respectively, and consisted of 12 subjects (9 LY3471851 and 3 placebo). Four additional subjects received 20.0 μg/kg of LY3471851 to assess the ability of Tregs to suppress Tcon proliferation. Safety, PK, and PD data from all cohorts are available, and are described in the IB and in the subsequent sections.

3.2.6.1. Study 16-358-01 Safety Results

Treatment-emergent adverse events (TEAEs) and treatment-related adverse events (TRAEs) were as follows for 100 healthy subjects.

- 69 subjects reported at least 1 drug-related TEAE.
- 57 subjects reported at least 1 TRAE, an AE that in the opinion of the investigator was attributed to study drug (either LY3471851 or placebo)

- Most TEAEs were mild (Grade 1) injection-site reactions (ISRs) characterized by localized erythema, pain, swelling, and induration, most of which lasted 4 to 8 days and all resolved without treatment
- 4 subjects reported TRAE of headache
- 1 subject at the highest dose tested (28 μg/kg) reported mild (Grade 1) fever, vomiting, diarrhea, increased heart rate, pain in the muscles, and lack of appetite, which resolved on its own within 2 to 8 days

No dose-limiting toxicities (DLTs), deaths, or AEs leading to study discontinuation occurred for any subjects across all 8 cohorts.

Importantly, the safety findings showed no evidence of the AEs that are known to be associated with high-dose IL-2 (aldesleukin), such as capillary leak syndrome, increased risk of infection, inflammatory disease, cardiac disorders (cardiac rhythm disturbances and angina or myocardial infarction), pulmonary disorders, central nervous system effects, or severe anemia/thrombocytopenia (Proleukin package insert, 2015).

3.2.6.2. Study 16-358-01 Pharmacokinetic/Pharmacodynamic Results

Pharmacokinetics: After SC administration of 0.3 to 28 μg/kg, plasma LY3471851 concentrations slowly increased, reaching maximum concentrations of 2 to 240 ng/mL by 5 to 7 days postdose. After reaching maximum observed plasma concentration (C_{max}), concentrations declined with an elimination half-life of approximately 8 to 11 days. Evaluation of C_{max} and area under the concentration versus time curve from zero to infinity (AUC0-∞) data indicated that LY3471851 exhibits linear PK in the tested dose range.

Pharmacodynamic results for $CD25^{bright}$ Treg cells, total Treg cells, Tcon cells, and NK cells are summarized as follows.

$CD25^{bright}$ Treg Cells

LY3471851 led to a dose-dependent increase in $CD4+FoxP3+CD25^{bright}$ Tregs. At doses greater than or equal to 3.0 μg/kg, there was a detectable increase in the percentage of $CD4+FoxP3+CD25^{bright}$ Tregs. [redacted] CCI [redacted]

There was a maximal mean increase in the percentage of $CD25^{bright}$ Tregs (as a percentage of CD4+ T cells) of 7.1-fold and 15.2-fold compared to baseline at the highest dose of 20.0 and 28.0 μg/kg, respectively. For more details, see the IB.

Tcon Cells

No changes in the absolute numbers or percentage of Tcon cell populations were observed in subjects who received either LY3471851 or placebo.

NK Cells

Circulating NK cells increased in absolute number and percentage at 13.5 µg/kg and higher dose levels, but not at lower dose levels.

Proliferating NK cells increased dose-dependently in percentage starting at 3.0 µg/kg CCI .

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3.2.7. *LY3471851 Multiple-Ascending-Dose Study*

The multiple-ascending dose (MAD) study of LY3471851 (Study 17-358-02) was a Phase 1, double-blind, randomized, placebo-controlled study evaluating the safety, tolerability, PK, and immunologic effects of multiple-ascending SC doses of LY3471851 in patients with minimal to moderate systemic lupus erythematosus (SLE) disease activity. Patients in this study received 3 doses of study drug at 2-week intervals. Four dose cohorts (9 LY3471851 and 3 placebo per cohort) were evaluated (3.0, 6.0, 12.0, or 24.0 µg/kg of LY3471851). Detailed safety, PK, and PD results for Study 17-358-02 can be found in the IB.

3.2.7.1. Study 17-358-02 Safety Results

The most common TEAEs were ISRs, which were reported with LY3471851 (91.7%) and not placebo. The overall mean onset of an ISR was 1.7 days postdose, with a mean duration of 15.4 days. No meaningful differences or trends across LY3471851 dose levels were observed. Most reactions were deemed mild in severity and related to study drug by the investigator. No deaths were reported.

One subject who received 3 µg/kg of LY3471851 was hospitalized for a severe (Grade 3) migraine approximately 3 weeks after the last dose of study drug.

Eosinophilia (24 µg/kg of LY3471851) was the only TEAE that led to discontinuation of study drug in 1 subject after the second dose by the sponsor. Treatment emergent adverse event related to increased eosinophil counts (eosinophilia and eosinophil count increased) were reported as TEAEs in a total of 4 subjects who received LY3471851 (12 or 24 µg/kg). Each event started approximately 1 week after the second dose and resolved after the last dose of study drug (duration: 22 to 50 days). All were deemed mild (Grade 1; n = 3) or moderate (Grade 2; n = 1). One resulted in discontinuation of study drug (24 µg/kg) by the sponsor. Peak eosinophil values associated with these events ranged from 1.4 to 3.1 × 10^9/L on Days 21 to 43.

One subject who received CCI [redacted] experienced 2 episodes of cytokine release syndrome (CRS) on Days 15 and 30 that recovered/resolved after 2 days, were deemed mild (Grade 1), and were considered related to study drug by the investigator. Neither episode was

associated with clinically relevant clinical laboratory or cytokine values. No clinically significant vital sign or ECG abnormalities were observed related to the CRS.

Overall, no meaningful changes from baseline and no meaningful differences or trends across the LY3471851 dose cohorts compared to placebo were observed for any hematology or chemistry parameter. Overall, few subjects had AST, ALT, and alkaline phosphatase values > ULN, and none were > 2 x ULN; no subject had a bilirubin value > ULN.

There was a trend in eosinophilia with respect to the LY3471851 dose, summarized in CCI .

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No clinically significant vital sign or ECG abnormalities were observed in the MAD study. No subject had a maximum QTcF interval >500 msec or maximum QTcF change from baseline >60 msec. No pregnancies were reported.

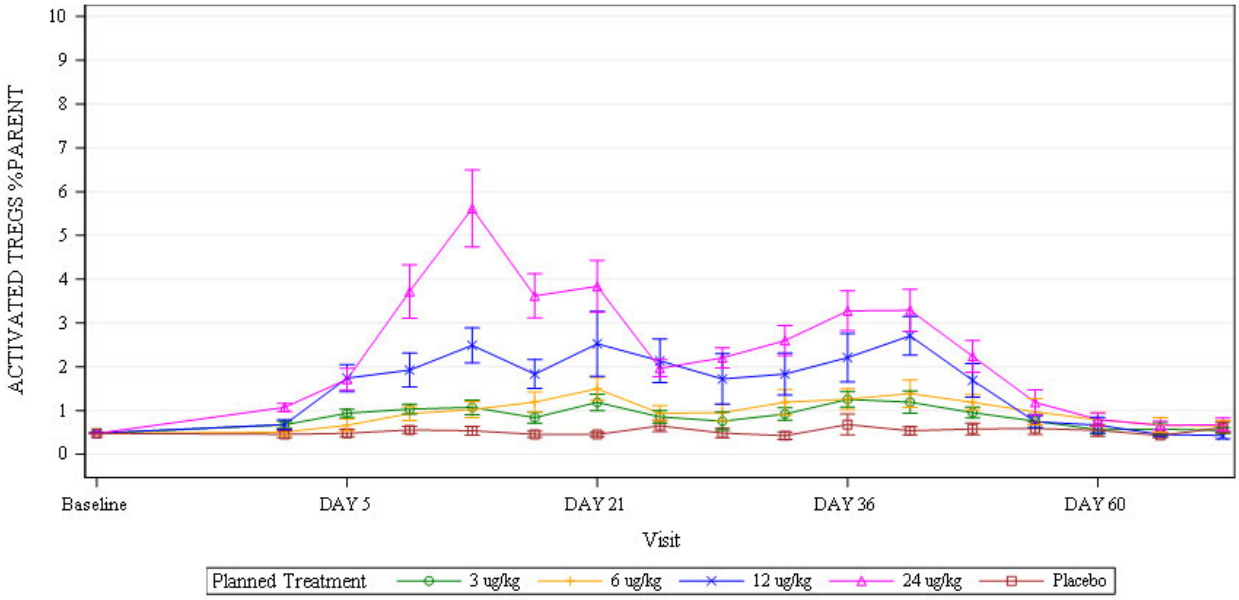
3.2.7.2. Study 17-358-02 Pharmacokinetic/Pharmacodynamic Results

PK Results from Study 17-358-02

LY3471851 at doses ranging from 3 to 24 µg/kg displayed dose-proportional PK in patients with mild to moderate SLE. After SC administrations, LY3471851 reached maximum plasma concentrations approximately 3 to 6 days postdose and declined with terminal half-life of 10 to 13 days. Mean accumulation ratios were estimated as 1.70 to 2.45 for $AUC_{0\text{-}14d}$ and 1.48 to 2.12 for C_{max} over 3 doses given 14 days apart.

PD Results from Study 17-358-02

LY3471851 led to a dose-dependent increase in CD4+FoxP3+$CD25^{bright}$ Tregs after each administration. The mean maximum increase after the first dose in the percentage of $CD25^{bright}$ Tregs was 4.5-fold and 11.7-fold, relative to baseline at the higher doses of 12 and 24 µg/kg, respectively. The induction of CD4+FoxP3+$CD25^{bright}$ Tregs did not return to baseline between doses but instead remained elevated throughout the dosing period, see Figure KFAD.1 depicting the changes of activated CD4+FoxP3+$CD25^{bright}$ Tregs in percentages.



Abbreviations: PD = pharmacodynamic; SE = standard error.

Figure KFAD.1. Mean (SE) percentages numbers of CD4+CD25^{bright} Tregs (activated Tregs) in peripheral blood after multiple dose administration of LY3471851 (PD population).

NK Cells and Tcon Cells

An increase in percentages of circulating NK cells (as a percentage of CD45+ cells) was observed at the highest (24.0 µg/kg) dose level. There was also a dose-dependent increase in the percentage of CD56+ NK cells expressing Ki67, a marker of proliferation, and therefore, a marker of activation, with increases seen at the 12.0 and 24.0 µg/kg dose levels.

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No changes in percentage of Tcon cell populations (CD4+ and CD8+) were observed in either the LY3471851- or placebo-treated subjects.

3.3. Benefit/Risk Assessment

Impairment of the development and the function of Tregs is a common immune defect that contribute to the development of inflammatory and autoimmune diseases. LY3471851 treatment is expected to restore Treg development and function, thereby stimulating mechanisms of immune resolution to overcome autoimmunity and inflammation in patients with inflammatory diseases such as PsO and AD, with minimal or absent effect on Tcon cells. These anticipated effects would reduce signs and symptoms of autoimmune and inflammatory conditions (desired pharmacology) without stimulating Tcon cells (undesired pharmacology). An increased number of Treg cells would regulate Tcon cells, restoring balance to the immune system. Patients in this study may demonstrate improvement in the symptoms of their AD.

Severe AEs associated with high-dose IL-2 include

capillary leak syndrome	autoimmune diseases
cytokine release syndrome	cardiopulmonary events
increased risk of disseminated infections	hematological toxicities

In addition, the most common AEs in patients treated with high-dose IL-2 include

hypotension	dyspnea	confusion
diarrhea	rash	oliguria
nausea	increased bilirubin	increased creatinine
vomiting	anemia	
chills	thrombocytopenia	

For more details see the Proleukin Package Insert 2015.

LY3471851 (PEGylated rhIL-2) has the same amino acid sequence as aldesleukin (Proleukin) but a more favorable PK profile and a longer half-life (10 days versus 85 minutes). These differences in PK profile allow less frequent and lower dosing of LY3471851 with anticipated lower occurrence and/or less severity of AEs.

Based on the clinical experience with LY3471851 to date, individuals may experience ISRs (which may manifest as any or a combination of redness, pain, itching, swelling, and/or hard lumps), which could persist for several days.

A single participant at the highest dose level administered in healthy subjects reported a clinical symptom complex attributed to elevated cytokine levels, which resolved on its own within 2 to 8 days.

One subject who received 24 µg/kg of LY3471851 experienced 2 episodes of CRS on Days 15 and 30 that recovered after 2 days, were deemed mild (Grade 1), resolved without intervention, and were considered related to study drug by the investigator. CCI [redacted]

CCI [redacted]

The preclinical and clinical findings related to LY3471851 might translate to a higher risk of infectious or allergic reactions in humans and possibly affect the skin, liver, or the lung. To avoid these potential risks to patients, blood, skin, lung, and liver function will be assessed during clinic visits and appropriate intervention taken if unwanted effects occur.

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated AEs of LY3471851 is to be found in the IB.

4. Objectives and Endpoints

Table KFAD.4 shows the objectives and endpoints of the study.

Table KFAD.4. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of multiple SC doses of LY3471851 administered to patients with AD	Incidence of adverse events, treatment-emergent adverse events, and serious adverse events
Secondary	
• To quantify LY3471851 plasma concentrations following multiple SC doses in patients with AD	C_{max}, T_{max}, and AUC after the first dose and trough concentrations after repeated dosing
Exploratory Objectives	
• To assess the effects of LY3471851 on the time course and extent of changes in PD in peripheral blood cell types	Peripheral blood PD markers - number and activation status of total Treg cells, $CD25^{bright}$ Treg cells, Tcon cells, and NK cells, as measured using flow cytometry and epigenetic marker immunomonitoring assays
• To assess the effects of LY3471851 on cutaneous PD markers	Cutaneous PD markers, as measured using standard histology, immunohistochemistry, and epigenetic marker immunomonitoring assays
• To assess effects of LY3471851 peripheral cytokine levels over time	Peripheral blood cytokine levels
• To assess the effects of LY3471851 on disease activity in patients with AD	Clinical rating scores: IGA; EASI; percentage BSA involvement
• To assess the effects of LY3471851 on PRO/QoL	DLQI; POEM; Itch NRS
• To explore the potential associations between exposure and PD/clinical responses for select biomarker and disease activity endpoints	Model parameters for the exposure-response relationship between LY3471851 plasma concentrations and biomarker and disease activity endpoints
• To assess injection sites	Erythema, bruising, induration, pain, pruritus, and edema; time to event, duration, and location Markers for tissue inflammation using standard histology and gene expression assays from optional biopsies

Abbreviations: AD = atopic dermatitis; AUC = area under the plasma concentration-time curve; BSA = body surface area; C_{max} = maximum observed plasma concentration; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; IGA = Investigator Global Assessment; NK = natural killer; NRS = Numeric Rating Scale; PD = pharmacodynamic; POEM = Patient Oriented Eczema Measure; PRO = patient-reported outcomes; QoL = quality of life; SC = subcutaneous; Tcon = conventional T; T_{max} = time to maximum observed plasma concentration; Treg = regulatory T.

5. Study Design

5.1. Overall Design

This is a double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability, PK, and PD effects of multiple doses of LY3471851 in up to 2 cohorts of patients with AD. The PK/PD, safety, and clinical outcome information obtained in this study will help guide dose selection for future Phase 2 studies.

Study governance considerations are described in detail in Appendix 3.

Treatment Period (through Week 12)

LY3471851 or placebo will be administered SC every 2 weeks for a total of 7 doses per patient. The treatment period will be 12 weeks, during which blood and skin samples will be collected for PK and PD measurements, as well as physician- and patient-assessed outcome and safety measures. The key exploratory disease activity assessment will be done at Day 85 (Week 12), prior to the final dose of study drug.

Follow-up Period (from Week 12 through Week 19)

All patients will be monitored through Day 134 (Week 19), which is 50 days (approximately 5 half-lives) after the last dose of study drug, for safety, PK, PD, and disease activity assessment. Patients who do not meet an Eczema Area and Severity Index (EASI) 50 response on Day 134 will be considered to have completed the study.

Follow-up Period for Sustained EASI 50 Responders (from Week 19 through Week 48)

To evaluate durability of response, patients who are EASI 50 (patient's EASI score reduced by at least 50% relative to their baseline score) responders on Day 134 and agree to continue, will continue through Week 48 or until they fail to meet an EASI 25 response. Patients who continue will visit every 4 weeks starting at Week 24 to evaluate disease activity, PD, and PK through Day 337 (Week 48).

Cohort 1

Cohort 1 stopped enrolling new subjects in CCI [redacted] at the time of the coronavirus disease 2019 (COVID-19) pandemic and will remain on hold until an interim review of safety, efficacy, PK, and PD data from Cohort 2 is performed. After that review of the data from Cohort 2, Cohort 1 may be restarted at the same dose or a dose lower than the Cohort 2 dose of 24 µg/kg.

Cohort 2

Cohort 2 enrollment was started with a dose of 24 µg/kg every 2 weeks. The initiation of Cohort 2 is supported by emerging safety, PK, and PD data from the MAD study at the highest dose level of 24 µg/kg (Study J1P-MC-KFAB) and longer-term toxicology studies.

5.2. Number of Participants

Approximately 50 patients with active AD are planned to be randomly assigned to either LY3471851 or placebo. Each cohort is planned to have up to 20 patients randomly assigned to receive LY3471851 and up to 5 patients randomly assigned to receive placebo (matching saline solution). This will allow for approximately 40 patients completing the study with both cohorts.

Reserve patients who were not enrolled in Cohort 1 may be reassessed once for enrollment and dosing in Cohort 2, or as replacement patients in either cohort. If the reserve patient is outside the 28-day screening window, inclusion and exclusion criteria, ECG, vital signs, routine laboratory safety tests (hematology, clinical chemistry, urinalysis), and medical examination will be repeated to confirm the patient's eligibility. However, other tests such as tuberculosis (TB) testing, hepatitis B/C, human immunodeficiency virus (HIV) serology, and AD disease markers do not need to be repeated. If rescreening is performed, the individual must sign a new ICF each time and will be assigned a new identification number.

If the reserve patients are not subsequently enrolled, they are not required to undergo early termination or follow-up procedures.

5.3. End of Study Definition

End of the study is the date of the last patient visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.

5.4. Scientific Rationale for Study Design

Placebo has been chosen as the control treatment to assess whether any observed effects are treatment related or simply reflect the trial conditions. The double-blind (ie, blinded to investigator, patient, and sponsor staff who are involved in the treatment or clinical evaluation of the patients), randomized, placebo-controlled design minimizes bias on safety and tolerability assessments, and allows a more robust comparison among LY3471851 and placebo doses.

5.5. Justification for Dose

Up to 3 dose levels will be tested in this study based on data from the following completed LY3471851 Phase 1 studies:

- a SAD study in healthy volunteers (Study 16-358-01) and
- a MAD study in patients with SLE (Study 17-358-02).

Safety data were reviewed and summarized in the IB.

Notably, dose justifications have been updated with the most recent nonclinical toxicity data. At the time of the initial protocol approval, the Cohort 1 dose justification was supported by the available 14-week repeat-dose rat toxicity study (Report LS-2017-020) and the 15-week repeat-dose monkey toxicity study (Report LS-2017-021).

Since the initial protocol approval, the 28-week repeat-dose rat toxicity study (Report LS-2017-022) and the 28-week repeat-dose monkey toxicity study

(Report LS-2017-023) have completed. The data from these chronic toxicity studies have been used to support the dose justification for Cohort 2 dose as described below.

Cohort 1

Cohort 1 started with a dose of 10 µg/kg for which the predicted mean steady-state AUC0-336h (equivalent to AUC0-14d) is 1783 ng•day/mL. This starting dose was chosen based on a favorable SAD and MAD safety profile and an ability to increase Treg cell counts without a concomitant increase in Tcon cells. Cohort 1 enrollment may be restarted with a dose based on interim data from Cohort 2. This dose will either remain the same as the dose prior to the pause, or it will be another dose, which will not exceed the Cohort 2 dose of 24 µg/kg.

Additionally, the 10 µg/kg dose is predicted to yield human exposures that are below the nonclinical exposures as determined by the FDA-defined NOAEL in rat and monkey toxicology studies available at the time of initiation of this study (Table KFAD.5).

Table KFAD.5. Margins of Safety for Subcutaneous LY3471851 for Cohort 1 Based on Systemic Exposure at the NOAEL in Sub-chronic Toxicity Studies

Species Dose (Frequency)	$AUC_{0\text{-}336hr}$ (ng•hr/mL)	$AUC_{0\text{-}14day}$ (ng•day/mL)	Margin of Safety[a]
Human[b] 10 µg/kg (Q14D)	42792	1783	--
Rat NOAEL; FDA-defined[c] 45 µg/kg (twice weekly)	43200	1800	1.0x
Monkey NOAEL[d] 300 µg/kg (Q14D)	769000	32042	18x

Abbreviations: $AUC_{0\text{-}336hr}$ = area under the plasma concentration versus time curve from 0 to 336 hours; $AUC_{0\text{-}14day}$ = area under the plasma concentration versus time curve from 0 to 14 days; FDA = Food and Drug Administration; NOAEL = no-observed-adverse-effect level; PK = pharmacokinetics; Q14D = once every 14 days.

a Margin of Safety = ($AUC_{0\text{-}336hr}$ in animals at the NOAEL) ÷ ($AUC_{0\text{-}336hr}$ in humans).

b Proposed human dose = 10 µg/kg; AUC based on projected human plasma PK simulated using a 1-compartment PK model.

c NOAEL for the 14-week repeat-dose rat toxicity study (Report LS-2017-020) as defined by the FDA (DPARP); plasma toxicokinetics was determined on Day 92.

d NOAEL was determined in a 15-week repeat-dose monkey toxicity study (Report LS-2017-021); plasma toxicokinetics was determined on Day 85.

Cohort 2

Cohort 2 enrollment was started in [redacted] after the COVID pause and its dose was selected so that it does not exceed the predicted exposure associated with a 24 µg/kg every 2 weeks dosing regimen ($AUC_{0\text{-}14d}$ = 4370 ng•day/mL) and could be a lower dose and/or less frequent administration, e.g. every 4 weeks. A dosing regimen of 24 µg/kg every 2 weeks is further supported by the recent 28-week toxicology studies in rats and monkeys (see Table KFAD.6 below). Additionally, completed safety, PK, and PD data from the SAD and MAD studies where

a dose of up to 28 µg/kg was administered as a single dose to healthy participants or 3 doses up to 28 µg/kg every 2 weeks to patients with SLE, respectively, further support a higher dose of up to 24 µg/kg in Cohort 2.

The margins of safety derived from the 28-week toxicology study NOAELs of 150 µg/kg in the rat study and 90 µg/kg in the monkey study were administered once-weekly and once every 2 weeks, respectively. These levels provide exposure multiples of 1.1x and 2.9x in the rat and monkey studies, respectively, to projected exposures at the maximum human dose proposed for Cohort 2 in AD patients (Table KFAD.6.).

Table KFAD.6. Margin of Safety for Subcutaneous Administration of LY3471851 in Cohort 2 as Based on Exposure at the NOAEL in Chronic Toxicity Studies

	Dose; Frequency (µg/kg)	AUC(0-336) (ng•h/mL)	Exposure Multiple[a]
Human Dose[b]	Up to 24 µg/kg, Q2/4W	104,880[b]	Not applicable
Rat NOAEL[c]	150 µg/kg[c]; QW	114,600	1.1x
Monkey NOAEL[d]	90 µg/kg[d]; Q2W	308,000	2.9x

Abbreviations: AUC = area under the plasma concentration versus time curve; AUC_{0-336} = AUC from time zero to 336 hours postdose; AUC_{0-14d} = AUC from time zero to 14 days postdose; N = number of subjects; NOAEL = no-observed-adverse-effect level; PK = pharmacokinetic; Q2W = every 2 weeks; Q2/4W = every 2 or 4 weeks; QW = once-weekly; SD = standard deviation.

a Exposure Multiple = [AUC_{0-336} in animals at given dose] ÷ [projected AUC_{0-336} in humans].

b Proposed maximum human dose = 24 µg/kg, administered Q2W, which was also the highest dose tested in Study 17-358-02. Mean AUC_{0-336} at 24 µg/kg is predicted from a simulation using a preliminary 1-compartment PK model based on single- and multiple-ascending dose pharmacokinetic data (N = 1000 subjects simulated, with mean [SD] weight based on prior studies in atopic dermatitis patients of 73.56 kg [SD = 16.67 kg]; min =32, max = 145.2). Mean AUC_{0-336} = 104,880 ng•h/mL (equivalent to AUC_{0-14d} = 4370 ng•day/mL).

c NOAEL for the 28-week repeat-dose rat toxicity study (Report LS-2017-022); plasma toxicokinetics determined on Day 190, AUC_{0-168} doubled to approximate AUC_{0-336}

d NOAEL for the 28-week repeat-dose monkey toxicity study (Report LS-2017-023); plasma toxicokinetics determined on Day 183.

6. Study Population

Eligibility of patients for the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and ECG.

Vital sign measurements may be repeated once if any measurement is out of range.

The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening may occur up to 28 days prior to enrollment. Patients who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Patients are eligible for inclusion in the study only if they meet all of the following criteria at screening and/or enrollment:

[1] present with a diagnosis of AD at least 12 months prior to screening, as defined by the American Academy of Dermatology: Guidelines of care for the management of atopic dermatitis; Section 1. Diagnosis and assessment of moderate to severe atopic dermatitis (Eichenfield et al. 2014), including all of the following:

a. EASI score ≥16 at baseline (Day 1)

b. Investigator Global Assessment (IGA) score of ≥3 at baseline (Day 1)

c. ≥10% of body surface area (BSA) involvement at baseline (Day 1)

[2] history, documented by a physician and/or investigator, of inadequate response to existing topical medications within 6 months preceding screening, or history of intolerance to topical therapy as defined by at least 1 of the following:

a. inability to achieve good disease control defined as mild disease or better (e.g., IGA ≤2) after use of at least a medium potency topical corticosteroid (TCS) for at least 4 weeks, or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super potent TCS), whichever is shorter,

(Note: a TCS may be used with or without topical calcineurin inhibitors [TCNIs]).

or

b. documented history of clinically significant adverse reactions with the use of TCS, such as skin atrophy, allergic reactions, or systemic effects that, in the opinion of the investigator, outweigh the benefits of retreatment, and/or

c. failed systemic therapies intended to treat AD, such as cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil, within 6 months preceding screening (will be considered as having inadequate response to topical therapy)

[3] agree to discontinue use of the following excluded medications for at least 2 weeks prior to baseline (Day 1) and throughout the study:

a. topical corticosteroids or topical immune modulators (e.g., tacrolimus or pimecrolimus), and

b. topical phosphodiesterase type 4 (PDE 4) inhibitor (crisaborole)

[4] have applied emollients daily for at least 14 days prior to baseline (Day 1) and agree to use emollient daily throughout the treatment period

[5] males and females, aged 18 through 70 years at the time of screening, who agree to adhere to the contraception requirements described in Section 6.3.2

[6] body mass index (BMI) of 18.0 to 45.0 kg/m^2, inclusive

[7] clinical laboratory test results within normal reference range for the population or study site, or results with acceptable deviations that are judged to be not clinically significant by the investigator

[8] venous access sufficient to allow for blood sampling

[9] reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

[10] willing and able to undergo skin lesion biopsies on study Days 1, 22, and 85 (see Section 9.1.3)

[11] willing and able to give signed informed consent, and

[12] willing and able to participate in the study for a duration of up to 6 months.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening and/or enrollment:

[13] study site personnel directly affiliated with this study and their immediate families (a spouse, biological or legal guardian, child, or sibling)

[14] Lilly employees or are employees of a third-party organization involved with the study

[15] currently enrolled in a clinical study involving an investigational product (IP) or any other type of medical research judged not to be scientifically or medically compatible with this study

[16] previously completed or withdrawn from this study or any other study investigating LY3471851, and have previously received the IP

[17] known allergies to LY3471851, related compounds, or any components of the formulation

[18] clinically significant ECG abnormalities including QT interval corrected using Fridericia's formula >450 msec for males and >470 msec for females

[19] history of additional risk factors for Torsades de Pointes (e.g., heart failure, hypokalemia, family history of long QT syndrome)

[20] use of concomitant medications (excluding medications which could be used to treat depression) that prolong the QT/QTc interval

[21] clinically relevant abnormal blood pressure (BP) and/or heart rate (HR) as determined by the investigator

[22] evidence of significant liver or kidney dysfunction, including any of the following at screening:

a. estimated glomerular filtration rate of ≤60 mL/min, using the Modification of Diet in Renal Disease equation:

   glomerular filtration rate (mL/min/1.73 m2) = 175 × (Scr)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if African American)

b. aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (ALP) >1.5X upper limit of normal (ULN); or
c. total bilirubin level (TBL) >1.5X ULN

[23] history of any significant cardiovascular disease (e.g., myocardial infarction, congestive heart failure, uncontrolled hypertension, cerebrovascular accident), thrombotic episode, or any severe medical illness, in the opinion of the investigator, within the previous 1 year.

[24] evidence of significant hematologic dysfunction, including any of the following at screening:

a. hemoglobin <10.0 g/dL
b. absolute neutrophil count <1.8 x 109/L
c. total white blood cell (WBC) <3.6 x 109/L
d. absolute lymphocyte count ≤0.8 x 109/L
e. platelet count <100 x 109/L, or
f. eosinophil count >3000 µL

[25] currently experiencing or have a history of other concomitant skin conditions (e.g., PsO or cutaneous lupus) that would interfere with evaluations of the effect of study drug on AD

[26] patients who, in the opinion of the investigator, are currently experiencing or have a history of erythrodermic, refractory, or unstable skin disease that requires frequent hospitalizations and/or IV treatment for skin infections that may interfere with participation in the study

[27] history of eczema herpeticum within 12 months prior to screening

[28] history of 2 or more episodes of eczema herpeticum

[29] patients who are currently experiencing a skin infection that requires treatment, or is currently being treated, with topical or systemic antibiotics

Note

Patients may not be rescreened until at least 4 weeks after the date of their previous screen failure and at least 2 weeks after resolution of the infection.

[30] any serious concomitant illness that is anticipated to require the use of systemic corticosteroids or otherwise interfere with study participation or require active frequent monitoring (e.g., unstable chronic asthma)

[31] history of any disease apart from AD that has required treatment with oral or parenteral corticosteroids for more than 2 weeks within the past 24 weeks prior to signing the informed consent form (ICF)

[32] history of a primary immunodeficiency, splenectomy, or any underlying condition that predisposes the subject to infection

[33] exclusion criterion [33] has been deleted

[34] history of major surgery within 12 weeks of screening or will require major surgery during the study

[35] are considered by the investigator to be at significant risk for suicide based on the following criteria:

- the ideation or behavior occurred within the past 6 months, and
- have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the Columbia Suicide Severity Rating Scale (C-SSRS), or
- have answered "yes" to any of the suicide-related behaviors on the "suicidal behavior" portion of the C-SSRS

[36] regularly use known drugs of abuse and/or show positive findings from drug screening

(positive cannabinoid test will not automatically exclude a patient from the study)

[37] history of alcohol or other drug abuse within the last year

[38] evidence of HIV infection and/or positive human HIV antibodies

[39] evidence of hepatitis B and/or positive hepatitis B surface antigen and/or are positive for hepatitis B core antibody (even if negative for hepatitis B surface antigen) at screening

[40] evidence of hepatitis C and/or positive hepatitis C antibody at screening

Note

Patients with a previous diagnosis of hepatitis C who have been treated with antiviral therapy and achieved a sustained virological response may be eligible for inclusion in the study, provided they have no detectable hepatitis C virus (HCV) RNA on the screening test for this protocol. A sustained virological response is defined as an undetectable HCV RNA 24 weeks after completion of a full, documented course of an approved antiviral therapy for HCV.

Patients who have spontaneously cleared HCV infection, defined as:

a. a positive HCV antibody test and

b. a negative HCV RNA test, with no history of anti-HCV treatment,

may be eligible for inclusion in the study, provided they have no detectable HCV RNA on screening for this study. Based on the judgment of the investigator, any patient exhibiting behaviors that would put them at risk for re-infection with HCV may be discontinued from the study.

Any patient with a history of HCV infection who develops elevated ALT level ≥3X ULN during the study will be tested for HCV RNA in addition to a full liver evaluation as described in Section 9.4.5.1. Anyone diagnosed with hepatitis C during the study will be discontinued from the study and should receive appropriate follow-up medical care.

[41] women who are breastfeeding

[42] donated blood of more than 500 mL within the previous 4 weeks of study screening

[43] received blood products within 6 months prior to screening

[44] symptomatic herpes zoster within 3 months of screening

[45] show evidence of active or latent TB, as documented through

a. medical history and examination

b. chest x-ray (posterior-anterior; read by a radiologist, pulmonologist, or designee; a lateral chest x-ray may be performed if clinically or radiologically indicated)

c. and/or positive TB testing, defined as:

i. either a positive tuberculin skin test (TST), defined as a skin induration >5 mm at 48 to 72 hours, regardless of prior bacille Calmette-Guerin (BCG) TB vaccination, or

ii. a positive or 2 consecutive indeterminate QuantiFERON®-TB Gold test results

Note

The choice to perform a TST or a QuantiFERON-TB Gold test will be made by the investigator according to local licensing and standard of care. The QuantiFERON-TB Gold test can only be used in countries where it is licensed.

[46] received live vaccine(s) (including live attenuated vaccines) within 4 weeks of screening or intend to receive during the study and for 5 drug half-lives after the last dose of the study drug (through week 19)

Note

Non-live or inactivated vaccine is allowed if it is received at least 2 weeks before randomization in the study or after the last visit. Inactivated influenza ("Flu") and pneumococcal vaccines are allowed during the study. SARS-CoV-2 vaccines are allowed during the study when authorized by local regulatory bodies.

[47] received BCG vaccine within 12 months of screening or intend to during the study and for 5 drug half-lives after the last dose of study drug

[48] received treatment with biologic agents (such as monoclonal antibodies, including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing

Note

Patients who have been treated with dupilumab must have not received it within 6 months of baseline (Day 1).

[49] received any small molecule IP within 4 weeks or 5 half-lives before screening, whichever is greater

[50] history of clinically significant

a. drug hypersensitivity reactions that in the opinion of the investigator may predispose the patient to a clinically significant hypersensitivity reaction to LY3471851 or its formula excipients, or

b. intolerance to TCS

[51] received any parenteral corticosteroid administered through intra-articular injection or intramuscular or IV injection within 2 weeks prior to study entry or within 6 weeks prior to planned baseline (Day 1) or are anticipated to require parenteral injection of corticosteroids during the study

Note

Intranasal or inhaled steroid use is allowed during the trial.

[52] received aldesleukin or any investigational IL-2 analog at any time

[53] received the following medications/treatments within 4 weeks prior to baseline (Day 1) or plan to continue use throughout the study:

a. oral systemic corticosteroids and leukotriene inhibitors

b. systemic immunomodulators, including, but not limited to, cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, and Janus kinase (JAK) inhibitors (tofacitinib, ruxolitinib)

c. any other systemic therapy used to treat AD or symptoms of AD (approved or off-label use), or

d. phototherapy, includes therapeutic phototherapy (psoralen plus ultraviolet A, ultraviolet B), excimer laser, or tanning beds

[54] history of organ or bone marrow transplant

[55] lymphoma, leukemia, or any malignancy within the past 5 years, with the following exceptions:

- basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years, or
- cervical carcinoma in situ, with no evidence of recurrence within the 5 years prior to baseline

[56] breast cancer within the past 10 years, or

[57] in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

[58] have a current or recent acute active infection. For at least 30 days prior to screening, patients must have no significant symptoms including fever of 100.5°F (38°C) or above, at screening or baseline, and/or signs of confirmed or suspected infection, and must have completed any appropriate anti-infective treatment.

[59] have had, within 6 months of screening, any of the following types of infection:

- Serious infections (requiring hospitalization, and/or IV antibiotic treatment)
- Opportunistic infections (as defined in Winthrop et al. 2015)
- Herpes zoster that is considered active and ongoing until all vesicles are dry and crusted over.
- Chronic infections (duration of symptoms, signs, and/or treatment of 6 weeks or longer)
- Recurring infection (including, but not limited to, herpes simplex, herpes zoster, recurring cellulitis, chronic osteomyelitis)
    - Patients with only recurrent, mild, and uncomplicated orolabial and/or genital herpes may be discussed with Lilly or Lilly-designated medical monitor for possible exemption from this exclusion criterion.

6.3. Lifestyle and/or Dietary Requirements

Throughout the study, patients may undergo medical assessments and review of compliance with requirements before continuing in the study.

6.3.1. *Meals and Dietary Restrictions*

There are no dietary restrictions.

6.3.2. *Contraception*

6.3.2.1. Highly Effective and Effective Methods of Contraception

Highly effective and effective methods of contraception for study patients, including men and their partners, and women of child-bearing potential and their partners, are listed below. As required, combine 1 highly effective with 1 effective method, or combine 2 effective methods, of contraception.

Highly effective methods of contraception (less than 1% failure rate)

- Combined oral contraceptive pill and mini-pill
- NuvaRing
- Implantable contraceptives
- Injectable contraceptives (such as Depo-Provera®)
- Intrauterine device (such as Mirena® and ParaGard®)
- Contraceptive patch – ONLY women less than 198 pounds (90 kg)
- Total abstinence
- Vasectomy – for men in clinical trials
- Fallopian tube implants (Essure®) if confirmed by hysterosalpingogram

Effective methods of contraception (use 2 forms combined except where noted)

- Male condom with spermicide[a]
- Female condom with spermicide[a]

[a] Male and female condoms should not be used in combination

- Diaphragm with spermicide
- Cervical sponge
- Cervical cap with spermicide

6.3.2.2. Men and Their Partners

Men, regardless of their fertility status, with nonpregnant women of child-bearing potential partners, must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use

condoms combined with 1 additional highly effective or effective method of contraception (see Section 6.3.2.1) for the entire study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus (predicted to be 50 days following the last dose of study drug plus 90 days).

Abstinence

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of the trial, and withdrawal are not acceptable methods of contraception.

Double-Barrier Method

Men and their partners may choose to use a double-barrier method of contraception. However, male and female condoms as a double-barrier method is not acceptable due to the high failure rate when these barrier methods are combined.

Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide.

Men with Pregnant Partners

Men with pregnant partners should use condoms during intercourse for the duration of the study and until the end of estimated relevant potential exposure in women of child-bearing potential, predicted to be 50 days following the last dose of the study drug plus 90 days.

Sperm Donation

Men should refrain from sperm donation for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 50 days following the last dose of study drug plus 90 days.

Same-Sex Relationship

Men who are in exclusively same sex relationships (as their preferred and usual lifestyle) are not required to use contraception.

6.3.2.3. Women of Child-Bearing Potential and Their Partners

Women of child-bearing potential must test negative for pregnancy and agree to the following contraception criteria for the entire study and for 30 days following the last dose.

Pregnancy Tests

Women of child-bearing potential must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to each exposure to study drug.

Abstinence or Same-Sex Relationship

If contraception is not to be used, women of child-bearing potential must agree to either remain abstinent (if complete abstinence is their preferred and usual lifestyle) or remain in a same-sex relationship (if part of their preferred and usual lifestyle) without sexual relationships with males. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of the trial, and withdrawal are not acceptable methods of contraception for this study.

Two Methods of Contraception Combined

Women of child-bearing potential and their male sexual partners must use 2 effective, or 1 effective and 1 highly effective, methods of contraception combined (see Section 6.3.2.1).

Male and female condoms as a double-barrier method is not acceptable due to the high failure rate when these barrier methods are combined.

Barrier protection methods without concomitant use of a spermicide are not reliable or acceptable. Thus, each barrier method must include use of a spermicide.

6.3.2.4. Women Not of Child-Bearing Potential

Women not of child-bearing potential may participate and include those who are

- infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or
- postmenopausal, defined as either
  - at least 50 years of age with an intact uterus, not on hormone therapy, who has had either
    - cessation of menses for at least 1 year, or
    - at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 mIU/mL
  - at least 55 years of age not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea, or
  - at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

6.4. Screen Failures

Patients who do not meet the criteria for participation in this study (screen failure) may not be rescreened until at least 2 weeks after the date of their previous screen failure. Patients may be rescreened 1 time and require a new identification number. Any patient with AD who has a screening laboratory assessment that falls outside of the protocol-specified inclusion/exclusion parameters may (based on investigator judgment) undergo repeat laboratory testing 1 time without being considered as a screen failure (this does not include TB testing).

If rescreening is performed, the individual must sign a new ICF each time and will be assigned a new identification number.

7. Treatment

7.1. Treatment Administered

LY3471851 drug product is a sterile solution for SC injection. The placebo dosing solution is 0.9% sodium chloride for injection (US Pharmacopeia). The LY3471851 drug product and placebo dose preparation for injection will be conducted by the unblinded pharmacist.

Study drug will be administered as an SC injection.

- The drug product will be administered using no more than [redacted] injections, with a volume of no more than [redacted] mL per injection (maximum total volume [redacted] mL).
- Injection sites selected for SC administration should be in the abdominal region approximately 5 cm from the umbilicus, and the injections should be administered with the needle applied at approximately 45° with pinching of the skin.
- When more than [redacted] injection will be administered on a given day, each additional injection should be given to the next abdominal quadrant following a clockwise sequence (only [redacted] injection per quadrant), and all planned injections to deliver the full intended dose should be administered within a maximum of 5 minutes.
- If there is a lingering ISR in one abdominal area, that site is not used until the ISR has resolved (so as not to confuse the AE assessment).
- Subcutaneous administration of study drug should be performed by a limited number of individuals for consistency.

7.1.1. *Packaging and Labeling*

LY3471851 and placebo will be supplied to the study site by Lilly or its designee. Clinical trial materials will be labeled according to the country's regulatory requirements. All IPs will be stored, inventoried, reconciled, and destroyed according to applicable regulations. Clinical trial materials are manufactured in accordance with current good manufacturing practices.

LY3471851 is supplied for clinical trial use as a solution in vial. Each [redacted]-mL vial is manufactured to deliver [redacted] mg of LY3471851. Vials will be supplied in cartons, with the appropriate quantity specific to the planned dispensing schedule of the IP.

Placebo for all cohorts is 0.9% sodium chloride.

When prepared for dosing according to instructions, it will not be possible to distinguish between LY3471851 and placebo.

Investigational products will be prepared by an unblinded pharmacy staff or pharmacist who is not involved in any other study-related procedures.

7.2. Method of Treatment Assignment

On Day 1 of each cohort period, the patients who meet all screening and eligibility criteria will be randomized in a 4:1 ratio to either LY3471851 or placebo within the dose group. Assignment

to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The block sizes will not be known to the investigator.

7.3. Blinding

The investigator, patients, and all study site and Lilly personnel involved in study activities will be blinded, with the following exceptions:

- those involved in drug preparation and accountability
- the Statistical Analysis Center (individuals from the statistical and PK group [which may include both Lilly and CRO personnel]) who will produce tables, figures, and listings for the interim analysis, and
- the assessment committee [AC] (Section 10.3.7).

The individuals or functional groups who are planned to be unblinded will be identified in the study unblinding plan. In certain rare circumstances when knowledge about the study drug received is required to adequately manage serious safety concerns or AEs reported by the patient, for expedited reporting of SAEs to the regulatory authorities, or evaluation of severe AEs per the stopping rules described in Section 8.1, it may be necessary to unblind a patient's treatment regimen before all outcome assessments have been performed. If the investigator believes that the study blind needs to be broken for a patient, the investigator must contact the Lilly medical monitor, except in the case of an emergency (see below). Unblinding will follow Lilly's internal procedures for unblinding and associated documentation. If the blind is broken, details surrounding the breaking of the blind (e.g., date, time, and reason) are to be recorded in the patient's study file. Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All unblinding events are recorded and reported using the IWRS. If a patient's treatment assignment becomes known to the patient or investigator, then that patient should be discontinued early from the study.

LY3471851 will be supplied open-label to the study site.

An unblinded pharmacist at each study site, who is not involved in any other aspect of the study conduct, will be designated to manage and account for LY3471851, and to prepare the LY3471851 or placebo dosing solution for blinded administration to each patient. The pharmacist will ensure that all other study personnel and patients remain blinded to treatment assignment.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. The patient's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

CCI [redacted]

7.5. Preparation/Handling/Storage/Accountability

LY3471851 and placebo must be stored per instructions provided on the IP packaging in a secured site with restricted access. LY3471851 must be stored in accordance with all federal, state, and local regulations.

Study drug accountability must be recorded by the study site's unblinded pharmacist or designee and verified by the sponsor's unblinded designee/monitor who is not involved with the day-to-day operational activities of the study. The pharmacist or designee will

- maintain up-to-date accountability records of product delivery, product inventory, patient administration, destruction, and/or return of product in the study accountability log
- maintain documentation of the study drug storage unit temperature monitoring
- notify the sponsor if a study drug shipment has a temperature monitoring device indicating that the temperature was out of range or if local storage of the study drug experiences an event, including storage temperature being out of range, and
- return/destroy unused study drug as per sponsor's instructions.

All doses of LY3471851 or placebo will be administered at the site by appropriately qualified and trained clinical staff.

LY3471851 will be prepared for injection by an unblinded pharmacist, or other qualified unblinded personnel, according to the instructions in the Pharmacy Manual. Individual patients may receive up to C injections to achieve the necessary dose. The preparation of the exact dose and volume injected will be recorded for each individual patient. For each dose, the actual date and time, total drug amount, and volume of drug administered will be recorded in the source documents and electronic case report forms (eCRFs).

7.6. Treatment Compliance

The IP will be administered at the study site, and documentation of treatment administration will occur at the site.

7.7. Concomitant Therapy

7.7.1. *Prior Medications*

Medications taken in the year prior to screening must be documented in the source documents and on the concomitant medications log eCRF with the following:

- the name of the medication (generic name)
- indication
- dose
- frequency of administration
- route of administration, and
- start and stop dates of administration.

Use of live or live attenuated vaccines is permitted up to 4 weeks before screening. Use of BCG vaccine is permitted up to 12 months before screening. A nonlive or inactivated vaccine is allowed if it is received at least 2 weeks before randomization in the study or after the last visit. As detailed in Exclusion Criterion [39], inactivated influenza ("Flu"), pneumococcal, and SARS-CoV-2 vaccines are allowed during the study.

7.7.2. *Concomitant Medications*

Any medication taken by a patient during the course of the study and the reason for its use must be documented in the source documents and the concomitant medications log eCRF with the following:

- the name of the medication (generic name)
- indication
- dose
- frequency of administration
- route of administration, and
- date of administration.

Treatment with concomitant therapies for AD during the study is permitted only as described below.

- Daily use of emollients is required as background treatment. Moisturizers with additives such as antipruritics or antiseptics are not permitted. If daily applications are missed, it will not be considered a protocol violation.
- Patients should not apply emollients on the day of their study visit prior to the procedures to allow adequate assessment of skin dryness.
- Oral and topical antihistamines are allowed.

All medications and treatments (e.g., IV solution, blood transfusion) for AEs and SAEs must be documented in the source documents and on the concomitant medications log through the Last Study Visit (Day 134 for EASI 50 nonresponders and Day 169 for EASI 50 responders).

7.7.3. *Prohibited Medications*

The following listed treatments are prohibited. If a prohibited treatment listed here is required, the study drug should be discontinued.

- Topical treatments: TCS, topical immune modulators (e.g., tacrolimus or pimecrolimus) or PDE-4 inhibitor (e.g., crisaborole) except when given as rescue therapy as described in Section 7.7.4.
- Systemic corticosteroids: oral or parenteral corticosteroids (intramuscular, intra-articular or IV). Note: Intranasal or inhaled steroid use is allowed during the trial.
- Synthetic (oral) immunomodulators, including, but not limited to
    - JAK inhibitors (e.g., tofacitinib, ruxolitinib)
    - cyclosporine
    - methotrexate
    - mycophenolate mofetil, or
    - azathioprine
- Biologics: Immunomodulating monoclonal antibodies (including but not limited to dupilumab, ustekinumab, omalizumab). Inactivated influenza and pneumococcal vaccinations are allowed. SARS-CoV-2 vaccinations are allowed, as well as biologic treatments for COVID-19, such as bamlanivimab, remdesivir, baricitinib, casirivimab, and imdevimab, where authorized by local regulatory bodies.
- Leukotriene inhibitors
- Phototherapy, including
    - therapeutic phototherapy (psoralen ultraviolet-A, ultraviolet-B)
    - excimer laser, or
    - self-treatment with tanning beds
- Any investigational therapy that is not LY3471851
- Bleach baths
- Allergen immunotherapy
- Receipt of any investigational study drug within 4 weeks or 5 half-lives (whichever is greater) before screening, and any other investigational study drug other than LY3471851 through the Last Study Visit (Day 134 for EASI 50 nonresponders and Day 169 for EASI 50 responders).
- Received aldesleukin or any investigational IL-2 analog at any time.

7.7.4. *Rescue Therapy*

Rescue therapy is permitted for patients at any time after Day 21 according to investigator's judgment.

Choice of rescue therapy treatment

- Triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment. In the event where either of these topical formulations is not available, an alternate, equivalent potency TCS cream and/or ointment may be used.
- Investigators may also select to use TCNIs and/or crisaborole where approved. If TCNIs are prescribed, use should be limited to problem areas only (e.g., face, neck, skin folds, genital areas).
- On the days of study visits, topical therapy should not be applied before the patient has undergone all study procedures and clinical evaluations to allow adequate assessment of skin dryness.
- Patients rescued to topical therapy will continue to take IP and use of rescue therapy will be documented in the eCRF.

In patients who do not improve sufficiently with the prescribed provided rescue topical therapy after 7 days, a higher potency TCS may be used and IP may continue. It is recommended that if a patient reaches "clear" to "almost clear" skin after topical rescue, then medium- and/or high-potency TCS and TCNI should be stopped, and low–potency TCS (e.g., hydrocortisone 2.5% ointment) should be used once daily for an additional 7 days, then stopped. If lesions return, patients can be re-treated with TCS with or without TCNIs and/or crisaborole as before at the discretion of the investigator.

If topical rescue therapy as described earlier fails to sufficiently control symptoms of AD and if the investigator determines that a patient requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of AD but is contraindicated in this study, the patient should be discontinued from the study. In such cases, discontinuation from the study occurs prior to introduction of the new agent.

Investigators should make every attempt to conduct efficacy and safety assessments immediately before administering any rescue treatment. An unscheduled visit can be used for this purpose if necessary.

7.8. Treatment after the End of the Study

Not applicable.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. *Rules for Stopping Dosing in Individual Patients*

Should a treatment-emergent SAE, or the AEs described below occur, dosing and enrollment for the individual patient will be suspended and the study team will consult the AC (see Section 10.3.7) for a recommendation.

Possible recommendations include:

- resume dosing or
- stop further dosing.

Adverse events requiring stopping dosing in an individual include:

- The patient experiences any of the following after receiving the first dose:
    - a treatment-emergent SAE that in the opinion of the investigator is related to the study drug or
    - a severe or life-threatening treatment-emergent AE that in the opinion of the investigator is related to the study drug.
- The patient experiences clinical manifestations of moderate-to-severe cytokine release syndrome, defined by a constellation of symptoms including fever, nausea, chills, hypotension, tachycardia, rash, headache, chest discomfort, fatigue/generalized weakness, and dyspnea/shortness of breath, which typically occur in close temporal relationship with study drug administration in the absence of another obvious cause (e.g. infection)
- The patient has 1 of the following laboratory abnormalities detected and confirmed, with no other obvious cause in the opinion of the investigator:
    - hemoglobin <8.0 g/dL
    - neutrophils <0.75 x 10^9/L
    - WBCs <2.0 x 10^9/L
    - total lymphocytes <0.4 x 10^9/L
    - platelets <50 x 10^9/L
- The patient has eosinophil counts as follows:
    - Asymptomatic patients with an eosinophil count >3000 cells/uL should have a repeat measurement to confirm the count, and if confirmed, should be discontinued from study treatment, or

  - Patients with eosinophil counts >1500 cells/uL and signs and symptoms of target organ involvement (e.g., involving the skin, airway, gastrointestinal tract, liver, cardiac or nervous system) should be discontinued from study medication and undergo appropriate medical evaluation.

- Any other AE/clinical findings that in the view of the sponsor warrants convening the AC.

Discontinuation of the investigational product for abnormal liver tests should be considered by the investigator when a patient meets 1 of the following conditions after consultation with the Lilly designated medical monitor:

- ALT (alanine aminotransferase) AST (aspartate aminotransferase) >[5X for healthy subjects, 8X for patients] ULN (upper limit of normal)
- ALT or AST >[3X ULN for healthy subjects, 5X ULN for patients] sustained for more than 2 weeks or
- ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or INR >1.5 or
- ALT or AST >3X ULN the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP (alkaline phosphatase) >3X ULN
- ALP>2.5X ULN and TBL >2X ULN
- ALP>2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Additional rules governing hepatic safety and assessment of suicide risk may be found in Sections 8.2 and 9.4.5.

8.1.2. *Rules for Stopping Dosing and Enrollment in a Cohort*

Should a treatment-emergent SAE, or the AEs described below occur, dosing and enrollment in the cohort will be suspended and the study team will consult the AC (the composition of the AC is described in Section 10.3.7), which has access to unblinded study data, for a recommendation.

Possible recommendations include:

- resume dosing/enrollment in the cohort,
- move to a lower dose, or
- stop study until further evaluation.

Adverse events requiring stopping dosing and enrollment in a cohort include:

- 2 or more patients experience any of the following:
  - a treatment-emergent SAE that in the opinion of the investigator is related to the study drug or

  - a severe or life-threatening treatment-emergent AE that in the opinion of the investigator is related to the study drug.

- 2 or more patients experience clinical manifestations of moderate-to-severe cytokine release syndrome, defined by a constellation of symptoms including fever, nausea, chills, hypotension, tachycardia, rash, headache, chest discomfort, fatigue/generalized weakness, and dyspnea/shortness of breath, which typically occur in close temporal relationship with study drug administration in the absence of another obvious cause (e.g. infection)
- 2 or more patients have 1 of the following laboratory abnormalities detected and confirmed, with no other obvious cause in the opinion of the investigator:
  - hemoglobin <8.0 g/dL
  - neutrophils <0.75 x 10^9/L
  - WBCs <2.0 x 10^9/L
  - total lymphocytes <0.4 x 10^9/L
  - platelets <50 x 10^9/L, or
- Any other AE/clinical findings that in the view of the sponsor warrants convening the AC.

The AC will document all decisions of their meetings.

8.1.3. *Discontinuation of Inadvertently Enrolled Patients*

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly clinical research physician (CRP) and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without continued treatment with IP.

8.2. Discontinuation from the Study

Patients can be withdrawn from the study for any of the following reasons:

- noncompliance of the patient with protocol-mandated procedures based on agreement of both the investigator and sponsor,
- continued participation is no longer in the patient's best interest, in the opinion of the investigator,
- enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study,
- the patient is lost to follow-up (see Section 8.3),

- patient's own decision to discontinue from the trial for any reason,
- it is determined that a patient should be discontinued from the study after responding on the C-SSRS as follows:
    - answers "yes" to Question 4 or 5 on the "Suicidal Ideation" portion of the C-SSRS, or
    - has suicide-related behavior as recorded on the C-SSRS,
- Note: It is recommended that the patient be assessed by an appropriately trained professional to assist in deciding whether the patient is to be discontinued from using the study treatment and the study, as well as what type of medical treatment and follow-up are appropriate.death, or
- the study is terminated by the sponsor.

Patients who discontinue before completing the Day 85 assessment may be replaced at the discretion of the sponsor. The replacement patient should be assigned to the same treatment allocation as the discontinued patient.

Subjects who discontinue the study early will have end-of-study procedures as outlined in Visit ED in the Schedule of Activities (Section 2).

Patients who discontinue due to AEs will be followed up for safety until resolution or stabilization of all AEs attributable to the study drug (see Section 9.2).

8.3. Patients Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site. Specifically, study personnel must contact the patient at least twice through phone and once through mail with documented receipt, before considering the patient "lost to follow-up".

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing.

Appendix 2 lists the laboratory tests that will be performed for this study.

Appendix 5 provides a summary of the maximum number of venipunctures and blood volumes for all blood sampling during the study.

9.1. Efficacy Assessments

9.1.1. *Disease Activity Measures for Patients with Atopic Dermatitis*

The following disease activity measures described will be collected at the times shown in the Schedule of Activities (Section 2). Only the EASI score, BSA, and the IGA score will be collected at screening.

- **Eczema Area and Severity Index:** The EASI assesses the extent of disease at 4 body regions and measures 4 clinical signs: (1) erythema, (2) induration/papulation, (3) excoriation, and (4) lichenification each on a scale of 0 to 3. The EASI confers a maximum score of 72. The EASI evaluates 2 dimensions of AD: extent of disease and clinical signs (Hanifin et al. 2001).
- **Percentage BSA** affected by AD will be derived as part of the EASI assessment. Body surface area is the percentage involvement of AD on a scale from 0% (no involvement) to 100% (full involvement), where 1% corresponds to the size of the patient's hand (including the palm and fingers) (Scarisbrick and Morris 2013).
- **Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD)**: The IGA used in this study, the vIGA-AD (referred to as the IGA throughout the protocol) measures the IGA of the patient's overall severity of their AD, based on a static, numeric 5-point scale from 0 (clear skin) to 4 (severe disease). The score is based on an overall assessment of the degree of erythema, papulation/induration, oozing/crusting, and lichenification. See Appendix 6.

9.1.2. *Patient-Reported Outcome/Quality-of-Life Measures for Patients with Atopic Dermatitis*

The following patient-reported outcomes/quality-of-life (QoL) measures described will be collected at the times shown in the Schedule of Activities (Section 2).

- **Dermatology Life Quality Index (DLQI):** The DLQI is a simple, patient-administered, 10-item, validated, QoL questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period of this scale is over the "last week." Response categories include "not at all," "a lot," and "very much," with corresponding scores of 1, 2, and 3, respectively, and unanswered ("not relevant") responses scored as 0. Scores range from 0 to 30 with higher scores indicating greater impairment of QoL. A DLQI total score of 0 to 1 is

considered as having no effect on a patient's health-related QoL (Hongbo et al. 2005), and a 4-point change from baseline is considered as the minimal clinically important difference threshold (Khilji et al. 2002; Basra et al. 2015).

- **Patient-Oriented Eczema Measure (POEM):** The POEM is a simple, 7-item, patient-administered scale that assesses disease severity in children and adults. Patients respond to questions about the frequency of 7 symptoms (itching, sleep disturbance, bleeding, weeping/oozing, cracking, flaking, and dryness/roughness) over the past week. Response categories include "No days," "1-2 days," "3-4 days," "5-6 days," and "Every day" with corresponding scores of 0, 1, 2, 3, and 4, respectively. Scores range from 0 to 28 with higher total scores indicating greater disease severity (Charman et al. 2004).
- **Itch Numerical Rating Scale (Itch NRS):** The Itch NRS is a patient-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no itch" and 10 representing "worst itch imaginable." Overall severity of a patient's itching is indicated by selecting the number that best describes the worst level of itching in the past 24 hours (Naegeli et al. 2015; Kimball et al. 2016).

9.1.3. *Skin Biopsies for Patients with Atopic Dermatitis*

Skin biopsies will be required for all patients still in the study and will be performed at baseline (Day 1), Day 22, Day 85, and Day 337. On Days 1 and 85, lesional and nonlesional biopsies will be collected. On Days 22 and 337 or ED visit for subjects in responder follow-up, whichever is earlier, only lesional biopsies will be collected.

Skin biopsies will be collected at the times shown in the Schedule of Activities (Section 2). A local anesthetic will be applied, and two 4-mm skin-punch biopsies will be obtained from the same target lesion on Days 1, 22, 85, and 337 (or responder ED). If the lesion has resolved, biopsy should be taken from the cleared skin in that area. The biopsies will be used for histological, immunohistochemical, mRNA, and epigenetic marker immunomonitoring analyses.

Detailed instructions for handling the biopsy tissue at the study site will be provided in a laboratory manual by the sponsor. These biopsies will be analyzed in relation to the changes in disease activity measures following treatment with LY3471851.

Biopsies will be retained for a maximum of 15 years after the last patient visit, or for a shorter period, if local regulations and ethical review boards (ERBs) allow, at a facility selected by the sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of the compound. Samples may be used for research on LY3471851, disease process, pathways associated with disease, mechanism of action, response to treatment with LY3471851, and/or research method, or in validating diagnostic tools or assay(s).

Technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. Existing approaches, including mutation profiling, copy number variability analysis, gene expression assays, multiplex assays, and/or immunohistochemistry may be

performed on these tissue samples to assess potential associations between these biomarkers and clinical outcomes.

9.1.4. *Clinical Photography*

Documentation of the clinical response will be permitted through sequential photography of a selected lesion before, during, and after treatment with LY3471851 for all patients. Clinical photographs will be collected at the times shown in the Schedule of Activities. Detailed instructions for obtaining clinical photographs will be provided in a study manual.

9.2. Adverse Events

The investigator will record all relevant AE/SAE information in the eCRF, whether reported by the patient or observed by study staff.

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the IP or the study, or that caused the patient to discontinue the IP before completing the study. The patient should be followed up until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

After the ICF is signed, study site personnel will record, via eCRF, the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a potential cause and effect relationship between the IP, study device and/or study procedure, and the AE.

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

Events related with the injection sites will be captured as a study endpoint and should not be reported as AEs.

If a patient's IP is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF.

9.2.1. *Grading Severity of Adverse Events*

Severity and seriousness of an AE are not synonymous. Severity is grading the intensity of an event. Seriousness of an event is based on the subject/event outcome.

In this study, AEs will be graded as mild, moderate, or severe using the following definitions:

- Mild: Condition does not interfere with activities of daily living. Use of a concomitant therapy can still be consistent with a mild severity as long as the patient is able to carry out activities of daily living.
- Moderate: Condition interferes with activities of daily living, but patient is able to compensate and do the daily activities that must be done (e.g., go to work, school, shop for groceries, etc.)
- Severe: Condition prevents patients from completing activities of daily living, confined to bed or must miss work or school.

Adverse events will be reported with an individual start and stop date for each AE severity grade. Please refer to the eCRF Completion Guidelines for detailed reporting instructions.

9.2.2. *Serious Adverse Events*

An SAE is any AE from this study that results in 1 of the following

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (ie, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect, or
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above.

Study site personnel must alert the Lilly clinical pharmacologist (CP)/CRP, or its designee, of any SAE as soon as practically possible.

Additionally, study site personnel must alert Lilly Global Patient Safety, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed up with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Although all AEs are recorded in the eCRF after signing informed consent, SAE reporting to the sponsor begins after the patient has signed informed consent and has received IP. However, if an

SAE occurs after signing informed consent, but prior to receiving IP, AND is considered Reasonably Possibly Related to a study procedure then it MUST be reported.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued from and/or completed the study (the patient summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Pregnancy (maternal or paternal exposure to IP) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

9.2.2.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator reports as related to IP or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.3. *Complaint Handling*

Lilly collects product complaints on IPs and drug delivery systems used in clinical trials to ensure the safety of study patients, monitor quality, and to facilitate process and product improvements.

Patients should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the IP so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY3471851 is considered any dose higher than the dose assigned through randomization. The treatment for suspected overdose is supportive care.

9.4. Safety

9.4.1. *Laboratory Tests*

Clinical laboratory tests consist of hematology, chemistry, and urinalysis (clean catch). Hepatic function (including AST, ALT, gamma-glutamyl transferase, ALP, lactate dehydrogenase, and TBL) will be tested as part of the chemistry panel. Blood and urine samples will be collected at the times specified in the Schedule of Activities (Section 2). A list of tests that will be performed is in Appendix 2. Instructions for the collection and processing of samples will be provided in a Laboratory Manual.

These clinical laboratory tests will be performed by a central laboratory vendor, unless otherwise denoted. Additional clinical laboratory tests, including local tests, may be performed at any time during the study as determined necessary by the investigator for immediate patient management/safety or as required by local regulations.

Clinical laboratory abnormalities will only be reported as AEs if they are deemed clinically significant by the investigator and/or associated with signs and symptoms, require treatment, or require nonstudy protocol follow-up.

Serology testing for hepatitis B surface antigen, hepatitis B core antibody positive, anti-HCV, HCV RNA as appropriate, and HIV will be performed at screening.

In the event of anaphylaxis or generalized urticaria, additional laboratory samples should be collected as close to the event as possible (ideally in 1 to 2 hours and no more than 12 hours after the event) to evaluate tryptase, complement levels, cytokines, antidrug antibodies (ADAs), and PK, whenever possible. If a tryptase sample is not obtained in 1 to 2 hours of the event, urine collection (24-hour urine collection or spot urine sample) for N-methylhistamine testing should be obtained. Follow-up samples to re-evaluate those measurements should be obtained at the next regularly scheduled visit or after 4 weeks, whichever is later. Specific instructions for the collection and handling of samples will be provided by the sponsor.

Unless otherwise stated in subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.4.2. *Vital Signs*

Vital sign measurements, including respiratory rate (RR; breaths/minute), HR (bpm), and BP (mm Hg) will be taken while the patient is supine, and has been resting for at least 5 minutes, and body temperature (°C) will be taken at the times specified in the Schedule of Activities (Section 2). On days when the study drug is administered, vital sign measurements will be taken predose and at 2 hours ±15 minutes postdose.

If vital sign measurements are out of range, 1 repeat will be allowed. Vital sign measurements should be considered out of range if

- RR: <16 or >20 breaths/minute
- HR: <40 or >100 bpm
- BP systolic: >140 or <90 mm Hg
- BP diastolic: >90 or <50 mm Hg, or
- Fever: >38°C (100.4°F).

Clinically significant findings will be documented as AEs/SAEs. Assessments of a patient's health and safety that are not specified in the protocol may be performed. The results of these assessments may be recorded as AEs, as determined by the investigator and consistent with Section 9.2.

9.4.3. *Electrocardiograms*

For each patient, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section 2). ECGs should be recorded before collecting any blood for safety or PK tests. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of additional ECGs at a particular time point is allowed to ensure high quality records.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the study site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria at the relevant visit(s) and for immediate patient management, should any clinically relevant findings be identified.

If a clinically significant finding is identified (including, but not limited to changes in QT/QTc interval from baseline) after enrollment, the investigator in conjunction with the sponsor will determine if the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly.

A cardiologist at the central ECG laboratory will then conduct a full overread on ECGs (including all intervals). A report based on data from this overread will be issued to the investigative site. All data from the overreads will be placed in the Lilly database for analytical and study report purposes.

If there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the investigator's (or qualified designee's) interpretation will be used for study entry and immediate subject management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes.

9.4.4. *Other Tests*

9.4.4.1. Injection-Site Assessments

According to the Schedule of Activities (Section 2), injection-site assessments will be performed at the end of each visit on Day 1 through Day 99 and at the ED visit, if occurs. The investigator will ask the patient if she/he had any injection-site concern since the preceding visit or, when assessed on Day 1, since the first injection. Patient's responses will be recorded per the Injection Site Assessment and Pain Visual Analog Scale tools to capture specific information relating to an injection site if there is injection-site concern and/or a reaction. Any event relating to an injection site will be captured as a study exploratory endpoint and not be recorded as an AE. Any

new and/or ongoing ISR symptoms from previous visits require injection-site assessment and visual analog scale to be completed.

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9.4.4.2. Physical Examination

Physical examinations will include an examination of all major organ systems including the following categories:

general appearance	hematologic/lymphatic	gastrointestinal
head	respiratory	extremities
eyes	cardiovascular	integumentary
ear/nose/mouth/throat	chest	psychiatric
neck	abdomen	

Prior to the dose of study drug on Day 1, clinically significant findings that are present are to be documented as medical history in the eCRF. After the dose of study drug on Day 1, clinically significant findings that meet the definition of an AE are to be recorded as an AE in the eCRF.

9.4.4.3. Pregnancy Test

A pregnancy test will be performed on all women of child-bearing potential at the times shown in the Schedule of Activities (Section 2). A serum pregnancy test will be employed at the screening visit only, and a urine pregnancy test will be employed at all other visits. Negative pregnancy test results must be obtained at screening and baseline (Day 1) to be eligible for the study.

9.4.5. *Safety Monitoring*

9.4.5.1. Hepatic Safety

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly CP or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

Additional safety data should be collected, as per the July 2009 FDA "Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation" documentation, if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests
- elevation of serum TBL to ≥2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests
- patient discontinued from treatment due to a hepatic event or abnormality of liver tests, or
- hepatic event considered to be an SAE.

9.4.5.2. Columbia Suicide Severity Rating Scale

The C-SSRS captures the occurrence, severity, and frequency of suicidal ideation and/or behavior during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if suicidal ideation and/or behavior occurred. The C-SSRS is administered by appropriately trained site personnel. The tool was developed by the National Institute of Mental Health trial group for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. For this study, the scale has been adapted (with permission from the scale authors) to include only the portion of the scale that captures the occurrence of the 11 preferred ideation and behavior categories.

The nonleading AE collection should occur prior to the collection of the C-SSRS. If a suicide-related event is discovered during the C-SSRS but was not captured during the nonleading AE collection, sites should not change the AE form. If an event is serious or leads to discontinuation, this is an exception where the SAE and/or AE leading to discontinuation should be included on the AE form and the process for reporting SAEs should be followed.

9.4.5.3. Self-Harm Supplement and Follow-up Forms

Suicide-related events (behavior and/or ideations) will be assessed and evaluated with each administration of the C-SSRS. The Self-Harm Supplement Form is a single question to enter the number of suicidal behavior events, possible suicide behaviors, or nonsuicidal self-injurious behaviors. If the number of behavioral events is greater than zero, it will lead to the completion of the Self-Harm Follow-up Form. The Self-Harm Follow-up form is a series of questions that provides a more detailed description of the behavior cases.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine the plasma concentrations of LY3471851. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Drug concentration information that may unblind the study will not be reported to study sites or blinded personnel until the study has been unblinded.

9.5.1. *Bioanalysis*

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of LY3471851 will be assayed using a validated PK assay. Analyses of samples collected from patients who received placebo are not planned.

Bioanalytical samples collected to measure IP concentrations will be retained for a maximum of 1 year following last patient visit for the study. During this time, samples remaining after the bioanalysis may be used for exploratory metabolism studies or exploratory analyses such as bioanalytical assay validation or cross-validation exercises.

9.6. Pharmacodynamics

The PD parameters include changes in T-cell subsets.

Blood and tissue for PD analysis will be collected as shown in the Schedule of Activities (Section 2).

The sample(s) will be stored for a maximum of 1 year after the last patient visit for the study at a facility selected by the sponsor.

9.6.1. *Immunogenicity Assessments*

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine antibody production against LY3471851. To interpret the results of immunogenicity, a venous blood PK sample will be collected at the same time points to determine the plasma concentrations of LY3471851. All samples for immunogenicity during the treatment period will be taken predose. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Treatment-emergent ADAs (ADAs) are defined in Section 10.3.6. Patients who are TE-ADA positive at the last scheduled assessment or discontinuation visit may have additional samples taken at 3, 6, 9 (optional), and 12 months post-last assessment until the titer returns to within 2-fold of baseline titer or for up to 1 year, whichever is less. Patients followed up for at least 1 year since last dose that have not returned to baseline as defined above will be assessed for safety concerns. If no clinical sequelae is recognized by the clinical team, then no further follow up will be required.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of LY3471851 at a laboratory approved by the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of LY3471851.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and ERBs allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the LY3471851 and/or disease state. Any samples remaining after 15 years will be destroyed.

9.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities, where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable exposure or response to LY3471851 and to investigate genetic variants thought to play a role in AD. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and/or ERBs/institutional review boards (IRBs) impose shorter time limits, for the study at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of the compound. Samples may be used for research on LY3471851, disease process, pathways associated with AD, mechanism of action of LY3471851, response to treatment with LY3471851, and/or research method or in validating diagnostic tools or assay(s) related to AD.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome-wide association studies, multiplex assays, and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.

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9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Approximately 25 patients with AD will be enrolled in each cohort for a maximum of 2 cohorts (50 patients). This will allow approximately 20 patients completing the study for a maximum of 2 cohorts (40 patients). The sample size is customary for Phase 1 studies evaluating safety and PK, and is not powered on the basis of statistical hypothesis testing.

Patients who discontinue the study before completing the Day 85 assessment may be replaced at the discretion of the sponsor. The replacement patient should be assigned to the same treatment allocation as the discontinued patient.

A key clinical assessment is the percentage change from baseline in EASI at Week 12. With a sample size of approximately 20 patients completing the study per cohort, randomized in a 4:1 ratio to LY3471851 or placebo, the half-width of the 95% confidence interval of the percentage change from baseline in EASI between LY3471851 and placebo will be within 22% with a standard deviation assumption of 20%.

10.2. Populations for Analyses

Safety analysis population

All randomized patients who receive at least 1 dose of study drug will be included according to the randomized treatment, regardless of whether they have completed all protocol requirements.

PK analysis population

The PK analysis population will consist of all randomized patients who receive LY3471851 and have adequate PK data to permit a meaningful analysis.

PD analysis population

Pharmacodynamic analyses will be conducted on the full analysis set, which includes all evaluable data from all patients receiving at least 1 dose of study drug according to the randomized treatment. Pharmacodynamics, immunogenicity, cytokine, and disease activity measures will be analyzed on this population.

10.2.1. *Study Participant Disposition*

The number of randomized patients will be summarized by treatment group. Frequency counts and percentages of all patients who complete the study or discontinue early will be presented for each treatment group.

10.2.2. *Study Participant Characteristics*

Demographics and baseline characteristics including age, race, ethnicity, weight, height, BMI, and sex at birth will be summarized descriptively.

10.3. Statistical Analyses

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Data listings and summary statistics will be provided for safety, PD, PK, and clinical data by treatment group over time. For continuous variables, summary statistics include the mean, standard deviation, minimum, maximum, median, and number of observations. For categorical variables, frequency counts and percentages will be provided.

The data from placebo groups will be pooled across cohorts as 1 placebo group.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate. Complete details of the planned analyses will be documented in the statistical analysis plan (SAP).

Statistical considerations and methodology for handling missing data will be detailed in the SAP.

10.3.1. *Safety Analyses*

The safety analysis will be based on the safety population. For patients who receive placebo in either cohort, the safety data will be pooled. Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events will be defined as AEs that occur on or after receiving the first dose of study drug. The frequency of TEAEs will be tabulated using MedDRA by system organ class and preferred terms and treatment. In addition, by-patient listings will be provided for TEAEs and SAEs. Clinical laboratory results, vital signs, and ISRs will also be summarized.

10.3.2. *Pharmacokinetic Analyses*

The following PK parameters will be calculated from plasma concentration-time data after the first dose using standard noncompartmental methods of analysis, as data permit:

- AUC
- C_{max}, and
- time to maximum observed plasma concentration (T_{max})

In addition, trough plasma LY3471851 concentrations will be summarized after repeat dosing. Pharmacokinetic parameters for LY3471851 will be tabulated and summarized by dose group using descriptive statistics.

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10.3.3. *Pharmacodynamic Analyses*

The observed value and the change from baseline for biomarkers and cytokines will be summarized by treatment over time using summary statistics and will be explored graphically.

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10.3.5. *Disease Activity Measures*

Clinical endpoints over time will be summarized by treatment. Treatment comparisons of continuous clinical endpoints will be explored using mixed effects for repeated measures. For categorical clinical data, endpoints will be explored using Fisher exact test. The details will be provided in the SAP.

The disease activity data are exploratory measures. No formal statistical inference based on efficacy is planned to be made. No adjustment of Type I error will be performed.

10.3.6. *Evaluation of Immunogenicity*

The frequency and percentage of patients with preexisting ADAs and with TE-ADAs to LY3471851 will be tabulated. Treatment-emergent-ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). For the TE-ADA$^+$ patients the distribution of maximum titers will be described. The frequency of neutralizing antibodies may also be tabulated in TE-ADA$^+$ patients if assessed.

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[redacted]

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AC	assessment committee
AD	atopic dermatitis
ADA	antidrug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BCG	bacille Calmette-Guerin
BMI	body mass index
BP	blood pressure
BSA	body surface area
C_{max}	maximum observed plasma concentration
CP	clinical pharmacologist
CRP	clinical research physician
CRS	cytokine release syndrome
C-SSRS	Columbia Suicide Severity Rating Scale
DLQI	Dermatology Life Quality Index
DLT	dose-limiting toxicity
EASI	Eczema Area and Severity Index
EASI 50	patient EASI score reduced by at least 50% relative to their baseline score
ECG	electrocardiogram
eCRF	electronic case report form
ERB	ethical review board

FDA	Food and Drug Administration
FoxP3	forkhead box P3
GCP	good clinical practice
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IGA	Investigator Global Assessment
IL-2	interleukin 2
IP	investigational product
IRB	Institutional Review Board
ISR	injection-site reaction
IV	intravenous
IWRS	interactive web-response system
MAD	multiple-ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
NK	natural killer
NOAEL	no-observed-adverse-effect level
NRS	Numeric Rating Scale
PD	pharmacodynamic(s)
PDE 4	phosphodiesterase type 4
PEG	polyethylene glycol
PK	pharmacokinetic(s)
POEM	Patient-Oriented Eczema Measure
PsO	psoriasis

QoL	quality of life
RR	respiratory rate
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SLE	systemic lupus erythematosus
TB	tuberculosis
TBL	total bilirubin level
TCNI	topical calcineurin inhibitor
Tcon	conventional T
TCS	topical corticosteroid
TEAE	treatment emergent adverse event
TRAE	treatment-related AE
T_{max}	time to maximum observed plasma concentration
Treg	regulatory T
TST	tuberculin skin test
ULN	upper limit of normal
USP	United States Pharmacopeia
VAS	visual analog scale
vIGA-AD	Validated Investigator Global Assessment for Atopic Dermatitis
WBC	white blood cell

Appendix 2. Clinical Laboratory Tests

<table>
<tr><th>Hematology</th><th>Chemistry</th><th>Serology</th></tr>
<tr><td rowspan="4">• Hemoglobin[a]
• Hematocrit[a]
• RBC
• WBC[a]
• Platelet count[a]
• Neutrophils (absolute)[a]
• Lymphocytes (absolute)
• Monocytes (absolute)
• Eosinophils (absolute)
• Basophils (absolute)
• Mean corpuscular volume (MCV)
• Mean corpuscular hemoglobin (MCH)
• Mean corpuscular hemoglobin concentration (MCHC)
• Peripheral blood mononuclear cell (PBMC) isolation</td><td rowspan="4">• AST (SGOT)[b]
• ALT (SGPT)[b]
• GGT[b]
• TBL[b]
• Alkaline phosphatase[b]
• LDH[b]
• Albumin
• Creatinine
• Glucose
• Total protein
• Sodium
• Potassium
• Chloride
• CO_2 content or bicarbonate
• Urea nitrogen</td><td>• Hepatitis B surface antigen (HBsAg)
• Hepatitis B core antibody (HBcAb+)
• Hepatitis C virus antibody (anti-HCV)
• Human immunodeficiency virus (HIV) antibody</td></tr>
<tr><td>Drug and Alcohol Screening</td></tr>
<tr><td>• Opioids (urine)
• Cocaine (urine)
• Amphetamines (urine)
• Cannabinoids (urine)
• Alcohol (urine)</td></tr>
<tr><td>Pregnancy (for Women of Child-bearing Potential)
• Serum human chorionic gonadotropin (hCG; mandatory for screening)
• Urine</td></tr>
<tr><td colspan="3">Urinalysis (by dipstick)</td></tr>
<tr><td>• Specific gravity
• pH
• Glucose
• Protein
• Bilirubin
• Ketones
• Leukocytes
• Blood</td><td colspan="2">For positive protein, WBC or blood, a microscopic examination including:
• RBC
• WBC
• Epithelial cells
• Bacteria
• Crystals
• Casts</td></tr>
</table>

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase, LDH = lactate dehydrogenase; RBC = red blood cell; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; TBL = total bilirubin level; WBC = white blood cell.

[a] Values for these parameters need to be in the normal range to be considered as normal hematologic function for the purpose of inclusion.

[b] These tests will constitute the additional testing of hepatic function.

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for

- ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of IP.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the patient or the patient's legal representative and retaining a copy on file.

Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes. Study-specific recruitment material should be approved by Lilly.

Ethical Review

The investigator or appropriate local representative must give assurance that the ERB was properly constituted and convened as required by the ICH guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the study site(s). Lilly or its representatives must approve the ICF before it is used at the study site(s). All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERB(s) should be provided with the following:

- the current IB or and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

This study will be conducted in accordance with the protocol and with

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- applicable ICH GCP Guidelines, and
- applicable laws and regulations.

Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Final Report Signature

The investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- provide training to instruct the investigators and study coordinators

  Note

  This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel through mail, telephone, and/or fax
- review and evaluate CRF data and/or use standard computer edits to detect errors in data collection, and
- conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

Data Collection Tools/Source Data

An electronic data capture system will be used in this study. The site must define and retain all source records and must maintain a record of any data where source data are directly entered into the data capture system.

Data Protection

Data systems used for the study will have controls and requirements in accordance with local data protection law.

The purpose and use of subject/patient personal information collected will be provided in a written document to the subject/patient by the sponsor.

Site and Study Closure

Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with Lilly or its designee CRP.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
TBL	Hepatitis E antibody, IgG
Conjugated bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear Antibody[a]**
AST	**Alkaline Phosphatase Isoenzymes[a]**
GGT	**Anti-smooth Muscle Antibody (or Anti-actin**
CPK	**Antibody)[a]**

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cell; TBL = total bilirubin level; WBC = white blood cell.

[a] Assayed by Lilly-designated or local laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Appendix 5. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Protocol J1P-MC-KFAD Blood Sampling Summary

		Screen and Treatment Period		Follow-up (Weeks 14-19)		Follow-up (Weeks 24-48)	
Purpose	**Blood Volume per Sample (mL)**	**Number of Samples**	**Total Volume (mL)**	**Number of Samples**	**Total Volume (mL)**	**Number of Samples**	**Total Volume (mL)**
Screening tests[a,b]	45	1	45	-	-	-	-
Clinical laboratory tests[a,b]	12	7	84	2	24	-	-
Hematology (eosinophil and other WBCs)	3	2	6				
Pharmacokinetics	3	12	36	3	9	3	9
Blood discard for cannula patency	1	12	12	4	4	-	-
PD blood collection (flow cytometry)	6	8	48	1	6	2	12
Cytokine blood sample	4	8	32	1	4	-	-
IL-19	2.5	8	20	3	7.5	-	-
Immunogenicity	10	5	50	1	10	-	-
Pharmacogenetics	4	1	4	-	-	-	-
CCI	C	C	[redacted]	C	C	-	-
CCI	C CI	C	C	C	C	-	-
Epigenetic marker immunomonitoring assays (T-cell subsets)	2	8	16	1	2	-	-
Peripheral blood mononuclear cell (PBMC) isolation	8	4	32	-	-	-	-
Total volume for each period		-	517	-	79		21
Total volume for each period (rounded up to the nearest 10 mL)		-	520	-	80		30
Total study volume (rounded up to the nearest 10 mL)							630

a Additional samples may be drawn if needed for safety purposes.

b Screening-tests sample includes the 12 mL sample for the first clinical laboratory tests.

Appendix 6. Validated Investigator Global Assessment Scale for Atopic Dermatitis – vIGA-AD™

Instructions:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

Score	Morphological Description
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Notes:

1. In indeterminate cases, please use extent to differentiate between scores.

   For example:

   - Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 – Moderate".

2. Excoriations should not be considered when assessing disease severity.

Source:

http://www.eczemacouncil.org/wp-content/uploads/2018/02/Validated-Investigator-Global-Assessment-Scale_vIGA-AD_2017.pdf

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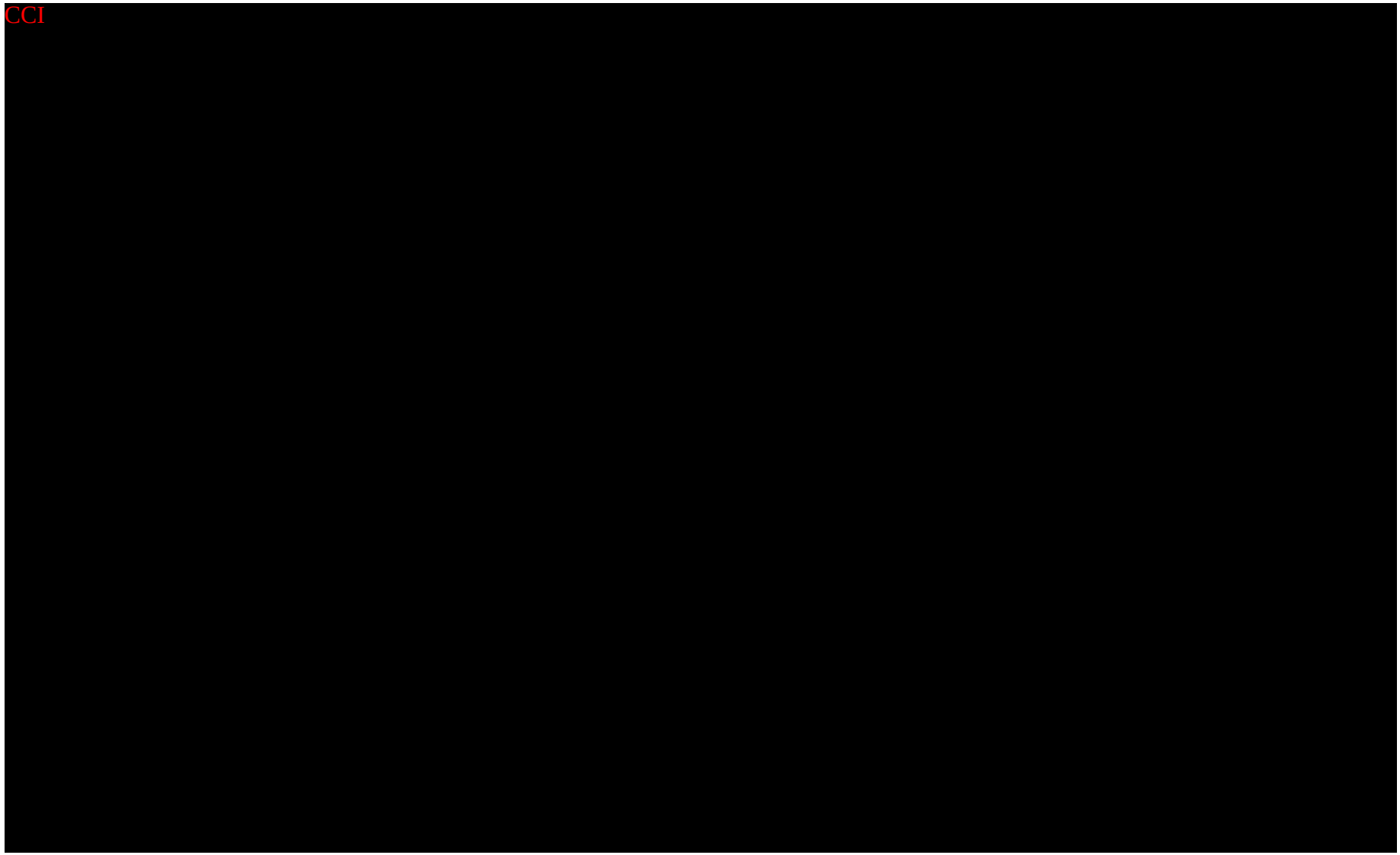
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Signature Page for VV-CLIN-006069 v1.0

Approval	PPD 04-Oct-2021 14:26:55 GMT+0000

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