Protocol I9H-MC-FFAA(b)

A Phase 1 Randomized, Placebo-Controlled Study of LY3316531 in Healthy Subjects and an Open-Label, Single-Dose Study in Patients with Psoriasis

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LY3316531

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1. Protocol Synopsis

Title of Study:

A Phase 1 Randomized, Placebo-Controlled Study of LY3316531 in Healthy Subjects and an Open-Label, Single-Dose Study in Patients with Psoriasis

Rationale:

LY3316531 is a humanized bispecific antibody that selectively binds to interleukin-23 and calcitonin gene-related peptide (CGRP). This dual inhibitor is an innovative attempt to target pathways that affect the pathology associated with auto-inflammatory conditions.

This first-in-human study will explore the safety, tolerability, and pharmacokinetics (PK) of single and multiple doses of LY3316531 in healthy subjects and the safety, tolerability, PK, and pharmacodynamics (PD) of a single dose of LY3316531 in patients with psoriasis.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary • To explore the safety and tolerability of single and multiple doses of LY3316531 in healthy subjects • To explore the safety and tolerability of a single dose of LY3316531 in patients with psoriasis	Incidence of adverse events, treatment-emergent adverse events, and serious adverse events
Secondary • To characterize the PK of LY3316531 following IV and SC administration in healthy subjects • To characterize the PK of LY3316531 following IV administration in patients with psoriasis	C_{max} and AUC

Abbreviations: AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; IV = intravenous; PK = pharmacokinetics; SC = subcutaneous.

Summary of Study Design:

Study I9H-MC-FFAA is a multicenter, randomized, sponsor unblind, subject- and investigator-blind (investigator will be partially blind for Cohorts 1 and 2 and unblind for cohort 5 in Part A), placebo-controlled, parallel-dose group, single-ascending dose design in healthy subjects (Part A), multiple-dose design in healthy subjects (Part B), and an open-label, single-dose design in patients with psoriasis (Part C).

Treatment Arms and Planned Duration for an Individual Patient/Subject:

Part A (Single-Ascending Dose [SAD] in Healthy Subjects): After a screening period up to 28 days, eligible subjects will be randomized to receive a subcutaneous (SC) or intravenous (IV) dose of LY3316531 (3 mg IV, 15 mg IV, 75 mg IV, 300 mg IV, 300 mg SC, 900 mg IV, or 2000 mg IV [planned dose]) or placebo (IV) on the morning of Day 1. Subjects will remain in the CRU for 24 hours after study drug administration and attend scheduled visits at the CRU for 12 weeks to assess the measurements for safety, tolerability, and PK. Sentinel dosing for the first 2 subjects of Cohorts 1 and 2 will be performed with 1 subject receiving LY3316531 and the other receiving placebo in a blinded manner.

Part B (Multiple-Dose in Healthy Subjects): After a screening period up to 28 days, eligible subjects will be randomized to receive a planned IV dose of LY3316531 (2000 mg [planned dose]) or placebo on the morning of Days 1, 29, and 57. The planned dose of 2000 mg LY3316531 may be adjusted based on safety, PK, and target-engagement data obtained in Part A of the study. An optional SC or IV second multiple-dose cohort will be determined after reviewing the data from the first cohort.

Subjects will be remain in the CRU for 24 hours after receiving each dose of study drug and attend scheduled visits at the CRU for 12 weeks following the final (third) dose of LY3316531 to assess the measurements for safety, tolerability, and PK.

Part C (Single-Dose in Patients with Psoriasis): After a screening period up to 35 days, eligible patients with psoriasis will be enrolled to receive a single dose of LY3316531 on the morning of Day 1. Patients will receive 300 mg IV in Cohort 1 or, in the 2 optional cohorts, receive either a SC or IV dose (to be determined) not to exceed the maximum tolerated dose in Part A or the highest dose previously evaluated in healthy subjects. Patients will remain in the CRU for 24 hours after study drug administration and attend scheduled visits at the CRU for 16 weeks following administration of the study drug to assess the measurements for safety, tolerability, PK, and PD. Patients who respond to LY3316531 therapy will enter an extended follow-up period, which requires monthly visits up to Week 52. Patients who enter the extended follow-up period should be discontinued from the study when additional therapy becomes necessary (as determined by the investigator and patient).

Number of Patients/Subjects:

Part A: It is planned that up to 52 subjects may be enrolled in Part A of this study to obtain evaluable data from 46 subjects. The healthy subject SAD is planned to include 7 cohorts. Cohorts 1 and 2 are each planned to have 4 subjects (3 LY3316531:1 placebo), whereas Cohorts 3, 4, 6, and 7 are each planned to have 8 subjects (6 LY3316531:2 placebo). Cohort 5 is planned to have 6 subjects, all receiving LY3316531.

Part B: It is planned that up to 20 subjects may be enrolled in Part B of this study to obtain evaluable data from 16 subjects (total number of subjects for planned and optional cohorts). The healthy subject multiple-dose part of the study is planned to include up to 2 cohorts (2000 mg IV cohort with the option for 1 additional cohort) with 8 subjects per cohort (6 LY3316531:2 placebo).

Part C: It is planned that up to 30 patients may be enrolled in Part C of this study to obtain evaluable data from up to 24 patients (total number of patients for planned and optional cohorts). The patients with psoriasis single-dose part of the study is planned to include up to 3 cohorts (300 mg IV cohort with the option for 2 additional cohorts) with a minimum of 7 patients planned but up to 8 patients allowed per cohort (8 LY3316531). The decision to initiate enrollment in the optional cohorts will be based on the clinical activity, safety, and tolerability of LY3316531 as observed in Cohort 1. For example, a lower dose of LY3316531 may be investigated if the dose used in Cohort 1 is highly efficacious, based on the clinical activity measurement (Psoriasis Area and Severity Index

[PASI] scores), or if safety concerns arise. Conversely, a higher dose may be explored in an optional cohort if it is determined that LY3316531 had minimal effect on PASI scores.

Statistical Analysis:

Safety: All investigational products (IPs) and protocol procedure adverse events will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology. The incidence of treatment-emergent adverse events and serious adverse events will be presented by severity and by association with treatment as perceived by the investigator. Symptoms reported to occur prior to treatment with study drug will be distinguished from those reported as new or increased in severity during the trial. Safety parameters that will be assessed include laboratory tests, vital signs, electrocardiogram, body weight, immunogenicity, and injection-site reactions.

Pharmacokinetics: PK parameter estimates for LY3316531 will be calculated using standard noncompartmental methods of analysis. Parameters for estimation will include absolute bioavailability following SC administration, maximum observed drug concentration (C_{max}), time to reach C_{max}, area under the concentration versus time curve (AUC) from time 0 to time of last measurable concentration (t_{last}), AUC from time zero to infinity ($AUC_{0-\infty}$), percentage extrapolated AUC from t_{last} to infinity, half-life, apparent clearance, and apparent volume of distribution. The dose proportionality of selected LY3316531 PK parameters will be examined across the dose range using a power model approach. Population PK analysis methods may be utilized if necessary.

Pharmacodynamics: Relationships between LY3316531 exposure and CGRP target engagement may be explored using graphical- and model-based approaches for all parts of the study (Parts A, B, and C). In patients with psoriasis (Part C), PD data obtained will be documented in the study report by dose, plasma drug concentrations, and time from dose. Figures showing values of potential PD markers versus time will be created for each dose, with a line for each patient. Absolute percentage change from baseline for all will be summarized by providing the mean, standard deviation, median, minimum, and maximum for each cohort and overall for each sample day/time combination and maximum over the entire study. Data may be log-transformed prior to summarizing if necessary. The interpatient and intrapatient variability in human PD responses may also be assessed if appropriate.

Exposure–response relationships for clinical activity measures in psoriasis (such as PASI score, static Physician Global Assessment, and body surface area) and safety endpoints will be investigated initially using graphical methods. Modeling approaches that relate exposure to the response at various time points or longitudinal models that relate the time course of exposure to the time course of response may be explored.

Statistical: PK/PD analyses will be conducted on data from all patients/subjects who receive at least 1 dose of the IP and have evaluable PK. Placebo data from all cohorts will be pooled across all dose-escalation cohorts for the purpose of analysis. Clinical activity and PD analyses will be conducted for all patients with psoriasis who receive the study drug (Part C only). Pharmacodynamic parameters, and their change from baseline, will be summarized at each applicable visit using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum for continuous variables and number of subjects, frequency, and percent for categorical variables). No statistical inferences will be made and no control for multiplicity is planned. Additional analyses may be performed.

2. Schedule of Activities

2.1. Part A (SAD in Healthy Subjects)

Study Schedule for Protocol I9H-MC-FFAA (Part A)

	Screening	Baseline		Postdose											
Visit No.	**V1**	**V2**			**V3**	**V4**	**V5[a]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**ED**
Study Day	**-26 d from Day -2**	**-1**	**1**	**2**	**4 ± 1 d**	**8 ± 1 d**	**11 ± 1 d**	**15 ± 2 d**	**22 ± 2 d**	**29 ± 2 d**	**43 ± 3 d**	**57 ± 3 d**	**71 ± 3 d**	**85 ±3 d**	
Admission to CRU		X													
Discharge from CRU				X											
Informed consent	X														
Review/confirm I/E criteria	X	X													
Complete medical history	X														
Complete physical examination	X													X	X
Weight	X													X	X
Height	X														
Symptom-directed physical examination			When needed												
Concomitant medications	X		X[b]	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (pulse rate, blood pressure, and temperature)[c,d]	X	X	Predose, end of infusion, and 2, 6, 12 h after SC injection or start of infusion	24 h after SC injection or start of infusion	X	X	X	X	X	X	X	X	X	X	X
Review preexisting conditions/AEs	X		X[b]	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Baseline		Postdose											
Visit No.	**V1**	**V2**			**V3**	**V4**	**V5[a]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**ED**
Study Day	**-26 d from Day -2**	**-1**	**1**	**2**	**4 ± 1 d**	**8 ± 1 d**	**11 ± 1 d**	**15 ± 2 d**	**22 ± 2 d**	**29 ± 2 d**	**43 ± 3 d**	**57 ± 3 d**	**71 ± 3 d**	**85 ±3 d**	
Injection-site assessment (including CCI)[a,e]			X	X		X		X							
ECGs[d,f]	X	See ECG sampling schedule (Appendix 6)													
LY3316531 or placebo administration (IV or SC)			X												
QuantiFERON®-TB Gold test or TST	X														
Read TST (if applicable)	X[g]														
HIV/HBV/HCV	X														
FSH[h]	X														
Pregnancy test[h]	X	X								X		X		X	X
Serum chemistry and hematology	X	X		X	X	X		X	X	X	X	X	X	X	X
Urinalysis	X	X			X			X		X	X			X	X
Urine drug screen and ethanol test	X	X													
Pharmacogenetics (exploratory storage samples for DNA)		X													
Immunogenicity[i]		See immunogenicity sampling schedule (Appendix 6)													
LY3316531 concentration (PK)[i]		See PK sampling schedule (Appendix 6)													
Target engagement assay (total CGRP)			X[j]	24 h after SC injection or start of infusion		X		X		X		X		X	X

	Screening	Baseline		Postdose											
Visit No.	**V1**	**V2**			**V3**	**V4**	**V5[a]**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**ED**
Study Day	**-26 d from Day -2**	**-1**	**1**	**2**	**4 ± 1 d**	**8 ± 1 d**	**11 ± 1 d**	**15 ± 2 d**	**22 ± 2 d**	**29 ± 2 d**	**43 ± 3 d**	**57 ± 3 d**	**71 ± 3 d**	**85 ±3 d**	
Skin Biopsy[k]		X[l]													

Abbreviations: AE = adverse event; CGRP = calcitonin gene-related peptide; CRU = clinical research unit; d = study day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; h = hour(s); HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; IV = intravenous; No. = number; PK = pharmacokinetic; SC = subcutaneous; CCI [redacted]; TB = tuberculosis; TST = tuberculin skin test; V = visit; CCI [redacted].

[a] Required for subjects receiving SC dosing only.

[b] At the discretion of the CRU, the baseline measurement for this assessment can be collected at any time after the subject's admission to the CRU up until LY3316531 or placebo administration on Day 1.

[c] Additional vital sign measurements may be obtained when clinically indicated. Vital signs should be taken following an approximate 5-minute rest in supine position. Temperature measurement is required only at screening and baseline.

[d] ECG, vital sign, and PK sampling should occur at approximately the same time. ECG recording and vital sign measurements should occur prior to the blood draw.

[e] Times are referenced to start of dosing. 0-hour assessments should be performed within 1 minute after giving all SC injections. Assessments should occur on Day 1 (0 min, 10 min, 0.5 h, 1 h, 3 h, and 6 h), Day 2 (24 h), Day 8 (168 h), and Day 15 (336 h) after SC injection of LY3316531. Additional assessments may be performed if deemed necessary by the investigator.

[f] Electrocardiograms should be taken following an approximate 5-minute rest in supine position. Electrocardiograms are requested to be taken at the specified time; however, aberrations to specified recording times will not be considered protocol deviations as long as the ECGs are taken and the actual recording time is documented. Electrocardiograms will be collected in triplicate except at screening where a single ECG will be collected (Section 9.4.3).

[g] The follow-up TST reading should occur 2 to 3 days after V1.

[h] A serum pregnancy test will be conducted at screening only. Urine pregnancy test will be used at all other time points. For women who are considered to be postmenopausal, FSH should be drawn to confirm postmenopausal status as defined in inclusion criterion [1b] and to be considered exempt for further pregnancy tests during the study.

[i] Refer to Appendix 6 for specific PK and immunogenicity sampling schedule. Samples are requested to be taken at the specified time; however, aberrations to specified sampling times will not be considered protocol deviations as long as the samples are taken and the actual sampling time is recorded. It is essential that the actual times of doses and samples are recorded accurately on the appropriate forms.

[j] This activity should be completed before LY3316531 or placebo administration (predose).

[k] Skin biopsies will be performed in the first 20 healthy subjects to volunteer for this procedure in Parts A and B, collectively.

[l] After subject eligibility is confirmed, skin biopsies can be collected at any time prior to dosing.

2.2. Part B (Multiple-Dose Study in Healthy Subjects)

Study Schedule for Protocol I9H-MC-FFAA (Part B)

	Screening	Baseline		Postdose									
Visit No.	**V1**	**Dose Periods 1, 2, and 3**								**V20**	**V21**	**V22**	**ED**
		V2,8,14			**V3,9,15**	**V4,10,16**	**V5,11,17[a]**	**V6,12,18**	**V7,13,19**				
Study Day(s)	**-26 d from Day -2**	**-1**	**1**	**2**	**4 ± 1 d**	**8 ± 1 d**	**11 ± 1 d**	**15 ± 2 d**	**22 ± 2 d**	**85 ±3 d**	**113 ±4 d**	**141 ±4 d**	
		28	**29**	**30**	**32 ± 1 d**	**36 ± 1 d**	**39 ± 1 d**	**43 ± 2 d**	**50 ± 2 d**				
		56	**57**	**58**	**60 ± 1 d**	**64 ± 1 d**	**67 ± 1 d**	**71 ± 2 d**	**78 ± 2 d**				
Week(s)			**0,4,8**			**1,5,9**		**2,6,10**	**3,7,11**	**12**	**16**	**20**	
Admission to CRU		X[b]											
Discharge from CRU				X[c]									
Informed consent	X												
Review/confirm I/E criteria	X	X[d]											
Complete medical history	X												
Complete physical examination	X											X	X
Weight	X											X	X
Height	X												
Symptom-directed physical examination			When needed										
Concomitant medications	X		X[e]	X	X	X	X	X	X	X	X	X	X
Vital signs (heart rate, blood pressure, and temperature)[f,g]	X	X	Predose, end of infusion, and 2, 6, 12 h after SC injection[h] or start of infusion	24 h after SC injection[h] or start of infusion	X	X	X	X	X	X	X	X	X
Review preexisting conditions/AEs	X		X[e]	X	X	X	X	X	X	X	X	X	X

	Screening	Baseline	Postdose									
Visit No.	V1	Dose Periods 1, 2, and 3								V20	V21	V22	ED
		V2,8,14			V3,9,15	V4,10,16	V5,11,17[a]	V6,12,18	V7,13,19				
Study Day(s)	-26 d from Day -2	-1	1	2	4 ± 1 d	8 ± 1 d	11 ± 1 d	15 ± 2 d	22 ± 2 d	85 ±3 d	113 ±4 d	141 ±4 d	
		28	29	30	32 ± 1 d	36 ± 1 d	39 ± 1 d	43 ± 2 d	50 ± 2 d				
		56	57	58	60 ± 1 d	64 ± 1 d	67 ± 1 d	71 ± 2 d	78 ± 2 d				
Week(s)			0,4,8			1,5,9		2,6,10	3,7,11	12	16	20	
Injection-site assessment CCI [redacted]			X	X		X		X					
ECGs[g,l]	X	See ECG sampling schedule (Appendix 6)											
LY3316531 or placebo administration (SC or IV)			X										
QuantiFERON®-TB Gold test or TST	X												
Read TST (if applicable)	X[m]												
HIV/HBV/HCV	X												
FSH[n]	X												
Pregnancy test[n]	X	X								X	X	X	X
Serum chemistry and hematology	X	X			X			X	X	X	X	X	X
Urinalysis	X		X			X				X	X	X	X
Urine drug screen and ethanol test	X	X											
Pharmacogenetics (exploratory storage samples for DNA)		X[d]											
Immunogenicity[o]		See immunogenicity sampling schedule (Appendix 6)											
LY3316531 concentration (PK)[o]		See PK sampling schedule (Appendix 6)											
C-SSRS/Self-Harm Supplement and FU	X	X		X[p]	X	X	X	X	X	X	X	X	X
Target engagement			X[q]	24 h after				X		X	X	X	X

	Screening	Baseline		Postdose									
Visit No.	**V1**	**Dose Periods 1, 2, and 3**								**V20**	**V21**	**V22**	**ED**
		V2,8,14			**V3,9,15**	**V4,10,16**	**V5,11,17[a]**	**V6,12,18**	**V7,13,19**				
Study Day(s)	**-26 d from Day -2**	**-1**	**1**	**2**	**4 ± 1 d**	**8 ± 1 d**	**11 ± 1 d**	**15 ± 2 d**	**22 ± 2 d**	**85 ±3 d**	**113 ±4 d**	**141 ±4 d**	
		28	**29**	**30**	**32 ± 1 d**	**36 ± 1 d**	**39 ± 1 d**	**43 ± 2 d**	**50 ± 2 d**				
		56	**57**	**58**	**60 ± 1 d**	**64 ± 1 d**	**67 ± 1 d**	**71 ± 2 d**	**78 ± 2 d**				
Week(s)			**0,4,8**			**1,5,9**		**2,6,10**	**3,7,11**	**12**	**16**	**20**	
assay (total CGRP)				SC injection[h] or start of infusion									
Skin biopsy[r]		X[s]											

Abbreviations: AE = adverse event; CGRP = calcitonin gene-related peptide; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; d = study day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; FU = follow-up; h = hour(s); HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; IV = intravenous; No. = number; PK = pharmacokinetic; SC = subcutaneous; CCI ; TB = tuberculosis; TST = tuberculin skin test; V = visit; CCI

[a] Visits 5, 11, and 17 (Days 11, 39, and 67) are required for subjects receiving SC injections only.

[b] Admission to the CRU occurs on Days -1, 28, and 56.

[c] Discharge from the CRU occurs on Days 2, 30, and 58.

[d] This activity should occur on Day -1 only.

[e] At the discretion of the CRU, the baseline measurement for this assessment can be collected at any time after the subject's admission to the CRU up until LY3316531 or placebo administration on Day 1.

[f] Additional vital sign measurements may be obtained when clinically indicated. Vital signs should be taken following an approximate 5-minute rest in supine position. Temperature measurement is required only at screening and baseline.

[g] ECG, vital sign, and PK sampling should occur at approximately the same time. ECG recording and vital sign measurements should occur prior to the blood draw.

[h] SC injection is only if an optional SC cohort is added.

[i] Times are referenced to start of dosing. 0-hour assessments should be performed within 1 minute after giving all SC injections. Assessments should occur on Day 1 (0 min, 10 min, 0.5 h, 1 h, 3 h, and 6 h), Day 2 (24 h), Day 8 (168 h), and Day 15 (336 h) after SC injection of LY3316531. Additional assessments may be performed if deemed necessary by the investigator.

[j] Required for subjects who will receive SC injections only.

[k] If the optional cohort uses SC dosing, then injection-site assessments will be performed.

[l] ECGs should be taken following an approximate 5-minute rest in supine position. ECGs are requested to be taken at the specified time; however, aberrations to specified recording times will not be considered protocol deviations as long as the ECGs are taken and the actual recording time is documented. Single safety ECGs will be collected unless the ECG values for subjects in Part A show clinically significant changes (for example, increase in PR or QT interval). See Section 9.4.3 for more details on ECGs.

[m] The follow-up TST reading should occur 2 to 3 days after V1.

[n] A serum pregnancy test will be conducted at screening only. Urine pregnancy test will be used at all other time points. For women who are considered to be postmenopausal, FSH should be drawn to confirm postmenopausal status as defined in Inclusion Criterion [1b] and to be considered exempt for further pregnancy tests during the study.

[o] Refer to Appendix 6 for specific PK and immunogenicity sampling schedule. Samples are requested to be taken at the specified time; however, aberrations to specified sampling times will not be considered protocol deviations as long as the samples are taken and the actual sampling time is recorded. It is essential that the actual times of doses and samples are recorded accurately on the appropriate forms.

[p] C-SSRS should be administered before subjects are discharged from the CRU on Day 2.

[q] This activity should be completed before LY3316531 or placebo administration (predose).

[r] Skin biopsies will be performed in the first 20 healthy subjects to volunteer for this procedure in Parts A and B, collectively.

[s] After subject eligibility is confirmed, skin biopsies can be collected at any time prior to dosing.

2.3. Part C (Single-Dose Study in Patients with Psoriasis)

Study Schedule for Protocol I9H-MC-FFAA (Part C)

	Screening	Baseline		Postdose												Extended FU	
Visit No.	**V1**	**V2**			**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**ED**	**FU[a]**	**ED**
Study Day(s)	**-33 d from Day -2**	**-1**	**1**	**2**	**4 ± 1 d**	**8 ± 1 d**	**15 ± 2 d**	**22 ± 2 d**	**29 ± 2 d**	**43 ± 3 d**	**57 ± 3 d**	**71 ± 3 d**	**85 ±3 d**	**113 ±4 d**		**Up to 365 ± 5 d**	
Week(s)			**0**			**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**16**		**Up to 52**	
Admission to CRU		X															
Discharge from CRU				X													
Informed consent	X																
Review/confirm I/E criteria	X	X															
Complete medical history	X																
Complete physical examination	X													X			
Weight	X		X											X	X	X	X
Height	X																
Symptom-directed physical examination			When needed														
Chest x-ray	X																
Concomitant medications	X		X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (heart rate, blood pressure, and temperature)[c,d]	X	X	Predose, end of infusion, and 2, 6, 12 h after SC injection[e] or start of infusion	24 h after SC injection[e] or start of infusion	X	X	X	X	X	X	X	X	X	X	X	X	X
Review preexisting conditions/AEs	X		X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECGs[d,f]	X		See ECG sampling schedule (Appendix 6)														
LY3316531 administration (IV or SC)			X														

	Screening	Baseline		Postdose											Extended FU	
Visit No.	**V1**	**V2**			**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**ED**	**FU[a]**	**ED**
Study Day(s)	**-33 d from Day -2**	**-1**	**1**	**2**	**4 ± 1 d**	**8 ± 1 d**	**15 ± 2 d**	**22 ± 2 d**	**29 ± 2 d**	**43 ± 3 d**	**57 ± 3 d**	**71 ± 3 d**	**85 ±3 d**	**113 ±4 d**		**Up to 365 ± 5 d**	
Week(s)			**0**			**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**16**		**Up to 52**	
QuantiFERON®-TB Gold test or TST	X																
Read TST (if applicable)	X[g]																
HIV/HBV/HCV	X																
FSH[h]	X																
Pregnancy test[h]	X	X							X		X		X	X	X	X	X
Serum chemistry and hematology	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X							X					X	X		X
Urine drug screen and ethanol test	X	X															
Pharmacogenetics (exploratory storage samples for DNA)		X															
Immunogenicity[d,i]			See immunogenicity sampling schedule (Appendix 6)														
LY3316531 concentration (PK)[d,i]			See PK sampling schedule (Appendix 6)														
C-SSRS/Self-Harm Supplement and FU	X	X		X[j]	X	X	X	X	X	X	X	X	X	X	X	X	X
Target engagement assay (total CGRP)			X[k]	24 h after SC injection[e] or start of infusion		X	X		X		X		X	X	X	X	X
Patient's Global Assessment and PSS[l]			X[k]			X	X		X		X		X	X	X	X	X
PASI, sPGA, and BSA	X		X[k]		X	X	X		X		X		X	X	X	X	X
HS-CRP	X		X[k]			X	X		X		X		X				
CCI Concentration			X[k]			X	X		X		X		X				

	Screening	Baseline		Postdose												Extended FU	
Visit No.	**V1**	**V2**			**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**ED**	**FU[a]**	**ED**
Study Day(s)	**-33 d from Day -2**	**-1**	**1**	**2**	**4 ± 1 d**	**8 ± 1 d**	**15 ± 2 d**	**22 ± 2 d**	**29 ± 2 d**	**43 ± 3 d**	**57 ± 3 d**	**71 ± 3 d**	**85 ±3 d**	**113 ±4 d**		**Up to 365 ± 5 d**	
Week(s)			**0**			**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**16**		**Up to 52**	
Exploratory storage samples (serum, plasma, RNA)			X[k]				X		X		X			X			
Skin biopsy		X[m]					X[n]										

Abbreviations: AE = adverse event; BSA = body surface area; CGRP = calcitonin gene-related peptide; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; d = study day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; FU = follow-up; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HS-CRP = high sensitivity-C reactive protein; I/E = inclusion/exclusion; IL = interleukin; IV = intravenous; No. = number; PASI = Psoriasis Area and Severity Index; PK = pharmacokinetic; PSS = psoriasis symptom scale; RNA = ribonucleic acid; SC = subcutaneous; sPGA= static Physician Global Assessment; TB = tuberculosis; TST = tuberculin skin test; V = visit.

[a] Monthly follow-up visits will occur during this time period for patients who respond to treatment with LY3316531 after the initial 16-week follow-up period (see Section 5.1.3 for more details).

[b] At the discretion of the CRU, the baseline measurement for this assessment can be collected at any time after the patient's admission to the CRU up until LY3316531 or placebo administration on Day 1.

[c] Additional vital sign measurements may be obtained when clinically indicated. Vital signs should be taken following an approximate 5-minute rest in supine position. Temperature measurement is required only at screening and baseline.

[d] ECG, vital sign, and PK sampling should occur at approximately the same time. ECG recording and vital sign measurement should occur prior to the blood draw.

[e] SC injection is only if an optional subcutaneous-injection cohort is added.

[f] ECGs should be taken following an approximate 5-minute rest in supine position. ECGs are requested to be taken at the specified time; however, aberrations to specified recording times will not be considered protocol deviations as long as the ECGs are taken and the actual recording time is documented. Single safety ECGs will be collected unless the ECG values for subjects in Part A show clinically significant changes (for example, increase in PR or QT interval). See Section 9.4.3 for more details on ECGs.

[g] The follow-up TST reading should occur 2 to 3 days after V1.

[h] All female subjects of childbearing potential will have serum pregnancy test at screening only. Urine pregnancy test will be used at all other time points. For women who are considered to be postmenopausal, FSH should be drawn to confirm postmenopausal status as defined in inclusion criterion [8b] and to be considered exempt for further pregnancy tests during the study.

[i] Refer to Appendix 6 for specific PK and immunogenicity sampling schedule. Samples are requested to be taken at the specified time; however, aberrations to specified sampling times will not be considered protocol deviations as long as the samples are taken and the actual sampling time is recorded. It is essential that the actual times of doses and samples are recorded accurately on the appropriate forms.

[j] C-SSRS should be administered before subjects are discharged from the CRU on Day 2.

[k] This activity should be completed on Day -1 or Day 1 before LY3316531 or placebo administration (predose).

[l] All patient-reported outcomes are to be collected from the subject prior to clinical assessment by the investigator.

[m] After patient eligibility is confirmed, baseline skin biopsies can be collected at any time starting on Day -7 up until dosing.

[n] Postdose skin biopsies should be collected on Day 15 ± 2 days.

3. Introduction

3.1. Study Rationale

LY3316531 is a humanized bispecific antibody that selectively binds to interleukin-23 (IL-23) and calcitonin gene-related peptide (CGRP). This dual inhibitor is an innovative attempt to target pathways that affect the pathology associated with auto-inflammatory conditions.

Study I9H-MC-FFAA (FFAA) is a Phase 1, first-in-human study to explore the safety, tolerability, and pharmacokinetics (PK) of single and multiple doses of LY3316531 in healthy subjects and the safety, tolerability, PK, and pharmacodynamics (PD) of a single dose of LY3316531 in patients with psoriasis. The evaluation of LY3316531 in patients with psoriasis will aid in the determination of a safe dose level or range, characterize PK and PD, and explore clinical activity data for future studies.

Skin biopsies will also be taken to observe the effects of LY3316531 on psoriatic skin lesions. CCI [redacted]

While Study FFAA will evaluate LY3316531 in patients with psoriasis, atopic dermatitis and Crohn's disease are also potential future indications.

3.2. Background

A typical organ-specific, T-cell-driven inflammatory disease, psoriasis had been considered a T helper (Th) 1-type skin disease for decades until a new Th population, Th17, was identified (Lew et al. 2004; Steinman 2007; Weaver et al. 2007). However, substantial clinical and basic research observations now suggest that the IL-23/Th17 axis is essential in the pathogenesis of psoriasis (Di Cesare et al. 2009). IL-23, a member of the IL-12 family of cytokines, is a heterodimeric protein comprised of 2 subunits; the p40 subunit, which it shares with IL-12, and the p19 subunit, believed to be specific to IL-23. IL-23 is produced by antigen-presenting cells, such as dendritic cells and macrophages, and plays an important role in maintenance and amplification of Th17 cells (Lee et al. 2004; Piskin et al. 2004). In addition, Th17 cells and their downstream effector molecules, including IL-17A, IL-17F, IL-21, IL-22, and tumor necrosis factor alpha (TNF-α), are found at increased levels in human psoriatic skin lesions and circulation (Boniface et al. 2007; Lowes et al. 2008; Caruso et al. 2009; Kagami et al. 2010).

Treatment of psoriasis with biologic therapy, particularly with those agents targeting the IL-23/Th17 axis, has demonstrated clinical activity in patients with psoriasis (Crow 2012). Agents specifically targeting the IL-23 p19 subunit have demonstrated clinical activity in psoriasis CCI [redacted] (Krueger et al. 2015; Papp et al. 2015; Gordon et al. 2015; Kopp et al. 2015; Sofen et al. 2014) and Crohn's disease (Sands et al. 2015).

Calcitonin gene-related peptide is a 37-amino acid neuropeptide member of a family of peptides that includes amylin, adrenomedullin, and calcitonin. The predominant form of CGRP is known as α-CGRP, with a second isoform, β-CGRP, being produced from a separate gene but having high sequence homology (Steenbergh et al. 1985). Both isoforms have similar biological activities, but differ in their expression patterns; α-CGRP is expressed mainly in the peripheral and central nervous system while β-CGRP is expressed mostly in the enteric nervous system (Mulderry et al. 1988). Calcitonin gene-related peptide is a potent vasodilator (Brain et al. 1985). While CGRP antagonists seem to restore normal tonus in CGRP-induced dilation of isolated arterial rings, the evidence to date suggests that CGRP antagonists do not alter basal vascular tone (Chaitman et al. 2012; Verheggen et al. 2002). Calcitonin gene-related peptide has a well-established role in neurogenic inflammation and nociception (Hirsch et al. 2013). It is able to facilitate the production and secretion of numerous pro-inflammatory mediators that lead to hyperemia, edema, and pain in inflamed tissues (Cady et al. 2011). The CGRP pathway may play a specific role in inflammatory skin disorders having direct effects on immune cells, cytokine production, and itch and pain pathologies in various dermatoses (Lotti et al. 2014; Kashem et al. 2015). Interestingly, CGRP regulates sensory neurons through the IL-23/IL-17 axis as well (Riol-Blanco et al. 2014; Ding et al. 2016). In addition to its involvement in inflammation and nociception, it is believed that CGRP can increase IL-23 production (Kashem et al. 2015).

Several nonclinical studies were performed to support the use of LY3316531 in humans. Weekly administration of LY3316531 to cynomolgus monkeys in a general toxicology study resulted in no adverse drug-related findings at doses of 20 or 60 mg/kg (subcutaneous [SC]), or 200 mg/kg (intravenous [IV]) for 3 months. The exposure multiple and dose multiple to the highest human dose, based on this monkey study, are 5× and 28×, respectively. Additionally, a tissue cross-reactivity study was performed with LY3316531 in human and monkey tissues, which produced no toxicologically important difference in tissue binding between the species.

3.3. Benefit/Risk Assessment

The nonclinical safety information for LY3316531 supports the transition from preclinical status to a clinical, first-in-human study. On the basis of the nonclinical data, LY3316531 is not considered to be a high-risk compound. This protocol reflects the fact that LY3316531 has not been administered to humans previously, and to mitigate this risk, the study has been designed to be conducted in accordance with principles outlined in the Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products. Any identified risks are considered to be monitorable and manageable at the planned dose range with starting dose of 3 mg up to a maximum dose not to exceed 2000 mg for LY3316531 in healthy subjects and patients with psoriasis.

There is no anticipated therapeutic benefit for the healthy subjects. There is a potential for patients with psoriasis to experience some level of therapeutic benefit during this study, as blockade of IL-23 is known to improve psoriasis.

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of LY3316531 are to be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

Table FFAA.4.1 shows the objectives and endpoints of the study.

Table FFAA.4.1. Objectives and Endpoints

Primary Objectives	Primary Endpoints
To explore the safety and tolerability of single and multiple doses of LY3316531 in healthy subjects To explore the safety and tolerability of a single dose of LY3316531 in patients with psoriasis	Incidence of adverse events, TEAEs, and SAEs

Objectives and Endpoints

Secondary Objectives	Secondary Endpoints
To characterize the PK of LY3316531 following IV and SC administration in healthy subjects To characterize the PK of LY3316531 following IV administration in patients with psoriasis	C_{max} and AUC
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the injection tolerance after SC administration of LY3316531	Pain scale scores and severity of ISR
To evaluate the formation of ADA to LY3316531	Presence of ADA against LY3316531
To evaluate the PD response (target engagement) of LY3316531 using total CGRP	Summary of total CGRP concentrations for each cohort and study time point
CCI	CCI
To evaluate patient-reported outcomes, including measurement of disease activity of LY3316531 in patients with psoriasis	Summary (mean, standard deviation, median, minimum, and maximum) of absolute percentage change from baseline for all of each cohort and overall for each sample day/time combination and maximum over the entire study for the patient's global assessment
To evaluate relationships between LY3316531 exposure and PD and clinical activity measures and safety endpoints	Graphical and model-based summaries of relationships between LY3316531 exposure and total CGRP, CCI, PASI, sPGA, ECGs, and safety endpoints of interest

Abbreviations: ADA = antidrug antibody; AUC = area under the concentration versus time curve; CGRP = calcitonin gene-related peptide; C_{max} = maximum observed drug concentration; ECG = electrocardiogram; IL = interleukin; ISR = injection-site reaction; IV = intravenous; PASI = Psoriasis Area and Severity Index; PD = pharmacodynamics; PK = pharmacokinetics; SAE = serious adverse event; SC = subcutaneous; sPGA = static Physician Global Assessment; TEAE = treatment-emergent adverse event.

5. Study Design

5.1. Overall Design

Study FFAA is a 3-part Phase 1, multicenter, randomized, sponsor unblind, subject- and investigator-blind (investigator will be partially blinded for Cohorts 1 and 2 and unblind for Cohort 5 in Part A), placebo-controlled, parallel-dose group, single-ascending dose (SAD) design (Part A), and multiple-dose design (Part B) in healthy subjects. In addition, Part C of this study is an open-label, single-dose design in patients with psoriasis. There are 3 parts to this study to explore the safety, tolerability, PK, and PD of LY3316531:

- Part A: SAD design in healthy subjects,
- Part B: Multiple-dose design in healthy subjects,
- Part C: Single-dose design in patients with psoriasis.

Table FFAA.5.1 provides a detailed description of subject/patient cohorts and planned doses for Parts A, B, and C. Figure FFAA.5.1 demonstrates the relationship among Parts A, B, and C. Part A will begin first and will trigger the initiation of Parts B and C, which will run in parallel.

Patients/subjects will be admitted to the clinical research unit (CRU) on Day -1 (Days -1, 28, and 56 in Part B) and fast overnight. Patients/subjects will receive a dose of study drug or placebo on Day 1 (Days 1, 29, and 57 in Part B) and will undergo the study assessments specified in the Schedule of Activities (Section 2). Patients/subjects may be discharged 24 hours after dose administration on Day 2 (Days 2, 30, and 58 in Part B). In case of safety concerns, patients/subjects will be required to stay in the CRU for a longer period at the discretion of the investigator. Patients/subjects will return to the CRU for outpatient visits for procedures specified in the Schedule of Activities (Section 2).

The decision to escalate to the next higher dose of LY3316531 will be based on safety data through Day 15 from at least 7 subjects (5 or 6 subjects will have received LY3316531 determined by randomization) from the preceding dose cohort. Exceptions will be for Cohorts 1 and 2, and Cohort 5 if available at the time of decision in Part A, where safety data from all subjects through Day 15 will be required. More detailed information about the safety reviews and dosing decisions may be found in Section 7.4.2.

Table FFAA.5.1. Summary of Maximum Number of Patients/Subjects per Cohort

Cohort #	Planned Dose/ Administration Route	Number of Planned Subjects		Total Number of Planned Subjects
		LY	PBO	
Part A				
SAD Cohort 1[a]	3 mg/IV	3	1	4
SAD Cohort 2[a]	15 mg/IV	3	1	4
SAD Cohort 3	75 mg/IV	6	2	8
SAD Cohort 4	300 mg/IV	6	2	8
SAD Cohort 5	300 mg/SC	6	0	6
SAD Cohort 6	900 mg/IV	6	2	8
SAD Cohort 7	2000 mg/IV	6	2	8
Part B				
Multiple-Dose Cohort 1	2000 mg/IV	6	2	8
Multiple-Dose Cohort 2[b]	Route and dose TBD	6	2	8
Part C				
Patient Cohort 1[c]	300 mg/IV	8	0	8
Patient Cohort 2[b,c]	Route and dose TBD	8	0	8
Patient Cohort 3[b,c]	Route and dose TBD	8	0	8

Abbreviations: IV = intravenous; LY = LY3316531; PBO = placebo; SAD = single-ascending dose; SC = subcutaneous; TBD = to be determined.

[a] Sentinel dosing will be used in this cohort.

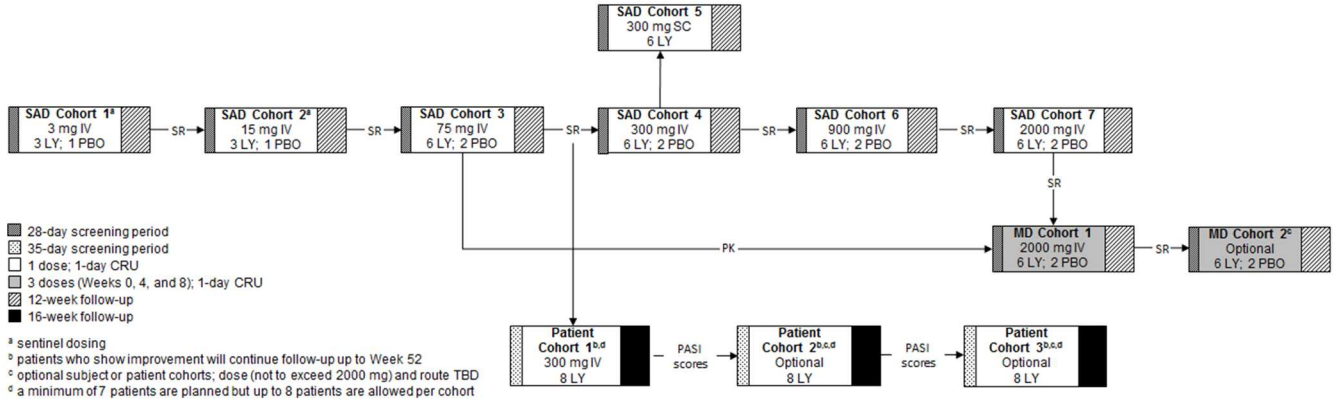
[b] Optional subject or patient cohort. Actual dose and route of administration will be determined based on cumulative data from previous cohorts, but will not exceed 2000 mg of LY3316531 administered IV.

[c] A minimum of 7 patients are planned but up to 8 patients are allowed per cohort.

A follow-up visit will be performed according to the Schedule of Activities (Section 2).

Study governance considerations are described in detail in Appendix 3.

Figure FFAA.5.1 illustrates the study design.



Abbreviations: IV = intravenous; LY = LY3316531; MD = multiple dose; PBO = placebo; PK = pharmacokinetic sampling; SAD = single-ascending dose; SC = subcutaneous; SR = safety review meeting; TBD = to be determined.

Figure FFAA.5.1. Illustration of study design for Protocol I9H-MC-FFAA.

5.1.1. Part A (SAD in Healthy Subjects)

Seven planned dose-escalation cohorts will be enrolled to receive either IV or SC administration of LY3316531 (3, 15, 75, 300, 900, or an additional dose not to exceed 2000 mg) or placebo.

Sentinel dosing will be used in Cohorts 1 and 2 to minimize the risk to subjects receiving this novel antibody. Initially, 2 subjects (1 receiving LY3316531 and 1 receiving placebo) will be dosed in a blinded manner (sentinel subjects) and these subjects will be followed for at least 24 hours postdose before the remaining subjects in that cohort are dosed (subject blind only). The remaining subjects may then be dosed on the same day or subsequent days (but not necessarily consecutive days), as determined by the investigator. Dose escalation to the next cohort can begin after a safety review of data from the preceding cohort (see Section 7.4.2 for a more detailed description). All 6 subjects in Cohort 5 will receive 300 mg of LY3316531 SC.

All subjects who meet eligibility criteria will be followed for 12 weeks post-treatment administration. A subject's participation is considered as complete if he/she received the study drug and completes all activities up to and including at least Day 57. Subjects may be replaced if PK data are not collected up to and including Day 57.

5.1.2. Part B (Multiple-Dose Design in Healthy Subjects)

One planned multiple-dose cohort will be enrolled to receive IV administration of LY3316531 (2000 mg) or placebo. The dose and route of administration (IV or SC) for an optional second multiple-dose cohort would be determined after reviewing the data from the first IV cohort.

It is planned that a review of the safety data from Cohort 7 (Part A) and the preliminary PK data (maximum observed drug concentration [C_{max}] and area under the concentration versus time

curve [AUC]) from Cohorts 1, 2, and 3 (through Day 29) in Part A will trigger enrollment to the first cohort in Part B. Section 7.4.1 provides detailed information on how the dose level for the optional cohort will be determined and when the cohorts will begin enrollment procedures.

All subjects who meet eligibility criteria will receive 3 doses of LY3316531 (1 dose every 4 weeks) and be followed for 12 weeks after the final treatment administration. A subject's participation is considered as complete if he/she received the study drug and completes all activities up to and including at least Day 85. Subjects may be replaced if PK data are not collected up to and including Day 85.

5.1.3. Part C (Single-Dose Design in Patients with Psoriasis)

One planned single-dose cohort will be enrolled to receive IV administration of LY3316531 with the option of 2 subsequent cohorts where the dose levels and route of administration (SC or IV) would be determined after reviewing the data from the first IV cohort.

The first cohort is planned to receive 300 mg of LY3316531 pending the analysis of available safety data from Part A. The safety scenarios for AEs, SAEs, and adverse laboratory abnormalities described in Section 7.4.2 that would prevent dose escalation in Parts A and B are the same that would prevent initiation of Part C. The actual starting dose and expected exposure will not exceed the dose/exposure that is concurrently being evaluated in Part A. Any available preliminary PK data from Cohorts 1, 2, and 3 (through Day 29) in Part A will be considered in the decision to initiate Part C as well.

Similarly, the dose for the optional cohorts will be determined based on cumulative data from previous cohorts, but will not exceed 2000 mg of LY3316531. Section 7.4.1 provides detailed information on how dose levels for the 2 optional cohorts will be determined and when the cohorts will begin enrollment procedures.

All patients who respond to LY3316531 treatment by exhibiting at least 50% reduction from baseline Psoriasis Area and Severity Index (PASI) score at Week 12 (Visit 11; Day 85) can enter an extended follow-up period for up to 52 weeks post-treatment administration (see Section 2.3). Other subjects who do not meet the above criterion for PASI reduction should be considered for discontinuation from the study at Week 16 (Visit 12; Day 113). Exceptions could be considered after a discussion between the sponsor and investigator.

A patient's participation is considered as complete if he/she received the study drug and completes all activities up to and including at least Day 85. Patients may be replaced if PK or PD data are not collected up to and including Day 85.

5.2. Number of Participants

5.2.1. Part A (SAD Design in Healthy Subjects)

Up to 52 subjects may be enrolled so that approximately 46 subjects complete Part A. For purposes of this study, a subject completes Part A when he/she completes all scheduled procedures up to and including at least Day 57.

Refer to the Schedule of Activities (Section 2.1) for data to be collected at the time of discontinuation and follow-up.

5.2.2. Part B (Multiple-Dose Design in Healthy Subjects)

Up to 20 subjects may be enrolled so that approximately 16 subjects complete Part B (total number of subjects for planned Cohort 1 and the 1 optional cohort). Subjects who drop out of the Part B prior to receiving the third dose will be replaced. However, subjects who drop out following administration of the third dose, or withdraw from Part B due to safety reasons will not be replaced, unless more than half of the subjects in a given cohort have dropped out after the third dose. For purposes of Part B, a subject completes the study when he/she completes all scheduled procedures up to and including at least Day 85.

Refer to the Schedule of Activities (Section 2.2) for data to be collected at the time of discontinuation and follow-up.

5.2.3. Part C (Single-Dose Design in Patients with Psoriasis)

Up to 30 patients may be enrolled so that up to 24 patients complete Part C (total number of patients planned for Cohort 1 and the 2 optional cohorts). For purposes of Part C, a patient completes the study when he/she completes all scheduled procedures up to and including at least Day 85.

Refer to the Schedule of Activities (Section 2.3) for data to be collected at the time of discontinuation and follow-up.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

This study will be the first assessment of the safety and tolerability of single and multiple (monthly) doses of LY3316531 in humans. A parallel-group design was selected based on the expected long half-life of the molecule in humans. Although a crossover design could provide more robust data, the long washout period required for the anticipated 2- to 3-week half-life would make it impractical. In addition, with an antibody such as LY3316531, there is the potential for developing antidrug antibodies (ADAs), which could confound analyses for subsequent doses.

Safety and tolerability assessments will be made over all dose levels. Subjects (all cohorts) will remain in the CRU for at least 24 hours after each dose of LY3316531 or placebo, to provide adequate and close safety monitoring. Sentinel dosing will be used in Cohorts 1 and 2 of Part A to minimize safety risks with this molecule.

For Part A, subjects are blinded and investigators are partially blinded to treatments to minimize bias during data collection (see Section 5.1.1). As there is only a single cohort of subjects receiving LY3316531 via the SC route in Part A, it is not planned to include subjects receiving

SC placebo, as adequate control data will be obtained from the IV cohort. A single-dose design is appropriate to assess the initial safety profile of the drug while minimizing subject risk; it also provides an opportunity to explore safety and PK across a broad range of doses in an adequate number of subjects to determine a range of doses and regimens to be evaluated in later studies.

For Part B, subjects and investigators are blinded to treatments to minimize bias during data collection. Intravenous placebo control subjects are included to allow for a more robust interpretation of data. Preliminary safety data from the SAD portion in Part A will support the utilization of healthy subjects in the multiple-dose portion in Part B. The multiple dose is the next logical step for clinical evaluation of an investigational product (IP).

The starting dose in Parts B and C of the study will be administered via the IV route. If additional cohorts are dosed, depending on the dose level chosen, the SC route may be used if feasible (maximum concentration of LY3316531 is 75 mg/mL). In addition, a wide dose range has been chosen in Part A as this study will support multiple indications, including inflammatory bowel disease, which may require higher doses of LY3316531 to reach therapeutic levels as compared to psoriasis.

A population of healthy subjects was selected to assess the PK, safety, and tolerability of LY3316531 based upon the likelihood of less physiologic variability in the absence of disease states that may affect multiple organ systems. Moreover, healthy subjects are usually devoid of other confounding factors such as concomitant medications. The inclusion of patients with psoriasis will aid in the determination of safe dose levels, a characterization of PK and PD, and the exploration of clinical activity data for future studies.

5.5. Justification for Dose

The wide dose range selected for Part A of the study is based on PK and efficacy data available from clinical studies with the IL-23 monoclonal antibody (mAb) (CCI) and the CGRP mAb (CCI), coupled with preclinical PK information for LY3316531 in cynomolgus monkeys and relative potency information collected in humanized IL-23 mouse PD model experiments. The planned starting dose of 3 mg IV is expected to have minimal biological activity and the maximum dose of 2000 mg IV is expected to support the highest doses that may be evaluated in the multiple-dose and Phase 2 studies. CCI [redacted] The starting and maximum doses are expected to produce AUCs that are 851 and 5× lower, respectively, than the AUC observed at the NOAEL dose in toxicology studies in cynomolgus monkeys (Table FFAA.5.2).

The dose(s) for Parts B and C will be selected based on available PK and safety data from Part A of the study. The highest dose that may be evaluated in Part B will not exceed the maximum tolerated dose (MTD) in Part A. In the event PK data from Part A indicate that significant drug accumulation is likely to occur with doses of 2000 mg LY33165314 administered every 4 weeks, the dose administered in Part B will be reduced.

The doses for Part C will also be selected based on data from Part A of this study and the single-dose study with CCI in patients with psoriasis, and will be selected to allow for comparative exposure-response analyses between LY3316531 and CCI using psoriasis efficacy measures.

Table FFAA.5.2. Margin of Safety for Administration of LY3316531 Based on Administered Dose and Predicted Exposure

Species Dose level	Human Dose	Dose Multiple	AUC (µg•hr/mL)	AUC Exposure Multiple	C_{max} (µg/mL)	C_{max} Exposure Multiple
Planned Human Starting Dose[a]	3 mg IV = 0.04 mg/kg		436		1.8	
Non-Human Primates						
200 mg/kg QW IV NOAEL[b]		5000 x[c]	371250[d]	851x[e]	6358[d]	3532x[f]
Species Dose level	**Human Dose**	**Dose Multiple**	**$C_{av,ss}$ (µg/mL)**	**$C_{av,ss}$ Exposure Multiple**	**$C_{max,ss}$ (µg/mL)**	**$C_{max,ss}$ Exposure Multiple**
Planned Human Maximum Dose[a]	2000 mg Q4W, IV = 28.6 mg/kg	-	432	-	1428	-
Non-Human Primates	-	-	-	-		-
200 mg/kg QW IV NOAEL[b]		28x[g]	2210[d]	5x[h]	6358[d]	4.5x[i]

Abbreviations: τ = dosing interval; AUC = area under the concentration versus time curve; $AUC_{0-\infty}$ = AUC from zero to infinity; AUC_{τ} = AUC during one dosing interval; AUC_{ss} = AUC at steady state; $C_{av,ss}$ = average predicted drug concentration under steady state conditions during a dosing interval; C_{max} or $C_{max,ss}$ = maximum observed drug concentration or maximum observed drug concentration during a dosing interval at steady state; ELISA = enzyme-linked immunosorbent assay; F = female; IV = intravenous; M = male; NOAEL = no-observed-adverse-effect level; PK = pharmacokinetics; QW = every week; Q4W = once every 4 weeks.

[a] Body weight of human is assumed to be 70 kg. Human PK parameters were predicted using scaling methods based on data collected following a single dose of LY3316531 in monkeys (Study 8340704).

[b] Large Animal Species Toxicology Study #20108516.

[c] Dose multiple for single start dose is the dose in animals/dose in humans based on mg/kg.

[d] Overall mean of exposures of male + female and exposures obtained from 2 ELISAs on Day 85. $C_{av,ss}$ = mean AUC_{τ} observed after the last dose in monkeys/τ in monkeys or predicted mean AUC_{ss} in human/τ in human.

[e] AUC exposure multiple = mean AUC_{tau} observed after the last dose in monkeys/predicted mean $AUC_{0-\infty}$ after a single dose in human.

[f] C_{max} exposure multiple = mean C_{max} observed after the last dose in monkeys/predicted mean C_{max} after a single dose in human.

[g] Dose multiple for multiple human dose is the dose in animals/dose in humans based on mg/kg, normalized by dosing frequency.

[h] $C_{av,ss}$ exposure multiple = $C_{av,ss}$ in monkey/$C_{av,ss}$ in human.

[i] $C_{max,ss}$ exposure multiple = mean $C_{max,ss}$ observed after the last dose in animals/predicted mean $C_{max,ss}$ at steady state in humans.

6. Study Population

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

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 (35 days for patients) prior to enrollment. Subjects who are not enrolled within 28 days (35 days for patients) 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/subjects are eligible for inclusion in the study only if they meet all of the following criteria at screening and/or enrollment:

6.1.1. For Healthy Subjects

[1] are overtly healthy males or females, as determined by medical history and physical examination.

[1a] male subjects:

agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms with spermicide as well as 1 additional highly effective method of contraception or effective method of contraception during the study and for 5 months following the last dose.

[1b] female subjects:

must test negative for pregnancy at the time of screening and be of non-childbearing potential, as defined by at least 1 of the following:

- at least 6 weeks have elapsed after bilateral oophorectomy, tubal ligation, or hysterectomy
- postmenopausal as defined in Section 6.3.4
- female infertility due to other causes that have been discussed with, and accepted, by the sponsor.

[2] are between 18 and 64 years of age, inclusive, at the time of screening.

[3] have a body mass index of 18 to 32.0 kg/m^2, inclusive, and a minimum body weight of 50 kg.

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

[5] have venous access sufficient to allow for blood sampling and administration of IP for IV administration as per the protocol.

[6] are willing and able to undergo punch biopsies according to the Schedule of Activities (Section 2.2).

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

[8] are able and willing to give signed informed consent.

6.1.2. For Patients with Psoriasis

[9] present with chronic plaque psoriasis based on an investigator-confirmed diagnosis of chronic psoriasis vulgaris for at least 6 months prior to baseline and meet the following criteria:

- plaque psoriasis involving ≥5% body surface area (BSA) in affected skin other than the face and scalp at screening (Visit 1) and baseline (Day 1, Visit 2)
- static Physician Global Assessment (sPGA) score of ≥2 at screening (Visit 1) and baseline (Day 1, Visit 2)
- are willing and able to undergo punch biopsies according to the Schedule of Activities (Section 2.3).

[9a] male patients:

agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms with spermicide as well as 1 additional highly effective method of contraception or effective method of contraception during the study and for 5 months following the last dose of the IP.

[9b] female patients:

both childbearing and non-childbearing potential must test negative for pregnancy at the time of screening.

agree to use 2 effective methods of contraception during the study and for 5 months following the last dose of the IP unless they are not of child-bearing potential, as defined by at least 1 of the following:

- at least 6 weeks have elapsed after bilateral oophorectomy, tubal ligation, or hysterectomy
- postmenopausal as defined in Section 6.3.4
- female infertility due to other causes that have been discussed with, and accepted, by the sponsor.

[10] are ≥18 years of age.

[11] have a minimum body weight of 50 kg.

[12] have adequate organ function, including:

- hematologic: absolute neutrophil count ≥1.5×10^9/L (≥1.5×10^3/µL or ≥1.5 GI/L), platelet count ≥100×10^9/L (≥100×10^3/µL or ≥100 GI/L), hemoglobin level ≥10.0 g/dL (≥100 g/L), lymphocyte count >500 cells/µL (>0.50×10^3/µL or >0.50 GI/L), and total white blood cell count ≥3.0×10^9/L (≥3.0×10^3/µL or ≥3.0 GI/L)
- chemistry:
  - serum creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels ≤2× upper limit of normal (ULN)
  - total bilirubin level (TBL) (subjects with Gilbert's syndrome must have serum direct bilirubin <1.5 mg/dL) and alkaline phosphatase (ALP) <1.5× ULN.

[13] have venous access sufficient to allow for blood sampling and administration of IP through IV (if applicable), as per the protocol.

[14] are reliable and willing to make themselves available for the duration of the study, and are able and willing to follow study procedures.

[15] have given written informed consent approved by Lilly and the ethical review board (ERB) governing the site.

6.2. Exclusion Criteria

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

6.2.1. For Healthy Subjects and Patients with Psoriasis

[16] are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.

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

[18] are currently enrolled in a clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study or have received any non-biologic IP within 30 days or 5 half-lives (whichever is longer) of their initial screening visit.

[19] have previously completed a clinical trial investigating CCI (IL-23 antibody) or CCI (CGRP antibody) and have previously received either of these IPs.

[20] a marked baseline prolongation of QT/corrected QT interval (QTc) (for example, repeated demonstration of a QTcB interval >470 ms);

A history of additional risk factors for Torsades de Pointes (for example, heart failure, persistent hypokalemia, family history of long QT syndrome);

The use of concomitant medications that prolong the QT/QTc interval.

[21] have known or ongoing neuropsychiatric disorders.

[22] for Parts B and C only, patients who have answered 'yes' to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the Columbia-Suicide Severity Rating Scale (C–SSRS), or answer "yes" to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, reparatory act or behavior) on the "Suicidal Behavior" portion of the C–SSRS; and the ideation or behavior occurred within the past month.

NOTE: a patient does not necessarily have to be excluded if they have self-injurious behavior that would be classified as non-suicidal self-injurious behavior. Of course, if this situation arises, it is likely the subject should be referred to a psychiatrist or appropriately trained professional.

[23] have evidence of clinically significant active infection, fever of 100.5°F (38°C) or above, at screening or baseline (Day 1).

[24] had any surgical procedure (except for minor surgery requiring local or no anesthesia and without any complications or sequelae) within 12 weeks prior to screening, or any planned surgical procedure scheduled to occur during the study.

[25] have received live vaccine(s) (including attenuated live vaccines) within 28 days of screening or intend to receive during the study (non-live or inactivated vaccinations are allowed).

[26] have a history of multiple or severe allergies or has had an anaphylactic reaction to prescription or non-prescription drugs or food.

[27] have a history of allergy to mAbs or to the drug excipients, or have clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or a history of severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A [IgA] dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis).

[28] have had serious, opportunistic, or chronic/recurring infection within 6 months prior to screening. Examples include but are not limited to infections requiring IV antibiotics, hospitalization, or prolonged anti-infective treatment.

[29] had any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no subsequent evidence of recurrence for at least 3 years prior to screening and cervical carcinoma in situ with no evidence of recurrence within the 5 years prior to baseline.

[30] current smoker >10 cigarettes or other tobacco products per day. Are unable/unwilling to stop smoking tobacco products while in the study unit. Heavy smokers (as per judgment of the investigator) should be excluded from the study.

[31] are regular users of known drugs of abuse and/or have positive findings on urinary drug tests at screening; OR an average weekly alcohol intake that exceeds 21 units per week (males) or 14 units per week (females), OR are unwilling to stop alcohol consumption during study visits/time in the research unit (1 unit of alcohol = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits).

[32] have donated blood of more than 500 mL within the previous 30 days of study screening.

[33] show evidence of active or latent tuberculosis (TB), as documented through medical history and examination, chest x-rays (posterior, anterior, and lateral) for patients with psoriasis only (Part C), and TB testing: either a positive tuberculin skin test (TST; defined as a skin induration >5 mm at 48 to 72 hours, regardless of Bacillus Calmette–Guérin or other vaccination history) or a positive (not indeterminate) QuantiFERON®-TB Gold test. 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, and the use of this test is dependent on previous treatment(s). This test may not be suitable if previous treatment(s) produce significant immunosuppression.

[34] have known hypogammaglobulinemia or a screening serum IgG <565 mg/dL, IgM <40 mg/dL, or IgA <70 mg/dL.

[35] are immunocompromised.

[36] have presence of significant uncontrolled cerebro-cardiovascular (for example, myocardial infarction, unstable angina, hypertension, moderate to severe [New York Heart Association Class III/IV] heart failure, or cerebrovascular accident), respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic or neuropsychiatric disorders or abnormal laboratory values at screening that, in the opinion of the investigator, pose an unacceptable risk to the subject if participating in the study or of interfering with the interpretation of data.

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

6.2.2. For Healthy Subjects Only

[38] intend to use herbal, over-the-counter, or prescription medication within 14 days prior to dosing and during the study, other than estrogen/progesterone as a form of hormone replacement therapy. Subjects taking these medications should be on stable doses for at least 28 days prior to screening. Certain medications, for example vitamin supplements and local anesthetics, may be permitted at the discretion of the investigator.

[39] have received Ig-based biologic therapies (such as mAbs, including marketed or investigational biologic therapy) within the past 6 months, or at any time received the compounds specified in criterion #19.

[40] have an abnormal blood pressure, pulse rate, and/or temperature as determined to be clinically significant by the investigator.

[41] have evidence of chronic viral infection:

[41a] show evidence of hepatitis C and/or positive hepatitis C antibody with confirmed presence of hepatitis C virus (HCV) ribonucleic acid (RNA) at screening.

[41b] show evidence of hepatitis B and/or positive hepatitis B surface antigen or are positive for hepatitis B core antibody (HBcAb) and negative for hepatitis B surface antibody (HBsAb) at screening.

[41c] show evidence of human immunodeficiency virus (HIV) infection and/or positive for HIV antibodies at screening.

[41d] have had symptomatic herpes zoster within 3 months (for patients in Part C) or 6 months (for healthy subjects in Parts A and B) prior to screening that constitutes (per investigator's judgment) a risk to the subject when taking the study medication or that may interfere with the interpretation of study data.

[42] are not willing to receive multiple subcutaneous injections.

6.2.3. For Patients with Psoriasis Only

[43] have any other skin conditions (excluding chronic psoriasis vulgaris) that would affect interpretation of the results (including, but not limited to, scleroderma, eczema, drug-induced psoriasis, guttate psoriasis, pustular psoriasis, parapsoriasis, or cutaneous manifestations of other autoimmune diseases such as systemic lupus erythematosus).

[44] have received systemic nonbiologic psoriasis therapy (including, but not limited to, oral psoralen plus ultraviolet A light therapy [PUVA]; cyclosporine; corticosteroids; methotrexate; oral retinoids; apremilast; tofacitinib; mycophenolate mofetil; thioguanine; hydroxyurea; sirolimus; tacrolimus; azathioprine; fumaric acid derivatives; or 1,25 dihydroxy vitamin D3 and analogs) or phototherapy (including either oral and topical PUVA, ultraviolet B, excimer laser, or self-treatment with tanning beds or therapeutic sunbathing) within 28 days prior to baseline.

[45] have received topical psoriasis treatment (including, but not limited to, corticosteroids [upper mid strength or lower potency topical steroids are permitted on the intertriginous areas and face], anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, pimecrolimus, tacrolimus, emollients, and other non-prescription topical products containing urea, >3% salicylic acid, alpha- or beta-hydroxyl acids, or medicated shampoos [for example, those that contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogs]) within 14 days prior to baseline.

[46] have received anti-TNF biologics and anti-IL-17 targeting biologics within 8 weeks prior to baseline.

[47] have previous exposure to any biologic therapy targeting IL-23 (including ustekinumab [redacted]) or CGRP ([redacted]), either licensed or investigational (previous briakinumab use is permitted) (see Exclusion #19).

[48] suffer chronic medical condition that are considered 'unstable' by the investigator. Subjects with well-controlled chronic conditions such as hypertension or hyperlipidemia may be permitted to participate, provided the treatment regimen has been stable for at least 28 days prior to screening and both the investigator and the Lilly clinical pharmacologist agree that the subject may participate in the study.

[49] have evidence of chronic viral infection:

[49a] show evidence of hepatitis C and/or positive hepatitis C antibody with confirmed presence of HCV RNA at screening.

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 HCV RNA on the screening test for this protocol. A sustained virological response is defined as an undetectable HCV RNA 12 weeks after completion of a full, documented course of an approved antiviral therapy for HCV.

Patients who have spontaneously cleared HCV infection, defined as:

(i) a positive HCV antibody test and

(ii) 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 >3× ULN during the study will be tested for HCV RNA in addition to a full liver evaluation as described in Section 9.4.4.1.

Anyone diagnosed with hepatitis C during the study will be discontinued from the study and should receive appropriate follow-up medical care.

[49b] show evidence of hepatitis B and/or positive hepatitis B surface antigen or are positive for HBcAb and negative for HBsAb at screening.

[49c] show evidence of HIV infection and/or positive for HIV antibodies at screening.

[49d] have had symptomatic herpes zoster within 3 months (for patients in Part C) or 6 months (for healthy subjects in Parts A and B) prior to screening that constitutes (per investigator's judgment) a risk to the subject when taking the study medication or that may interfere with the interpretation of study data.

[50] are unable or unwilling to avoid excessive sun exposure or use of tanning booths for at least 4 weeks prior to baseline and during the study.

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

Subjects should not eat after midnight during the night before study drug administration. Water is permitted. Subjects may eat breakfast approximately 2 hours postdose. A normal diet may be consumed at all other times during the study.

6.3.2. Caffeine, Alcohol, and Tobacco

6.3.2.1. Caffeine

Subjects and patients should not consume caffeine from the start of each dosing day to 12 hours postdose. Consumption of non-caffeinated beverages is permitted at any time during the study.

6.3.2.2. Alcohol

Subjects should not consume alcohol for at least 24 hours prior to dosing. During outpatient periods, all subjects should be advised to limit alcohol consumption to no more than 2 units per day.

6.3.2.3. Smoking

Subjects should be willing and able to abide by smoking restrictions at the study sites during both the in-house period and outpatient visits.

6.3.3. Activity

Subjects should avoid strenuous exercise and/or activity for at least 48 hours prior to dosing and scheduled visits.

6.3.4. Contraception

Women of childbearing potential (WOCBP) are excluded from Parts A and B of the study. For Part C, WOCBP who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males. Otherwise, WOCBP must use 2 effective methods of contraception for the entirety of the study. Abstinence or contraception must continue following completion of study drug administration for 5 half-lives or until plasma concentrations are equal to or below the pharmacologic effect level, whichever is longer.

- The WOCBP must test negative for pregnancy prior to initiation of treatment as indicated by a negative urine pregnancy test at the screening visit followed by a negative serum pregnancy test within 24 hours prior to exposure to LY3316531 or placebo.
- Two effective methods of contraception (such as male or female condoms with spermicide, diaphragms with spermicide or cervical sponges) will be used. The subject may choose to use a double-barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, female condom with spermicide). It should be noted that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these methods are combined.
    - Of note, 1 of the 2 methods of contraception may be a highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices).

Women not of childbearing 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
    - a woman 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; or

- A woman 55 years of age or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or
- A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

Men, regardless of their fertility status, with non-pregnant WOCBP partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as 1 additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) or effective method of contraception (such as diaphragms with spermicide or cervical sponges) 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 5 months following the last dose of study drug.

- Men and their partners may choose to use a double–barrier method of contraception. (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. It should be noted, however, that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined).
- 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 WOCBP (5 months following the last dose of study drug).
- 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 5 months following the last dose of study drug.
- Men who are in exclusively same sex relationships (as their preferred and usual lifestyle) are not required to use contraception.

6.4. Screen Failures

Healthy subjects who do not meet the criteria for participation in this study (screen failure) may not be re-screened; however, re-assessment of laboratory parameters will be allowed once if handling issues, damaged samples, or hemolyzed samples may have confounded the measurement results.

Any patient with psoriasis 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 a screen failure (this does not include TB testing).

In addition, participants who were eligible for inclusion in previous cohorts, but were not randomized for nonmedical reasons, may be reassessed, following a discussion with the sponsor.

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

7. Treatment

7.1. Treatment Administered

The drug product LY3316531 is supplied for clinical trial use as solution formulation in glass vials. Further dilution may be needed for SC and IV administration. See Pharmacy Instructions for more information.

Placebo will be sterile saline (0.9% NaCl). Placebo doses should be held in the pharmacy for an equivalent amount of time as is required to prepare doses of LY3316531.

The IP or placebo will be administered as SC injection(s) or a slow IV infusion over at least 30 minutes. Sites must have resuscitation equipment, emergency drugs, and appropriately trained staff available during the infusion and for at least 6 hours after subjects have completed receiving their infusion.

Injection site selected for SC administration should be the abdominal region approximately 5 cm from the umbilicus and the treatment is administered through the needle applied at approximately 45° with pinching of the skin. Because subjects may receive multiple injections per dose, each injection should be administered in a different abdominal quadrant (right upper quadrant, left upper quadrant, right lower quadrant, or left lower quadrant) and the quadrant used should be recorded at the time of the injection. Subcutaneous administration of LY3316531 should be done by a limited number of individuals for consistency. The same type of syringe and needle (CCI) should be used for all subjects to ensure all injections are delivered to a consistent depth target into the SC space.

All clinical trial materials provided to the investigator will be stored in a secure place, assigned using the interactive web response system, and dispensed by appropriately trained persons. The dispensing of the IPs will be fully documented. Detailed records of the amounts of the IP received, dispensed, and remaining at the end of the study will be maintained.

The investigator or designee is responsible for

- explaining the correct use of the IP(s) to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of IP dispensing and collection, and
- returning all unused medications to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

7.1.1. Packaging and Labeling

LY3316531 will be supplied to the investigative sites by Lilly. 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.

LY3316531 is supplied for clinical trial use as solution in vial with study-specific labels. The 2-mL vial is manufactured to contain 150 mg of LY3316531 (75 mg/mL). 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 (sterile saline).

When prepared for dosing according to instructions, it will not be possible to distinguish between LY3316531 and placebo.

Detailed instructions for the preparation and handling of LY3316531 will be provided by the sponsor.

The IP must be prepared by an unblinded pharmacist who is not involved in any other study-related procedures.

7.2. Method of Treatment Assignment

Randomization tables for allocation of LY3316531 or placebo will be prepared by the statistician or designee for the study and provided to the site pharmacists involved in dose preparation.
The allocation and dispensation of the IP will be fully documented and verified by a second person. Detailed records of the amounts of the IP received, dispensed, and remained at the end of the study will be maintained by the site pharmacy.

7.2.1. Selection and Timing of Doses

The doses will be administered at approximately the same times on each day. The actual time of all dose administrations will be recorded in the patient's/subject's electronic case report form (eCRF).

7.3. Blinding

Parts A and B of Study FFAA are subject- and investigator-blind except for the non-sentinel subjects and the open-label SC administration cohort in Part A (Cohort 5). Part C of Study FFAA is open-label. As a result, all patients with psoriasis who enter the study will receive LY3316531.

Pharmacy staff who prepare and dispense study medication are required to be unblinded to treatment allocation.

Subject treatment assignments and drug accountability records will be held in a secure location accessible only by individuals involved with study drug preparation or dispensation.

Blinding will be maintained throughout the conduct of the study as described in the separate Blinding Plan.

If a subject's study treatment assignment is unblinded, the subject must be discontinued from the study, unless the investigator obtains specific approval from a Lilly clinical pharmacologist or clinical research physician (CRP) for the study participant to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. The subject's safety must always be the first consideration in making such a determination. At the discretion of the investigator, if a subject's treatment assignment is unblinded, as judged by the investigator, Lilly must be notified immediately. It is the responsibility of the investigator to document the decision and rationale, promptly.

7.4. Dose Modification

7.4.1. Dose Decision (Part C)

The decision to initiate the first patient cohort in Part C will be based on the trial-level safety review for Cohort 3; however, any available preliminary PK data from Cohorts 1, 2, and 3 (through Day 29) in Part A will be considered as well. Progression to the optional cohorts in Part C will occur when at least 4 weeks of clinical activity data (PASI scores) are available from at least 7 patients in the preceding cohort. In addition to the PASI scores, any available PK and applicable safety data from Part A will be considered for determining the dose for the optional patient cohorts. Dosing at the current level and further dose escalation will be discontinued if any of the scenarios described in Section 7.4.2 occur.

CCI [redacted]

7.4.2. Dose Escalation (Parts A and B)

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis. The highest dose level that is tolerated will be designated as the MTD.

Safety data will be the primary criteria for the dose escalation. In addition, if available at the time of dose-escalation decision, PK results (C_{max} and AUC) will be used as supporting data for dose escalation, but such data are required only for Cohort 1 in Part B. No dose decision can occur without prior discussion and agreement between the investigator and the Lilly clinical pharmacologist or CRP.

Prior to dose escalation, a safety review meeting will be undertaken by the sponsor (unblinded) and the investigator (blinded) to evaluate the safety data and agree on the appropriate dose for the next cohort. Emerging PK data (if available) may inform dose selection for the higher dose levels, based on planned PK preliminary analyses after SAD Cohort 3 (Part A). If considered appropriate, previous dose levels may be repeated, or lower/intermediate dose levels may be

tested. The magnitude of the dose escalation may be reduced after data review, but subsequent escalations cannot be increased by more than approximately 3-fold (a half-log increment).

For Cohorts 1 and 2 in Part A, the decision to escalate to the next cohort will occur when at least 15 days have elapsed after all subjects in the preceding cohorts have been dosed. In Cohorts 3, 4, 6, and 7, the decision to dose the next cohort will occur when all subjects in the preceding cohorts have been dosed and data for a minimum of 15 days are available from at least 7 subjects in the preceding cohort. If at the time of the trial level safety review for Cohort 4, data are also available from Cohort 5, all available data from Cohorts 4 and 5 will be considered in the review to dose the next cohort.

The decision to initiate the first multiple-dose cohort in Part B will occur when at least 15 days have elapsed after all subjects in the last cohort in Part A have been dosed (Cohort 7 unless safety concerns prevent escalation to this cohort). The trial-level safety review for all previous cohorts and the preliminary analyses of PK data (planned to occur after the completion of Day 29 for Cohort 3) will be considered in the decision to initiate Part B of the study. Progression to the optional cohort in Part B will occur when all subjects have received the second dose of study drug and data for a minimum of 15 days (after the second dose) are available from at least 7 subjects in Cohort 1 of Part B.

Throughout Part A and Part B, safety data up to and including Day 15 are required for dose-escalation decisions. If any subjects withdraw before the Day 15 assessment, all available safety data for those subjects will be evaluated.

Safety data, in particular AEs, SAEs, and adverse laboratory abnormalities, will be independently assessed by the investigator, and will be considered related to the IP unless there is clear evidence that the event is not related.

After review of these data, an agreement on the appropriate dose will be made by the investigator and sponsor for the next cohort/dose level. The magnitude of dose escalations may be reduced following data review, but subsequent escalations cannot be increased by more than approximately 3-fold (a half-log increment).

If any of the following scenarios occur, dosing at the current level and further dose escalation will be discontinued:

> A single patient/subject experiences an SAE or clinically significant event that is related to LY3316531 administration

OR

> Two or more patients/subjects develop AEs within 14 days of dosing that are considered to be related to study treatment and graded as at least moderate, clinically significant, and not responsive to supportive care

OR

> One or more patients/subjects develop AEs within 14 days of dosing that are considered to be related to study treatment and graded as severe

OR

Two or more subjects develop AEs that are graded as severe, unless there is an obvious explanation other than IP or study procedures for the event(s)

OR

After the introduction of premedication in accordance with the protocol, 2 or more patients/subjects develop (according to Common Terminology Criteria for Adverse Events) ≥Grade 2 acute AEs related to the infusion, during or within 2 hours of completing the infusion that do not resolve with a reduced infusion rate and/or supportive care.

7.4.3. Special Treatment Considerations

Premedication for the infusions is not planned. However, if an infusion reaction occurs, appropriate medication may be used as determined by the study investigator(s). If infusion reactions are observed, but review of the data suggests that dose escalation may continue, acetaminophen 500 to 1000 mg and/or an antihistamine may be administered orally 30 to 60 minutes prior to the start of infusion for subsequent patients/subjects.

The decision to implement premedication for infusions in subsequent cohorts will be made by the investigator and sponsor and recorded in the study documentation, along with the dose-escalation decision.

Any premedications given will be documented as a concomitant therapy (see Section 7.7).

7.4.3.1. Management of Infusion Reactions

There is a risk of infusion reaction with any biological agent; therefore, all patients/subjects should be monitored closely. Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash, pruritus, myalgia, and dizziness. In the event that a significant infusion reaction occurs, the following guidance should be followed:

- The IP infusion should be slowed (for example, reduce infusion rate by 50% [for example, an infusion rate of 12 mL/h becomes 6 mL/h or slower]) or stopped, depending on the symptoms/signs present:
    - if slowed, the infusion should be completed at the slower rate, as tolerated
    - if determined by the investigator that the infusion should no longer continue, no further attempts to dose the patient/subject should be made
- Supportive care should be employed in accordance with the symptoms/signs
- If a patient/subject's infusion reaction is sufficiently severe to discontinue the infusion, subsequent infusions may be administered with premedication at the discretion of the investigator following agreement with the Lilly CRP or clinical pharmacologist

- If a patient/subject's infusion rate is reduced due to an infusion reaction, subsequent infusions may be administered at the discretion of the investigator following agreement with the Lilly CRP or clinical pharmacologist. If further infusions are administered, the infusion rate must not exceed the slowest rate used to complete the infusion when the infusion reaction occurred. Premedication may be administered at the discretion of the investigator
- If it is determined that the patient/subject should not receive further doses of IP, the patient/subject should complete AE and other follow-up procedures per Section 2 of this protocol.

7.5. Preparation/Handling/Storage/Accountability

All clinical trial materials provided to the investigator will be stored in a secure place and allocated and dispensed by appropriately trained personnel. The allocation and dispensation of the IP will be fully documented and verified by a second person. Detailed records of the amounts of the IP received, dispensed, and remaining at the end of the study will be maintained.

The investigator or designee must confirm appropriate temperature conditions have been maintained, as communicated by the sponsor, during transit for all IPs received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive IPs or study materials, and only authorized site staff may supply or administer IP. All IPs should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

Investigational products will be supplied by Lilly or its representative, in accordance with current good manufacturing practices and will be supplied with lot numbers, expiry dates, and certificates of analysis, as applicable.

7.6. Treatment Compliance

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

7.7. Concomitant Therapy

In general, concomitant medication should be avoided. Use of chronic, stable doses of Thyroxine or hormone replacement therapy (estrogens/progesterones) is allowed in both healthy subjects and patients with psoriasis.

Acetaminophen (1 g, maximum 2 g/24 hours) may be administered at the discretion of the investigator for treatment of headache, etc. If the need for concomitant medication (other than acetaminophen) arises, inclusion or continuation of the patient/subject may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist or CRP. Any medication used during the course of the study must be documented.

Uses of nonlive (inactivated) vaccinations are allowed for all subjects. Use of live, attenuated vaccines is prohibited.

Patients in Part C who are on stable concomitant medication at the time of study entry should continue their regular, unchanged dose throughout the study and the extended follow-up period (up to Week 52). Concomitant therapies for treatment of psoriasis during the study are permitted only as outlined in Table FFAA.7.1.

Table FFAA.7.1. Permitted Medications for Treatment of Psoriasis

Drug Class	As Needed	Chronic Use	Conditions for Use
Topical steroids	Yes	Yes	Topical steroids Class 6 [mild] or 7 [least potent] will be permitted for use limited to the face, axilla, and/or genitalia, as needed. These topical medications should not be used within approximately 24 hours prior to study visits.
Topical medications for psoriasis	No[a]	No	

[a] Exceptions: topical steroids will be permitted for use limited to the face, axilla, and/or genitalia.

Topical moisturizers/emollients may be used on nontarget lesions (that is, plaque psoriasis lesions that have not been or will not be biopsied) following the Day 1 visit.

7.8. Treatment after the End of the Study

Not Applicable.

8. Discontinuation Criteria

Patients/subjects discontinuing from the study prematurely for any reason must complete AE and follow-up procedures per Section 2 of this protocol.

8.1. Discontinuation from Study Treatment

Discontinuation of the IP for abnormal liver tests **should be considered** by the investigator when a patient/subject meets 1 of the following conditions after consultation with the Lilly-designated medical monitor:

- ALT or AST >5× ULN for healthy subjects, 8× ULN for patients
- ALT or AST >3× ULN for healthy subjects, 5× ULN for patients sustained for more than 2 weeks or
- ALT or AST >3× ULN and TBL >2× ULN or international normalized ratio >1.5 or
- ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3× ULN
- ALP >2.5× ULN and TBL >2× ULN
- ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

8.1.1. Discontinuation of Inadvertently Enrolled Patients/Subjects

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 pharmacologist or 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 clinical pharmacologist or 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/subjects will be discontinued under the following circumstances:

- 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
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator Decision
    - the investigator decides that the patient/subject should be discontinued from the study

  - if the patient/subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent

- Subject Decision
  - the patient/subject, or legal representative, requests to be withdrawn from the study.
- Sponsor Decision
  - Lilly stops the study or stops the subject's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- Suicidal Ideation and/or Behavior
  - When a subject discontinues from a study due to suicidal ideation and/or behavior, the same follow-up procedures can be used as would be done for discontinuation due to any other AEs leading to discontinuation. It is not necessary to collect additional information (except what is already requested on the C-SSRS, the Self-Harm Supplement Form, and the Self-Harm Follow-up Form).
  - Investigators are responsible for monitoring the safety of patients/subjects 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/subject.
  - The investigator is responsible for the appropriate medical care of patients/subjects during the study.
  - The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or that caused the patient/subject to discontinue before completing the study. The patient/subject should be followed up until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator
- Adverse event
  - if a clinically significant event (CSE) occurs, the IP has to be discontinued and appropriate measures taken. Lilly or its designee should be alerted immediately. A CSE will be defined as a moderate to severe AE, abnormal clinical sign, or clinical laboratory finding that may pose a risk to the wellbeing of the subject. Refer to Safety Section (Section 9.4).
  - A clinically significant systemic hypersensitivity reaction occurs following administration of the IP (for example, drug-related symptomatic bronchospasm,

allergy-related edema/angioedema, or hypotension) that requires parenteral medication, does not respond to symptomatic medication, or results in clinical sequelae or an anaphylactic reaction.

Following the investigator's determination that CSE criteria have been met and the investigator's judgment of relatedness to the IP is documented, a decision will be made between the investigator and Lilly or its designee regarding subject discontinuation.

The nature of any conditions, clinical signs or symptoms, or abnormal laboratory values present at the time of discontinuation and any applicable follow-up procedures will be documented.

Refer to the Schedule of Activities (Section 2) for data to be collected at the time of discontinuation and follow-up.

8.3. Patients/Subjects Lost to Follow-up

A patient/subject 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/subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing (including tolerance limits for timing).

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

Appendix 5 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

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.

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients/subjects 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/subject.

The investigator is responsible for the appropriate medical care of patients/subjects 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/subject to discontinue the IP before completing the study. The patient/subject should be followed 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 electronic data entry/designated data transmission methods, the occurrence and nature of each patient/subject'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 and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's/subject's IP is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via electronic data entry/designated data transmission methods.

9.2.1. 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 (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- 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
- when a condition related to the injection syringe or IV drug delivery system necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

Study site personnel must alert the Lilly CRP/clinical pharmacologist, 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 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 electronic data entry/designated data transmission methods after signing informed consent, SAE reporting to the sponsor begins after the patient/subject 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 subjects once they have discontinued from and/or completed the study (the patient/subject summary eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject 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.

9.2.1.1. 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.

9.2.2. Complaint Handling

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

Patients/subjects 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 LY3316531 is considered any dose higher than the dose assigned through randomization. There is no specific antidote to LY3316531 and in the case of overdose, subjects should be observed and treated with the appropriate supportive care.

Refer to the IB for LY3316531.

9.4. Safety

9.4.1. Laboratory Tests

For each patient/subject, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2).

With the exception of safety laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the study.

9.4.2. Vital Signs

For each patient/subject, vital sign measurements should be conducted according to the Schedule of Activities (Section 2) and as clinically indicated. Vital sign measurements may be repeated at the discretion of the investigator.

Blood pressure and pulse rate should be measured after at least 5 minutes supine (or semi-recumbent if subject is unable to lie supine).

If orthostatic measurements are required, patients/subjects should be supine for at least 5 minutes and stand for at least 3 minutes.

If the patient/subject feels unable to stand, supine vital signs only will be recorded.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted.

Body temperature will be measured as specified in the Schedule of Activities (Section 2) and as clinically indicated.

Body weight will be recorded as specified in the Schedule of Activities (Section 2) and as clinically indicated.

9.4.3. Electrocardiograms

For each subject in Part A, a centralized 12-lead digital ECG will be collected as triplicates according to the Schedule of Activities (Section 2), except at screening where a single ECG will be collected.

For each patient/subject in Parts B and C, a single ECG will be collected locally and stored at the investigator's site unless the ECG values for subjects in Part A show clinically significant changes (for example, increase in PR or QT interval). In this situation, the ECGs for patients/subjects in Parts B and/or C will be collected as in Part A of the study.

Electrocardiograms should be recorded up to 5 minutes before collecting any blood for safety or PK tests. Consecutive triplicate ECGs will be obtained at approximately 1-minute intervals. Patients/subjects should be supine for approximately 5 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 site as soon after the time of ECG collection as possible, and ideally while the subject is still present, to determine whether the patient/subject meets entry criteria at the relevant visit(s) and for immediate patient/subject management should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the patient/subject for symptoms (for example, palpitations, near syncope, syncope) to determine whether the patient/subject can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient/subject management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the triplicate ECGs from each time point.

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

The machine-read ECG intervals and heart rate may be used for data analysis and report writing purposes unless a cardiologist overread of the ECGs is conducted prior to completion of the final study report (in which case the overread data would be used).

9.4.4. Safety Monitoring

The Lilly clinical pharmacologist or CRP/scientist will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical pharmacologist or CRP will periodically review the following data:

- trends in safety data
- laboratory analytes
- adverse events including monitoring of incidence and nature of any infections, infusion reactions, and injection-site reactions.

When appropriate, the Lilly clinical pharmacologist or CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

9.4.4.1. Hepatic Safety

If a study patient/subject experiences elevated ALT ≥3× ULN, ALP ≥2× ULN, or elevated TBL ≥2× 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 clinical pharmacologist or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

Additional safety data should be collected if 1 or more of the following conditions occur:

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

9.4.4.3. C-SSRS

The Columbia-Suicide Severity Rating Scale (C-SSRS) captures the occurrence, severity, and frequency of suicidal ideation and/or behavior during the assessment period (Posner et al. 2011; Columbia University Medical Center [WWW]). 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 an appropriately trained health care professional with at least 1 year of patient care/clinical experience. 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.

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.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 5 mL each will be collected to determine the serum concentrations of LY3316531. A maximum of 2 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 investigative 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.

Serum concentrations of LY3316531 will be assayed using validated enzyme-linked immunosorbent assay methods. Analyses of samples collected from subjects who received placebo are not planned.

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

9.6. Pharmacodynamics

Measurements of total CGRP concentrations will be used to evaluate target engagement in Part A of the study. Samples collected in Parts B and C of the study will be analyzed based on the concentrations of total CGRP observed in Part A. Samples for CGRP measurements will be analyzed in a validated assay at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

The sample(s) will be stored for up to a maximum of 15 years after the last patient/subject visit for the study at a facility selected by the sponsor.

9.6.1. Pharmacodynamic Assessments

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9.6.1.2. Disease Activity Measures for Patients with Psoriasis

The disease activity measures described below will be collected at the times shown in the Schedule of Activities (Section 2.3).

- The PASI scores the severity of disease on a scale from 0 to 72 (where a score of 72 indicates extreme disease severity) by combining assessments of the extent of body surface involvement in the head, trunk, arms, and legs together with the severity of desquamation, erythema, and plaque induration.
- Percent BSA will be evaluated as the percent involvement of psoriasis on each patient's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), where 1% corresponds to the size of the patient's hand (including the palm, fingers, and thumb) (National Psoriasis Foundation 2009).
- The sPGA provides the physician's determination of the patient's psoriasis lesions overall at a given time point. Overall lesions are graded for induration, erythema, and

scaling, and the sum of the 3 scores is divided by 3 to obtain a final sPGA score (range 0 to 5). For the analysis of responder rates, the sPGA scores are rounded to the nearest whole number, and the patient's psoriasis is assessed as clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).

- In the Patient's Global Assessment of Disease Severity, patients are asked to rank on a 0 to 5 numeric rating scale the severity of their psoriasis "today" from 0 (clear; no psoriasis) to 5 (severe; worst their psoriasis has ever been).
- The Psoriasis Symptom Scale (PSS) is a patient-reported assessment of 8 symptoms: itch, pain, discomfort, stinging, burning, redness, scaling, and cracking. Respondents are asked to answer the questions based on their psoriasis symptoms. Numeric rating scales are used to assess the self-reported overall severity of each of the 8 symptoms individually on an 11-point horizontal scale anchored at 0 (no) and 10 (worst imaginable). The overall severity for each individual symptom from psoriasis is indicated by selecting the number from 0 to 10 that best describes the worst level of each symptom in the preceding 24 hours. The instructions for completion are embedded within the PSS questionnaire for subjects to read before responding to the items. The symptom severity scores, ranging from 0 to 10, are the values of the selected numbers indicated by the subject on the instrument's horizontal scale. Each of the 8 individual items will receive a score of 0 to 10 and will be reported as item scores for itch, pain, discomfort, stinging, burning, redness, scaling, and cracking. In addition, a total score ranging from 0 (no psoriasis symptoms) to 80 (worst imaginable psoriasis symptoms) will be reported.

9.6.2. 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 the LY3316531. To interpret the results of immunogenicity, a PK sample will be collected at the same time points. All samples for immunogenicity should be taken predose when applicable. In the event of drug hypersensitivity reactions (immediate or non-immediate), additional samples will be collected as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. 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.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of LY3316531 at a laboratory approved by the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of LY3316531. Patients/subjects who are treatment-emergent (TE) ADA positive at the end of the study or early discontinuation will be followed up with samples taken approximately every 3 months, until they return to 2-fold titer of baseline or for a maximum of 1 year. Treatment-emergent ADAs are defined in Section 10.3.4.

Samples will be retained for a maximum of 15 years after the last patient/subject 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 LY3316531. 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 (Section 2), 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 LY3316531 and to investigate genetic variants thought to play a role in psoriasis. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient/subject number. These samples and any data generated can be linked back to the patient/subject only by the investigative 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 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 LY3316531 or after LY3316531 is commercially available.

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.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

The sample size for each cohort is customary for the first-in-human study in which formal power analyses is not necessary to address the objectives associated with safety, tolerability, PK, and/or PD assessments. Approximately 86 patients/subjects are planned for enrollment; however, up to 102 subjects may be enrolled to allow for replacement of subjects and any additional dose cohorts (Parts A, B, and C).

Subjects/patients who withdraw from the study before completing the Day 57 (Part A) or Day 85 (Parts B and C) assessment may be replaced if necessary to have the planned number of subjects/patients complete a dose cohort. A replacement subject/patient will be assigned the same treatment as the subject/patient he or she replaces (Parts A, B, and C).

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

A detailed description of patient/subject disposition will be provided at the end of the study.

All subjects who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. A disposition table for all enrolled subjects will be provided.

10.2.2. Study Participant Characteristics

The subject's/patient's age, sex, weight, height, racial designation, or other demographic and study disease characteristics will be recorded and summarized.

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee.

Pharmacokinetic/PD analyses (CGRP target engagement) will be conducted on data from all patients/subjects who receive at least 1 dose of the IP and have evaluable PK.

Clinical activity and PD analyses will be conducted for all patients with psoriasis who receive the study drug (Part C only).

Safety analyses will be conducted for all enrolled patients/subjects, whether or not they completed all protocol requirements.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations prior to database lock and unblinding. Details of subject assignment to the analysis populations will be listed.

The placebo data from all cohorts will be pooled across all dose-escalation cohorts for the purpose of analysis.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post hoc analyses and incomplete disclosures of analyses.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All IPs and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with IP as perceived by the investigator. Symptoms reported to occur prior to treatment with study drug will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities.

Safety analyses will include summaries of the following:

- AEs and SAEs, including severity and possible relationship to study drug
- laboratory measures

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The number of IP-related SAEs will be reported and summarized by preferred term.

Suicidal ideation and/or behavior and self-injurious behavior with no suicidal intent, based on the C-SSRS, will be listed by patient/subject (Parts B and C).

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters, vital signs, and ECG parameters. The parameters will be listed, and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

Baseline for safety parameters will be defined as the last evaluable value before the first dose.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Analyses

Pharmacokinetic parameter estimates for LY3316531 will be calculated using standard noncompartmental methods of analysis.

The primary parameters for analysis will be C_{max} and AUC of LY3316531. Other noncompartmental parameters, such as half-life, apparent clearance, absolute bioavailability, and apparent volume of distribution may be reported. Mean and individual plasma concentration

versus time profiles and individual and summary statistics of PK parameter estimates by treatment group will be generated.

Population-based methods of analyses may also be performed, to understand factors that influence the PK, characterize the inter- and intra-subject variability in PK and support simulations of multiple dose administration.

10.3.2.2. Pharmacokinetic Statistical Inference

The dose proportionality of selected LY3316531 PK parameters following IV administration in Part A of the study, including logarithm of C_{max} and relevant AUC values, will be examined across the entire dose range using a power-model approach (Smith et al. 2000). Other analyses of PK parameters may be performed as deemed appropriate.

10.3.3. Pharmacodynamic Analyses and Clinical Activity

Clinical activity and PD data obtained will be documented in the study report by dose, plasma drug concentrations, and time from dose. However, the data collected at the visits leading up to and including the Week 4 visit will be the data used for evaluation of changes in clinical activity and PD measures. Figures showing values of potential PD markers versus time will be created for each dose, with a line for each patient. Absolute percentage change from baseline for all will be summarized by providing the mean, standard deviation, median, minimum, and maximum for each cohort and overall for each sample day/time combination and maximum over the entire study. Data may be log-transformed prior to summarizing if necessary. The interpatient and intrapatient variability in human PD responses may also be assessed if appropriate.

10.3.3.1. Pharmacokinetic/Pharmacodynamic Analyses

Analyses of the relationship between LY3316531 exposure and efficacy endpoints collected in Part C (such as PASI score, sPGA, and BSA) will be investigated initially using graphical methods. Modeling approaches that use a simple direct response relationship (using AUC) or longitudinal models that link the time course of LY3316531 concentrations to the time course of response may be explored.

Analyses of the relationship between LY3316531 exposure and total CGRP serum concentrations will also be conducted using graphical- and model-based approaches. Additional PD endpoints and safety endpoints may be explored for exposure-response relationships if warranted upon review of the data.

10.3.3.2. Health Outcome Measures for Subjects with Psoriasis

The Patient's Global Assessment of Disease Severity will be reported and summarized at each applicable visit using standard descriptive statistics including number of subjects, mean, standard deviation, median, minimum, and maximum for continuous variables and number of subjects, frequency, and percentages for categorical variables. Comparisons between each active treatment and pooled placebo group will be made. Results from statistical analyses will be provided for descriptive purposes only; therefore, no statistical inferences will be made, and no control for multiplicity is planned.

10.3.4. Evaluation of Immunogenicity

The frequency and percentage of patients/subjects with baseline ADA, with ADA anytime postbaseline, and/or with TE ADA to LY3316531 will be tabulated. For patients/subjects who are ADA negative at baseline, TE ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution of the assay. For patients/subjects who are ADA positive at baseline, TE ADAs are defined as those with a 4-fold (2 dilutions) increase in titer compared to baseline. For the patients with TE ADA, the distribution of maximum titers will be described. The frequency and percentage of patients with neutralizing antibodies may also be tabulated for patients with TE ADA.

The relationship between the presence of antibodies and the PK parameters and PD response including safety to LY3316531 may be assessed.

10.3.5. Data Review During the Study

Access to safety data is scheduled to occur after every dosing session. The purpose of these reviews is to guide dose selection for the next dosing session, and/or to inform the design of subsequent studies. The investigator and the Lilly sponsor team will make the determination regarding dose escalation, based upon their review of the data. The investigator will remain blinded, and the Lilly sponsor team will be unblinded during these reviews.

In addition, data snapshots for preliminary analyses of PK data are planned to occur after Day 29 of Cohort 3 (Part A) prior to the initiation of the multiple-dose cohorts (Part B). The evaluation of these data will aid in determining the dose, margin of safety, and adjustment of PK sampling schedule. Data snapshots are also planned to occur after Day 29 of Cohort 6 in Part A and Day 57 of Cohort 1 in Part B. Additional data snapshots may be conducted as required. These snapshots and analyses will be conducted while the trial is ongoing, but no changes to the study design are planned.

10.3.6. Interim Analyses

An interim analysis will occur when all patients/subjects in Parts A, B, and C have completed all requirements stated in the Schedule of Activities (Section 2; up to Day 85 for Part A, up to Day 141 for Part B, and up to Day 113 for Part C) or discontinued early from the study. Lilly employees and employees of any third-party organization involved in the interpretation of data collected during the study are authorized to evaluate unblinded data for the interim analyses. This interim analysis will include all planned analyses of available data. The data will be used for the development of a clinical study report (CSR). Results that are not available at the time a CSR is developed can be provided in a separate report or CSR addendum.

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Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject 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
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and potential risks involved in participating in a study (required by some institutional review boards [IRBs]/ethical review boards [ERBs]).
AST	aspartate aminotransferase
blinding	A procedure in which 1 or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient/subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient/subject are not. A double-blind study is one in which neither the patient/subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
CGRP	calcitonin gene-related peptide
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be re-tested at some defined time point, depending on the steps required to obtain confirmed results.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRU	clinical research unit
CSE	clinically significant event

CSR	clinical study report
C–SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a patient/subject to a treatment. Patients/subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients/subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
GCP	good clinical practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
Ig	immunoglobulin
IL	interleukin
informed consent	A process by which a patient/subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's/subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IV	intravenous

legal representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective patient/subject, to the patient's/subject's participation in the clinical study.
mAb	monoclonal antibody
MTD	maximum tolerated dose
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participant are aware of the drug therapy received during the study.
PASI	Psoriasis Area and Severity Index
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PSS	Psoriasis Symptom Scale
PUVA	psoralen plus ultraviolet A light therapy
QTc	QT interval
randomize	The process of assigning subjects/patients to an experimental group on a random basis.
RNA	ribonucleic acid
SAD	single-ascending dose;
SAE	serious adverse event
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBL	total bilirubin level
TE	treatment emergent
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
Th	T helper
TNF	tumor necrosis factor

TST	tuberculin skin test
ULN	upper limit of normal
CCI	[redacted]
WOCBP	women of childbearing potential

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
- Platelets

Absolute Counts of:
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

Urinalysis
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Leukocyte esterase or nitrite
- Microscopic examination of sediment[f]

Clinical Chemistry
- Sodium
- Potassium
- Glucose, random
- Blood urea nitrogen (BUN)
- Uric acid
- Total cholesterol
- Total protein
- Albumin
- Total bilirubin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST/SGOT)
- Alanine aminotransferase (ALT/SGPT)
- Creatinine
- Gamma-glutamyl transferase (GGT)
- Immunoglobulins (IgA, IgM and IgG)[a]

Serology
- Hepatitis B surface antigen[a]
- Hepatitis B core antibody[a]
- Hepatitis B surface antibody[a]
- Hepatitis C antibody[a,c]
- Hepatitis C virus (HCV) ribonucleic acid (RNA)[c]
- HIV[a]

Other
- Urine ethanol test[d]
- Urine drug screen[d]
- QuantiFERON®-TB Gold test or TST[a]
- Pregnancy test[e] (serum[a] and urine)
- FSH[a,e]
- HS-C-reactive protein[b]
- Serum concentration of LY3316531 (PK)
- Target engagement assay (CGRP)
- CCI [redacted]
- Pharmacogenetics (exploratory storage samples for DNA)
- Exploratory storage samples (serum, plasma, RNA)[b]
- Immunogenicity (anti-LY3316531 antibodies)

Abbreviations: CGRP = calcitonin gene-related peptide; DNA = deoxyribonucleic acid; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; HS = high sensitivity; IL = interleukin; PK = pharmacokinetic; RBC = red blood cell; RNA = ribonucleic acid; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; TB = tuberculosis; TST = tuberculin skin test; WBC = white blood cell.

[a] Performed at screening only.

[b] Performed in patients with psoriasis only.

[c] A positive hepatitis C antibody laboratory assessment will be confirmed with a test for hepatitis C virus (HCV) ribonucleic acid (RNA).

[d] Urine drug screen and ethanol test will be performed at screening and repeated prior to admission to the clinical research unit (Day -1), and when clinically indicated.

[e] For female patients/subjects only.

[f] Will only be performed if urine dipstick evaluation shows abnormality.

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for

- ensuring that the patient/patient's legal representative/subject 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/subject 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/subject or patient's/subject's legal representative may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's/subject's or patient's/subject's legal representative's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the participant or the participant'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 International Council for Harmonisation (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 investigative site(s). Lilly or its representatives must approve the ICF before it is used at the investigative 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 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

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

Some of the obligations of the sponsor will be assigned to a third-party organization.

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.

The investigator with the most enrolled patients/subjects will serve as the final report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

The sponsor's responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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. 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 by mail, telephone, and/or fax.
- review and evaluate CRF data and/or use standard computer edits to detect errors in data collection.

- conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the patient/subject 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.

Study and Site 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 TE 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
Total bilirubin	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; 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

APP. 5.1. Part A (SAD in Healthy Subjects)

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

Protocol I9H-MC-FFAA Sampling Summary (Part A)

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Clinical laboratory tests[a]	12	13	156
Pharmacokinetics[b]	5	18	90
Blood discard for cannula patency	1	4	4
Pharmacodynamics (total CGRP)	2	8	16
Immunogenicity[b]	7.5	7	52.5
Pharmacogenetics	6	1	6
Total			369.5
Total for clinical purposes			370

Abbreviation: CGRP = calcitonin gene-related peptide.

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

[b] Includes 3 additional samples to be drawn if needed to aid in the assessment of anti-drug hypersensitivity reactions.

APP.5.2. Part B (Multiple-Dose in Healthy Subjects)

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

Protocol I9H-MC-FFAA Sampling Summary (Part B)

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Clinical laboratory tests[a]	12	9	108
Pharmacokinetics[b]	5	30	150
Blood discard for cannula patency	1	4	4
Pharmacodynamics (total CGRP)	2	9	18
Immunogenicity[b]	7.5	11	82.5
Pharmacogenetics	6	1	6
Total			413.5
Total for clinical purposes			420

Abbreviation: CGRP = calcitonin gene-related peptide.

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

[b] Includes 3 additional samples to be drawn if needed to aid in the assessment of anti-drug hypersensitivity reactions.

APP.5.3. Part C (Single Dose in Patients with Psoriasis)

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

Protocol I9H-MC-FFAA Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a,b]	45	1	45
Clinical laboratory tests[a,b]	12	15	180
Pharmacokinetics[c]	5	21	105
Blood discard for cannula patency	1	4	4
Pharmacodynamics (total CGRP)	2	11	22
Pharmacodynamics (CCI	2.5	6	15
Immunogenicity[c]	7.5	10	75
Pharmacogenetics	6	1	6
Exploratory samples (serum, plasma, RNA)	15	5	75
Total			527
Total for clinical purposes			530

Abbreviations: CGRP = calcitonin gene-related peptide; IL = interleukin; RNA = ribonucleic acid.

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

[b] The screening and clinical laboratory tests will include a hsCRP sample draw when indicated in the Schedule of Activities (Section 2.3).

[c] Includes 3 additional samples to be drawn if needed to aid in the assessment of anti-drug hypersensitivity reactions.

Appendix 6. Protocol FFAA PK, Immunogenicity, and ECG Sampling Schedule

APP.6.1. Part A (SAD in Healthy Subjects)

Visit	Week	Day Relative to LY/PL Treatment	PK Sampling Time IV Dosing[a]	PK Sampling Time SC Dosing[a]	Immunogenicity Sampling[a]	ECG[b]
2	0	1	Predose	Predose	Predose	Predose
2	0	1	End of infusion[c]	NA	NA	End of infusion[c]
2	0	1	2 h after start of infusion	NA	NA	NA
2	0	1	6 h after start of infusion	6 h post-injection	NA	6 h after SC injection or start of infusion
2	0	1	NA	NA	NA	12 h after start of infusion
2	0	2	24 h after start of infusion	24 h post-injection	NA	24 h after SC injection or start of infusion
3	0	4 ± 1 day	Any time during day	Any time during day	NA	NA
4	1	8 ± 1 day	Any time during day	Any time during day	NA	Any time during day
5	1	11 ± 1 day	NA	Any time during day	NA	NA
6	2	15 ± 2 days	Any time during day	Any time during day	Any time during day	Any time during day
7	3	22 ± 2 days	Any time during day	Any time during day	NA	NA
8	4	29 ± 2 days	Any time during day	Any time during day	Any time during day	NA
9	6	43 ± 3 days	Any time during day	Any time during day	NA	Any time during day
10	8	57 ± 3 days	Any time during day	Any time during day	NA	NA
11	10	71 ± 3 day	Any time during day	Any time during day	NA	NA
12	12	85 ± 3 days	Any time during day	Any time during day	Any time during day[d]	Any time during day
ED		ED	Any time during day	Any time during day	Any time during day[d]	Any time during day

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; ED = early discontinuation; h = hour(s); IV = intravenous; LY = LY3316531; PL = Placebo; NA = not applicable (no sampling needed at this time point); PK = pharmacokinetic; SC = subcutaneous; TE = treatment emergent.

[a] In the event of drug hypersensitivity reactions (immediate or non-immediate), up to 3 additional samples will be collected each for pharmacokinetics and immunogenicity as close to the onset of the reaction event as possible, at the resolution of the event, and 30 days following the event.

[b] ECG measurement should occur prior to the blood draw.

[c] Required for subjects receiving intravenous dosing only. ECGs (and vital signs) should be measured within 5 minutes prior to the end of infusion and PK samples as soon as possible after the infusion is completed

[d] Subjects who are TE ADA positive at the end of the study or early discontinuation will be followed with samples for ADA and PK being taken approximately every 3 months, until they return to 2-fold titer of baseline or for a maximum of 1 year.

Note: Samples that are requested to be taken predose through Day 2 should be collected as close to the sampling time as possible. Aberrations to the specified sampling times will not be considered protocol deviations as long as the samples are taken and the actual sampling time is recorded.

APP.6.2. Part B (Multiple-Dose in Healthy Subjects)

Visit	Week	Day Relative to First Dose LY/PL Treatment	PK Sampling Time IV Dosing[a]	PK Sampling Time SC Dosing[a,b]	Immunogenicity Sampling[a]	ECG[c]
2	0	1	Predose	Predose	Predose	Predose
2	0	1	End of infusion	NA	NA	End of infusion[d]
2	0	1	2 h after start of infusion	NA	NA	NA
2	0	1	6 h after start of infusion	6 h post-injection	NA	6 h after SC injection or start of infusion
2	0	2	24 h after start of infusion	24 h post-injection	NA	24 h after SC injection or start of infusion
3	0	4 ± 1 day	Any time during day	Any time during day	NA	NA
4	1	8 ± 1 day	Any time during day	Any time during day	NA	Any time during day
5	1	11 ± 1 day	NA	Any time during day	NA	NA
6	2	15 ± 2 days	Any time during day	Any time during day	Any time during day	Any time during day
7	3	22 ± 2 days	Any time during day	Any time during day	NA	NA
8	4	29	Predose	Predose	Predose	Predose
8	4	29	End of infusion	NA	NA	End of infusion[c]
8	4	30	24 h after start of infusion	24 h post-injection	NA	24 h after SC injection or start of infusion
9	4	32 ± 1 days	Any time during day	Any time during day	NA	NA
10	5	36 ± 1 days	Any time during day	Any time during day	NA	NA
11	5	39 ± 1 day	NA	Any time during day	NA	NA
12	6	43 ± 2 days	Any time during day	Any time during day	NA	NA
13	7	50 ± 2 days	Any time during day	Any time during day	NA	NA
14	8	57	Predose	Predose	Predose	Predose
14	8	57	End of infusion	NA	NA	End of infusion[d]
14	8	58	24 h after start of infusion	24 h post-injection	NA	24 h after SC injection or start of infusion
15	8	60 ± 1 day	Any time during day	Any time during day	NA	NA
16	9	64 ± 1 day	Any time during day	Any time during day	NA	Any time during day

17	9	67 ± 1 day	NA	Any time during day	NA	NA
18	10	71 ± 2 days	Any time during day	Any time during day	NA	Any time during day
19	11	78 ± 2 days	Any time during day	Any time during day	NA	NA
20	12	85 ± 3 days	Any time during day	Any time during day	Any time during day	Any time during day
21	16	113 ± 4 days	Any time during day	Any time during day	NA	NA
22	20	141 ± 4 days	Any time during day	Any time during day	Any time during day[e]	Any time during day
ED		ED	Any time during day	Any time during day	Any time during day[e]	Any time during day

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; ED = early discontinuation; h = hour(s); IV = intravenous; LY = LY3316531; PL = Placebo; NA = not applicable (no sampling needed at this time point); PK = pharmacokinetic; SC = subcutaneous; TE = treatment emergent.

[a] In the event of drug hypersensitivity reactions (immediate or non-immediate), up to 3 additional samples will be collected each for pharmacokinetics and immunogenicity as close to the onset of the reaction event as possible, at the resolution of the event, and 30 days following the event.

[b] Use this sampling schedule if SC dosing is utilized in the optional cohort.

[c] ECG measurement should occur prior to the blood draw.

[d] Required for subjects receiving intravenous dosing only.

[e] Subjects who are TE ADA positive at the end of the study or early discontinuation will be followed with samples for ADA and PK being taken approximately every 3 months, until they return to 2-fold titer of baseline or for a maximum of 1 year.

Note: Samples that are requested to be taken predose through Day 2 should be collected as close to the sampling time as possible. Aberrations to the specified sampling times will not be considered protocol deviations as long as the samples are taken and the actual sampling time is recorded.

APP.6.3. Part C (Single Dose in Patients with Psoriasis)

Visit	Week	Day Relative to LY Treatment	PK Sampling Time IV Dosing[a]	PK Sampling Time SC Dosing[a,b]	Immunogenicity Sampling[a]	ECG[c]
2	0	1	Predose	Predose	Predose	Predose
2	0	1	End of infusion	NA	NA	End of infusion
2	0	1	2 h after start of infusion	NA	NA	NA
2	0	1	6 h after start of infusion	6 h post-injection	NA	6 h after SC injection or start of infusion
2	0	2	24 h after start of infusion	24 h post-injection	NA	24 h after SC injection or start of infusion
3	0	4 ± 1 day	Any time during day	Any time during day	NA	NA
4	1	8 ± 1 day	Any time during day	Any time during day	NA	Any time during day
5	2	15 ± 2 days	Any time during day	Any time during day	Any time during day	Any time during day
6	3	22 ± 2 days	Any time during day	Any time during day	NA	NA
7	4	29 ± 2 days	Any time during day	Any time during day	Any time during day	NA
8	6	43 ± 3 days	Any time during day	Any time during day	NA	Any time during day
9	8	57 ± 3 days	Any time during day	Any time during day	NA	NA
10	10	71 ± 3 days	Any time during day	Any time during day	NA	NA
11	12	85 ± 3 days	Any time during day	Any time during day	Any time during day	Any time during day
12	16	113 ± 4 days	Any time during day	Any time during day	Any time during day[d]	Any time during day
ED		ED	Any time during day	Any time during day	Any time during day[d]	Any time during day
Up to 20[e]	Up to 52[e]	Up to 365[e]	Any time during day[f]	Any time during day[f]	Any time during day[g]	Any time during day
ED		ED	Any time during day	Any time during day	Any time during day	Any time during day

Abbreviations: ADA = antidrug antibody; ECG = electrocardiogram; ED = early discontinuation; h = hour(s); IV = intravenous; LY = LY3316531; NA = not applicable (no sampling needed at this time point); PK = pharmacokinetic; TE = treatment emergent.

a In the event of drug hypersensitivity reactions (immediate or non-immediate), up to 3 additional samples will be collected each for pharmacokinetics and immunogenicity as close to the onset of the reaction event as possible, at the resolution of the event, and 30 days following the event.

b Use this sampling schedule if SC dosing is utilized in an optional cohort.

[c] ECG measurement should occur prior to the blood draw.

[d] Patients who are TE ADA positive at the end of the study or early discontinuation will be followed with samples for ADA and PK being taken approximately every 3 months, until they return to 2-fold titer of baseline or for a maximum of 1 year.

[e] An extended follow-up period that requires monthly follow-up visits for patients who respond to treatment with LY3316531 after the initial 16-week follow-up period (see Section 5.1.3 for more details).

[f] PK sampling will be conducted at each monthly visit during the extended follow-up period for patients who responded to LY3316531 treatment.

[g] Patients should be assessed for ADAs during Weeks 26 (Day 183 ± 7 days) and 52 (Day 365 ± 7 days) of the extended follow-up period.

Note: Samples that are requested to be taken predose through Day 2 should be collected as close to the sampling time as possible. Aberrations to the specified sampling times will not be considered protocol deviations as long as the samples are taken and the actual sampling time is recorded.

Appendix 7. Protocol Amendment I9H-MC-FFAA (b) Summary
A Phase 1 Randomized, Placebo-Controlled Study of LY3316531 in Healthy Subjects and an Open-Label, Single-Dose Study in Patients with Psoriasis

Overview

Protocol I9H-MC-FFAA, A Phase 1 Randomized, Placebo-Controlled Study of LY3316531 in Healthy Subjects and an Open-Label, Single-Dose Study in Patients with Psoriasis has been amended. The new protocol is indicated by Amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

The number of patients to be enrolled in the planned and 2 optional cohorts of Part C was decreased from 8 patients to a minimum of 7 patients. A minimum of 7 patients are required to complete a cohort but up to 8 patients would still be allowed if 8 eligible patients can be identified in a timely manner. The reduced minimum required sample size was deemed sufficient to assess if there is evidence of clinical activity of LY3316531 based on PASI scores at 4 weeks, and is adequate for assessment of safety, tolerability and PK of the compound in the patient population at this stage of development.

Decreasing the cohort size to 7 patients will facilitate analysis of PASI scores for the purpose of determining if an optional cohort is needed to proceed once 4 weeks of data have been collected from 7 patients in a preceding cohort, thus preventing delay if 8 eligible patients cannot be identified in a timely manner. This overall decrease in cohort size from 8 patients to 7 patients has resulted in the specific changes outlined below. The rationale described for the overall change applies to these specific changes.

- Section 1 Protocol Synopsis
    - Number of Patients/Subjects
        - Part C: The number of patients from which evaluable data will be obtained was changed from 24 patients to up to 24 patients (total number of patients for planned and optional cohorts).
        - Part C: The number of patients per cohort was changed from 8 patients to a minimum of 7 patients planned but up to 8 patients allowed per cohort.
- Section 5 Study Design
    - 5.1 Overall Study Design

        - Table FFAA.5.1. Title was changed from "Summary of Patient/Subject Cohorts" to "Summary of Maximum Number of Patients/Subjects per Cohort" to reflect the planned number of subjects are the maximum number per cohort
        - Table FFAA.5.1.1 Summary of Maximum Number of Patients/Subjects per Cohort Part C: Footnote c was added to Patient Cohorts 1, 2, and 3 to explain that a minimum 7 patients are planned but up to 8 patients are allowed per cohort.
        - Figure FFAA.5.1. Study Design: Footnote d was added to Patient Cohorts 1, 2, and 3 to explain that a minimum 7 patients are planned but up to 8 patients are allowed per cohort.
    - 5.2 Number of Participants
        - 5.2.3. Part C (Single-Dose Design in Patients with Psoriasis): The number of patients to complete was changed from approximately24 patients to up to 24 patients.
- Section 7 Treatment
    - 7.4. Dose Modification
        - 7.4.1. Dose Decision (Part C): The number of patients from which 4 weeks of clinical activity data are needed in order to progress to the optional cohorts in Part C was changed from all patients (which in prior to amendment b is 8 patients) to at least 7 patients.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

1. Protocol Synopsis

Part C: It is planned that up to 30 patients may be enrolled in Part C of this study to obtain evaluable data from up to 24 patients (total number of patients for planned and optional cohorts). The patients with psoriasis single-dose part of the study is planned to include up to 3 cohorts (300 mg IV cohort with the option for 2 additional cohorts) with a minimum of 7 patients planned but up to 8 patients allowed per cohort (8 LY3316531).

5.1. Overall Design

Table FFAA.5.1. Summary of Maximum Number of Patients/Subjects per Cohorts~~

Cohort #	Planned Dose/ Administration Route	Number of Planned Subjects		Total Number of Planned Subjects
		LY	PBO	
Part A				
SAD Cohort 1[a]	3 mg/IV	3	1	4
SAD Cohort 2[a]	15 mg/IV	3	1	4
SAD Cohort 3	75 mg/IV	6	2	8
SAD Cohort 4	300 mg/IV	6	2	8
SAD Cohort 5	300 mg/SC	6	0	6
SAD Cohort 6	900 mg/IV	6	2	8
SAD Cohort 7	2000 mg/IV	6	2	8
Part B				
Multiple-Dose Cohort 1	2000 mg/IV	6	2	8
Multiple-Dose Cohort 2[b]	Route and dose TBD	6	2	8
Part C				
Patient Cohort 1[c]	300 mg/IV	8	0	8
Patient Cohort 2[b,c]	Route and dose TBD	8	0	8
Patient Cohort 3[b,c]	Route and dose TBD	8	0	8

Abbreviations: IV = intravenous; LY = LY3316531; PBO = placebo; SAD = single-ascending dose; SC = subcutaneous; TBD = to be determined.

[a] Sentinel dosing will be used in this cohort.

[b] Optional subject or patient cohort. Actual dose and route of administration will be determined based on cumulative data from previous cohorts, but will not exceed 2000 mg of LY3316531 administered IV.

[c] A minimum of 7 patients are planned but up to 8 patients are allowed per cohort.

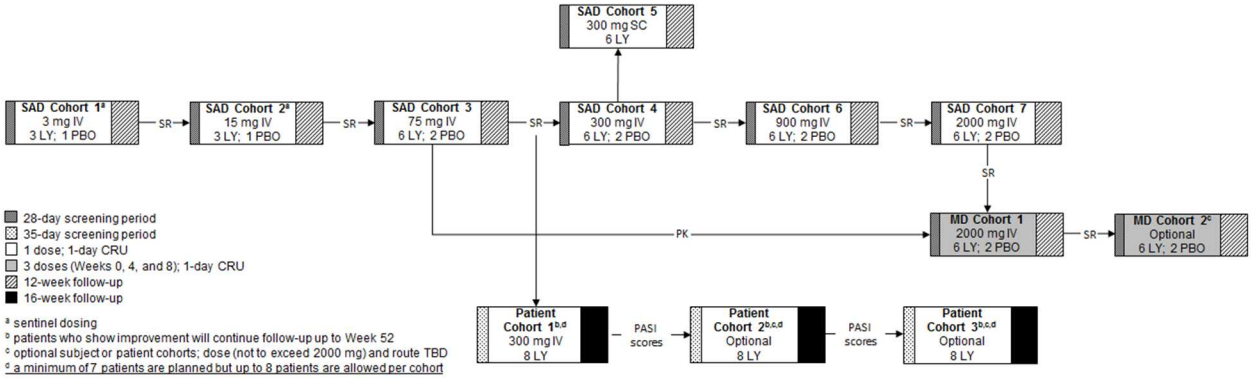

Figure FFAA.5.2. Illustration of study design for Protocol I9H-MC-FFAA.

5.2.3. Part C (Single-Dose Design in Patients with Psoriasis)

Up to 30 patients may be enrolled so that up to ~~approximately~~ 24 patients complete Part C (total number of patients planned for Cohort 1 and the 2 optional cohorts). For purposes of Part C, a patient completes the study when he/she completes all scheduled procedures up to and including at least Day 85.

7.4.1. Dose Decision (Part C)

The decision to initiate the first patient cohort in Part C will be based on the trial-level safety review for Cohort 3; however, any available preliminary PK data from Cohorts 1, 2, and 3 (through Day 29) in Part A will be considered as well. Progression to the optional cohorts in Part C will occur when at least 4 weeks of clinical activity data (PASI scores) are available from ~~all~~ at least 7 patients in the preceding cohort. In addition to the PASI scores, any available PK and applicable safety data from Part A will be considered for determining the dose for the optional patient cohorts. Dosing at the current level and further dose escalation will be discontinued if any of the scenarios described in Section 7.4.2 occur.

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