Protocol I6T-MC-AMAF(b)

A Phase 2, Multicenter, Randomized, Parallel-Arm, Placebo-Controlled Study of LY3074828 in Subjects with Moderate-to-Severe Plaque Psoriasis

NCT02899988

Approval Date: 21-Aug-2018

Protocol I6T-MC-AMAF(b)
A Phase 2, Multicenter, Randomized, Parallel-Arm, Placebo-Controlled Study of LY3074828 in Subjects with Moderate-to-Severe Plaque Psoriasis

Confidential Information

LY3074828

Study I6T-MC-AMAF is a Phase 2, multicenter, randomized, placebo-controlled study of LY3074828 in subjects with moderate-to-severe plaque psoriasis. The study consists of a double-blind, 16-week induction period where subjects will receive 1 of 4 treatment arms (LY3074828 30 mg, 100 mg, 300 mg, or placebo) at baseline and Week 8, a maintenance period consisting of 88 weeks of treatment, and 16 weeks of follow-up.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly on 24-May-2016.
Amendment (a) Electronically Signed and Approved by Lilly: 20 December 2017
Amendment (b) Electronically Signed and Approved by Lilly
on approval date provided below.

Approval Date: 21-Aug-2018 GMT

Table of Contents

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Appendices

Appendix **Page**

1. Synopsis

Title of Study:

A Phase 2, Multicenter, Randomized, Parallel-Arm, Placebo-Controlled Study of LY3074828 in Subjects with Moderate-to-Severe Plaque Psoriasis.

Rationale:

Study I6T-MC-AMAF (AMAF) is a Phase 2 study designed to determine whether subcutaneous (SC) administration of LY3074828, CCI monoclonal antibody that is directed against the p19 subunit of IL-23, is safe and efficacious in subjects with moderate-to-severe plaque psoriasis. This study will help determine the clinical activity defined by improvement in skin disease severity measures and key patient reported outcomes measures, as well as safety findings, that will support design of Phase 3 studies.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To test the hypothesis that treatment with LY3074828 is superior to placebo in inducing PASI 90 response at Week 16 in subjects with moderate-to-severe plaque psoriasis	The proportion of subjects achieving PASI 90 at Week 16 (NRI)
Secondary • To evaluate the safety and tolerability of treatment with LY3074828	• Adverse event and discontinuation rates
• To evaluate the efficacy of treatment with LY3074828 compared to placebo in inducing PASI 100 and PASI 75 at Week 16	• The proportion of subjects achieving PASI 100 and PASI 75 at Week 16 (NRI)
• To evaluate the efficacy of treatment with LY3074828 compared to placebo in inducing sPGA 0 (clear) and sPGA 0/1 at Week 16	• The proportion of subjects achieving sPGA 0 and sPGA 0/1 at Week 16 (NRI)
• To evaluate the effect of LY3074828 on patient reported outcome measures: PSS, PatGA, DLQI, and SF-36 at Week 16	• The mean change from baseline for PSS, PatGA, DLQI, and SF-36 at Week 16
• To characterize the long-term efficacy of LY3074828 on the PASI 100, PASI 90, and PASI 75 responses at Week 52, 104, and 120	• The proportion of subjects achieving PASI 100, PASI 90, and PASI 75 at Weeks 52, 104, and 120
• To characterize the long-term efficacy of LY3074828 on patient reported outcome measures PSS, PatGA, DLQI, and SF-36 at Weeks 52, 104, and 120	• The mean change from baseline for PSS, PatGA, DLQI, and SF-36 at Weeks 52, 104, and 120
• To characterize the PK of LY3074828	• Clearance and volume of distribution

Abbreviations: DLQI = Dermatology Life Quality Index; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PASI 75 = 75% improvement in PASI from baseline; PASI 90 = 90% improvement in PASI from baseline; PASI 100 = 100% improvement in PASI from baseline; PatGA = Patient Global Assessment; PK = pharmacokinetics; PSS = Psoriasis Symptom Scale; SF-36 = Short-Form Health Survey; sPGA = static Physician's Global Assessment.

Summary of Study Design:

Study AMAF is a multicenter, randomized, parallel-arm, placebo-controlled trial with 4 study periods in subjects with moderate-to-severe plaque psoriasis. Subjects who complete the third study period may be eligible to participate in a separate long-term extension study as an alternative to participating in the fourth AMAF study period.

Treatment Arms and Duration:

The study will include 4 arms: 3 experimental arms in which LY3074828 will be dosed SC at 30 mg, 100 mg, or 300 mg and 1 placebo comparator arm. During the double-blind, 16-week induction period, study drug will be administered at Week 0 and Week 8. At the end of the induction period (Week 16), subjects will continue treatment in the maintenance period which is intended to explore 1 of 2 treatment strategies through Week 104. Dose levels in the maintenance period will remain double-blind; however, dosing strategy will be open-label. The maintenance period consists of 88 weeks of treatment. All placebo subjects and subjects assigned to treatment with LY3074828 who have a <90% improvement in Psoriasis Area and Severity Index (PASI) from baseline (PASI 90) at Week 16 will receive LY3074828 300 mg SC every 8 weeks (Q8W) during the entire maintenance treatment period. Subjects with ≥PASI 90 (as needed [PRN] dosing group) at Week 16 will only be dosed with LY3074828 at the baseline dose level assignment no more frequently than Q8W when disease activity level is <PASI 90, and this will continue until ≥PASI 90 is regained. The maintenance period will be followed by a 16-week follow-up period to assess subject safety and study drug efficacy. Subjects who complete the maintenance period may be eligible to participate in separate long-term extension study.

Number of Subjects:

Approximately 200 subjects will be randomized at a 1:1:1:1 ratio in the blinded induction dosing period to LY3074828 30 mg, 100 mg, 300 mg, and placebo (50 subjects per dosing regimen, respectively). Randomization will be stratified by prior exposure to biologic therapy for psoriasis use (yes/no).

Statistical Analysis:

Induction period analyses of efficacy and health outcomes will be conducted on the intent-to-treat (ITT) population. Maintenance period analyses of efficacy and health outcomes will be conducted on ITT subjects who receive at least 1 dose of study treatment and who enter the maintenance period at Week 16 (Visit 7). Safety analyses will be conducted on the safety population.

The primary analysis method for treatment comparisons of categorical efficacy and health outcome variables will be a logistic regression analysis with treatment, geographic region, and previous exposure to biologic therapy (yes/no) in the model, using the nonresponder imputation (NRI) method.

The primary analysis method for treatment comparisons of the continuous efficacy and health outcome variables will be a mixed-effects model for repeated measures (MMRM) analysis with treatment, geographic region, previous exposure to biologic therapy (yes/no), baseline value, visit, treatment-by-visit interaction, and baseline-by-visit interaction in the model as fixed factors.

No multiplicity control procedures will be used in the testing of the primary endpoint in this study. Fisher's exact test will be used for all adverse events (AE), baseline, discontinuation, and other categorical safety data. Continuous vital sign and laboratory values will be analyzed by an analysis of covariance (ANCOVA) with treatment and baseline value in the model.

2. Schedule of Activities

Induction Dosing Period (Visits 1-7)								
Visit No.	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Comments**
Week Relative to Study Drug Start	**-4**	**0**	**2**	**4**	**8**	**12**	**16**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**≤28 from V2**	**0**	**14 ± 2**	**28 ± 3**	**56 ± 5**	**84 ± 5**	**112 ± 5**	Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the allowable visit tolerance (at least 3 days should be allowed for receipt of laboratory test results).
Informed consent	X							
Demographics	X							
Height	X							
Physical examination & weight	X	X					X	One complete physical examination (excluding pelvic, rectal, and breast examinations) will be performed at screening. All physical examinations throughout the study should include a symptom-directed evaluation as well as examination of heart, lungs, and abdomen and visual examination of all skin areas (including genitalia and breast areas).
Review & confirm inclusion/exclusion criteria	X	X						
Complete medical/surgical history and habits	X							
Concomitant medications	X	X	X	X	X	X	X	
Preexisting conditions	X							
Adverse events	X	X	X	X	X	X	X	

Induction Dosing Period (Visits 1-7)								
Visit No.	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Comments**
Week Relative to Study Drug Start	**-4**	**0**	**2**	**4**	**8**	**12**	**16**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**≤28 from V2**	**0**	**14 ± 2**	**28 ± 3**	**56 ± 5**	**84 ± 5**	**112 ± 5**	Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the allowable visit tolerance (at least 3 days should be allowed for receipt of laboratory test results).
Vital signs (BP and heart rate), body temperature only at V1 and V2, unless clinically indicated	X	X	X	X	X	X	X	Sitting blood pressure and pulse, to be obtained at approximately the same time as ECG measurements or blood sampling. When multiple assessments are scheduled for the same time point, the order of completion should be as follows: ECG, vital signs, and then blood sampling.
Chest radiography for TB screening (required only if not already done within 3 months prior to screening)	X							Chest radiography (Section 9.4.4.1) will be performed at screening unless such radiography has been performed within 3 months before initial screening (provided the radiographs and/or formal report are available for the investigator's review).
PPD/QuantiFERON-TB Gold (per local guidelines)	X							Subjects will return 2 to 3 days after Visit 1 to have their PPD test read.
ECGs	X						X	This should be completed prior to any study dose administration or blood draw. Subjects should be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
C-SSRS	X	X	X	X	X	X	X	
CCI [redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study drug dosed		X			X		X	At Week 16, subjects will only receive study drug dosing if PASI <90.

Induction Dosing Period (Visits 1-7)								
Visit No.	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Comments**
Week Relative to Study Drug Start	**-4**	**0**	**2**	**4**	**8**	**12**	**16**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**≤28 from V2**	**0**	**14 ± 2**	**28 ± 3**	**56 ± 5**	**84 ± 5**	**112 ± 5**	Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the allowable visit tolerance (at least 3 days should be allowed for receipt of laboratory test results).
Clinical Efficacy								
PASI	X	X	X	X	X	X	X	
sPGA	X	X	X	X	X	X	X	
PSSI, if applicable		X	X	X	X	X	X	Once a subject experiences symptoms related to scalp involvement, this form should be completed at all remaining indicated visits.
Whole body photographs		X					X	If subject has agreed to whole body photographs.
Health Outcomes								
PSS	Electronic Diary Taken Daily from Screening (V1) up to Week 16 (V7)						X	
PatGA		X	X	X	X	X	X	
DLQI		X	X	X	X	X	X	
SF-36		X					X	
Laboratory Tests								
Hematology	X	X	X	X	X	X	X	Unscheduled blood chemistry and hematology panels may be performed at the discretion of the investigator.
Lymphocyte subsets		X					X	
Serum chemistry	X	X	X	X	X	X	X	Unscheduled blood chemistry and hematology panels may be performed at the discretion of the investigator.
Urinalysis	X	X			X		X	

Induction Dosing Period (Visits 1-7)								
Visit No.	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Comments**
Week Relative to Study Drug Start	**-4**	**0**	**2**	**4**	**8**	**12**	**16**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**≤28 from V2**	**0**	**14 ± 2**	**28 ± 3**	**56 ± 5**	**84 ± 5**	**112 ± 5**	Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the allowable visit tolerance (at least 3 days should be allowed for receipt of laboratory test results).
HBsAg, HBcAb, HBsAb	X							
HBV PCR	X					X		Any enrolled subject who is HBcAb+ will undergo monitoring of HBV PCR. Any subject with a positive HBV PCR test at any time must be discontinued from the study and receive appropriate follow-up medical care, including consideration for antiviral therapy.
Hep C antibody	X							Positive HCV antibody will be confirmed via HCV PCR.
HIV	X							
Immunogenicity		X	X	X	X	X	X	
Serum for LY3074828 concentrations (PK)		X	X	X	X	X	X	
Serum pregnancy test	X							To be performed only on women of child bearing potential.
Urine pregnancy test		X		X	X	X	X	To be performed only on women of child bearing potential.
FSH	X							FSH test is to be performed at screening for women who have had spontaneous amenorrhea for 6 to 12 months to confirm lack of childbearing potential.
hsCRP		X	X	X	X	X	X	
CCI [redacted]		[redacted]					[redacted]	
[redacted]		[redacted]			[redacted]		[redacted]	

Induction Dosing Period (Visits 1-7)								
Visit No.	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Comments**
Week Relative to Study Drug Start	**-4**	**0**	**2**	**4**	**8**	**12**	**16**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**≤28 from V2**	**0**	**14 ± 2**	**28 ± 3**	**56 ± 5**	**84 ± 5**	**112 ± 5**	Visit 1 procedures may be conducted over more than 1 day as long as all tasks are completed within the allowable visit tolerance (at least 3 days should be allowed for receipt of laboratory test results).
CCI [redacted]		[redacted]			[redacted]		[redacted]	
[redacted]		[redacted]						

Maintenance Dosing Period (Visits 8-18)												
Visit No.	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**Comments**
Week Relative to Study Drug Start	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**140 ± 5**	**168 ± 5**	**196 ± 5**	**224 ± 5**	**252 ± 5**	**280 ± 5**	**308 ± 5**	**336 ± 5**	**364 ± 5**	**392 ± 5**	**420 ± 5**	
Physical examination & weight				X					X			All physical examinations throughout the study should include a symptom-directed evaluation as well as examination of heart, lungs, and abdomen and visual examination of all skin areas (including genitalia and breast areas).
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	
Vital signs (BP and heart rate), body temperature only if clinically indicated	X	X	X	X	X	X	X	X	X	X	X	Sitting blood pressure and pulse, to be obtained at approximately the same time as ECG measurements or blood sampling. When multiple assessments are scheduled for the same time point, the order of completion should be as follows: ECG, vital signs, and then blood sampling.
ECGs									X			ECGs should be performed before any blood is drawn. Subjects should be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Maintenance Dosing Period (Visits 8-18)												
Visit No.	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**Comments**
Week Relative to Study Drug Start	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**140 ± 5**	**168 ± 5**	**196 ± 5**	**224 ± 5**	**252 ± 5**	**280 ± 5**	**308 ± 5**	**336 ± 5**	**364 ± 5**	**392 ± 5**	**420 ± 5**	
Study drug dosed	X	X	X	X	X	X	X	X	X	X	X	Subjects assigned to PRN will be evaluated at every visit to determine if dose needed. Subjects assigned to Q8W will get dosed on odd number visits.
Clinical Efficacy												
PASI	X	X	X	X	X	X	X	X	X	X	X	
sPGA	X	X	X	X	X	X	X	X	X	X	X	
PSSI, if applicable	X	X	X	X	X	X	X	X	X	X	X	Once a subject experiences symptoms related to scalp involvement, this form should be completed at all remaining indicated visits.
Whole body photographs				X					X			If subject has agreed to whole body photographs.
Health Outcomes												
PSS				X					X			
PatGA				X					X			
DLQI				X					X			In addition to the marked visits, DLQI also taken at PRN dosing or rescue treatment visits.
SF-36				X					X			
Laboratory Tests												
Hematology	X	X	X	X	X	X	X	X	X			Unscheduled blood chemistry and hematology panels may be performed at the discretion of the investigator.
Lymphocyte subsets									X			

Maintenance Dosing Period (Visits 8-18)												
Visit No.	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**Comments**
Week Relative to Study Drug Start	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**140 ± 5**	**168 ± 5**	**196 ± 5**	**224 ± 5**	**252 ± 5**	**280 ± 5**	**308 ± 5**	**336 ± 5**	**364 ± 5**	**392 ± 5**	**420 ± 5**	
Serum chemistry	X	X	X	X	X	X	X	X	X			Unscheduled blood chemistry and hematology panels may be performed at the discretion of the investigator.
Urinalysis				X					X			
HBV PCR		X			X			X			X	Any enrolled subject who is HBcAb+ will undergo monitoring of HBV PCR. Any subject with a positive HBV PCR test at any time must be discontinued from the study and receive appropriate follow-up medical care, including consideration for antiviral therapy.
Immuno-genicity		X		X		X		X		X		
Serum for LY3074828 concentration (PK)	X	X		X		X		X	X	X		
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	X	To be performed only on women of child bearing potential.
hsCRP	X	X	X	X	X	X	X	X	X	X	X	
Skin punch biopsy									X			
Serum/ plasma for storage/ exploratory biomarkers	X	X	X	X	X	X	X	X	X	X	X	
CCI [redacted]		[redacted]			[redacted]				[redacted]		[redacted]	

Maintenance Dosing Period (Visits 19-29)												
Visit No.:	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**Comments**
Week Relative to Study Drug Start	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**448 ± 5**	**476 ± 5**	**504 ± 5**	**532 ± 5**	**560 ± 5**	**588 ± 5**	**616 ± 5**	**644 ± 5**	**672 ± 5**	**700 ± 5**	**728 ± 5**	
Physical examination & weight				X							X	All physical examinations throughout the study should include a symptom-directed evaluation as well as examination of heart, lungs, and abdomen and visual examination of all skin areas (including genitalia and breast areas).
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	
Vital signs (BP and heart rate), body temperature only if clinically indicated	X	X	X	X	X	X	X	X	X	X	X	Sitting blood pressure and pulse, to be obtained at approximately the same time as ECG measurements or blood sampling. When multiple assessments are scheduled for the same time point, the order of completion should be as follows: ECG, vital signs, and then blood sampling.
ECGs					X						X	ECGs should be performed before any blood is drawn. Subjects should be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Maintenance Dosing Period (Visits 19-29)												
Visit No.:	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**Comments**
Week Relative to Study Drug Start	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**448 ± 5**	**476 ± 5**	**504 ± 5**	**532 ± 5**	**560 ± 5**	**588 ± 5**	**616 ± 5**	**644 ± 5**	**672 ± 5**	**700 ± 5**	**728 ± 5**	
Study drug dosed	X	X	X	X	X	X	X	X	X	X	X	Subjects assigned to PRN will be evaluated at every visit to determine if dose needed. Subjects assigned to Q8W will get dosed on odd number visits. For subjects who enter the separate long-term extension study, the Visit 29 dose will be determined by the protocol of that study.
Clinical Efficacy												
PASI	X	X	X	X	X	X	X	X	X	X	X	
sPGA	X	X	X	X	X	X	X	X	X	X	X	
PSSI, if applicable	X	X	X	X	X	X	X	X	X	X	X	Once a subject experiences symptoms related to scalp involvement, this form should be completed at all remaining indicated visits.
Whole body photographs											X	If subject has agreed to whole body photographs.
Health Outcomes												
PSS											X	
PatGA											X	
DLQI											X	
SF-36											X	
Laboratory Tests												
Hematology	X				X				X		X	Unscheduled blood chemistry and hematology panels may be performed at the discretion of the investigator.
Lymphocyte subsets											X	

Maintenance Dosing Period (Visits 19-29)												
Visit No.:	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**Comments**
Week Relative to Study Drug Start	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**448 ± 5**	**476 ± 5**	**504 ± 5**	**532 ± 5**	**560 ± 5**	**588 ± 5**	**616 ± 5**	**644 ± 5**	**672 ± 5**	**700 ± 5**	**728 ± 5**	
Serum chemistry	X				X				X		X	Unscheduled blood chemistry and hematology panels may be performed at the discretion of the investigator.
Fasting lipid profile											X	Patients should not eat or drink anything except water for 12 hours prior to sample collection. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation.
Urinalysis	X				X				X		X	
HBV PCR			X			X			X		X	Any enrolled subject who is HBcAb+ will undergo monitoring of HBV PCR. Any subject with a positive HBV PCR test at any time must be discontinued from the study and receive appropriate follow-up medical care, including consideration for antiviral therapy.
Immuno-genicity	X		X		X		X		X		X	
Serum for LY3074828 concentration (PK)	X		X		X		X		X	X	X	
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	X	To be performed only on women of child bearing potential.
hsCRP	X	X	X	X	X	X	X	X	X	X	X	
Serum/ plasma for storage/ exploratory biomarkers	X	X	X	X	X	X	X	X	X	X	X	

Maintenance Dosing Period (Visits 19-29)												
Visit No.:	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**Comments**
Week Relative to Study Drug Start	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**448 ± 5**	**476 ± 5**	**504 ± 5**	**532 ± 5**	**560 ± 5**	**588 ± 5**	**616 ± 5**	**644 ± 5**	**672 ± 5**	**700 ± 5**	**728 ± 5**	
CCI [redacted]			[redacted]			[redacted]			[redacted]		[redacted]	

Follow-up Period (Visits 801-804)					
Visit No.:	**V801[a]**	**V802[a]**	**V803[a]**	**V804/ET**	**Comments**
Week Relative to Study Drug Start	**108**	**112**	**116**	**120**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**756 ± 5**	**784 ± 5**	**812 ± 5**	**840 ± 5**	
Physical examination & weight				X	All physical examinations throughout the study should include a symptom-directed evaluation as well as examination of heart, lungs, and abdomen and visual examination of all skin areas (including genitalia and breast areas).
Concomitant medications	X	X	X	X	
Adverse events	X	X	X	X	
Vital signs (BP and heart rate), body temperature only if clinically indicated	X	X	X	X	Sitting blood pressure and pulse, to be obtained at approximately the same time as ECG measurements or blood sampling. When multiple assessments are scheduled for the same time point, the order of completion should be as follows: ECG, vital signs, and then blood sampling.
ECGs				X	ECGs should be performed before any blood is drawn. Subjects should be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
C-SSRS	X	X	X	X	
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical Efficacy					
PASI	X	X	X	X	
sPGA	X	X	X	X	
PSSI, if applicable	X	X	X	X	Once a subject experiences symptoms related to scalp involvement, this form should be completed at all remaining indicated visits.
Whole body photographs				X	If subject has agreed to whole body photographs.
Health Outcomes					
PSS				X	
PatGA				X	
DLQI				X	
SF-36				X	
Laboratory Tests					

Follow-up Period (Visits 801-804)					
Visit No.:	**V801[a]**	**V802[a]**	**V803[a]**	**V804/ET**	**Comments**
Week Relative to Study Drug Start	**108**	**112**	**116**	**120**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**756 ± 5**	**784 ± 5**	**812 ± 5**	**840 ± 5**	
Hematology				X	Unscheduled blood chemistry and hematology panels may be performed at the discretion of the investigator.
Serum chemistry				X	Unscheduled blood chemistry and hematology panels may be performed at the discretion of the investigator.
Fasting lipid profile				X	Patients should not eat or drink anything except water for 12 hours prior to sample collection. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation.
Urinalysis				X	
HBV PCR	X			X	Any enrolled subject who is HBcAb+ will undergo monitoring of HBV PCR. Any subject with a positive HBV PCR test at any time must be discontinued from the study and receive appropriate follow-up medical care, including consideration for antiviral therapy.
Immunogenicity		X		X	
Serum for LY3074828 concentration (PK)		X		X	
Urine pregnancy test				X	To be performed only on women of child bearing potential.
hsCRP	X	X	X	X	
Serum/ plasma for storage/ exploratory biomarkers	X	X	X	X	
CCI [redacted]				[redacted]	

Abbreviations: BP = blood pressure; C-SSRS = Columbia–Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET = early termination; FSH = follicle stimulating hormone; HBcAb = anti-hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; Hep C = hepatitis C; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; mins = minutes; PASI = Psoriasis Area and Severity Index; PatGA = Patient's Global Assessment; PCR = polymerase chain reaction; PK = pharmacokinetic; PPD = purified protein derivative; PRN = as needed; PSS = Psoriasis Symptom Scale; PSSI = Psoriasis Scalp Severity Index; Q8W = every 8 weeks; RNA = ribonucleic acid; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; sPGA = static Physician's Global Assessment; TB = tuberculosis; V = visit.

[a] A subject who chooses to enter the separate long-term extension study but is not able (for example, due to unresolved safety concerns) will continue to be evaluated at the follow-up period visits in Study AMAF until the subject is determined to be eligible for the separate long-term extension study, at which time the assessments for V804/ET will be performed.

3. Introduction

3.1. Study Rationale

Study I6T-MC-AMAF (AMAF) is a Phase 2 study designed to determine whether subcutaneous (SC) administration of LY3074828, CCI [redacted] monoclonal antibody that is directed against the p19 subunit of interleukin (IL)-23, is safe and efficacious in subjects with moderate-to-severe plaque psoriasis. Clinical evaluation of LY3074828 in psoriasis subjects (Section 3.2) supports the overall strategy of development of the compound in psoriasis and potentially other autoimmune diseases. This Phase 2 study will help determine the clinical activity defined by improvement in skin disease severity measures and key patient reported outcomes measures, as well as safety findings, that will support design of Phase 3 studies.

3.2. Background

The worldwide prevalence of psoriasis is nearly 3% (IFPA 2014), with rates varying across ethnic groups, ages, gender, and geographic regions (Parisi et al. 2013). Histologically, psoriasis is characterized by inflammatory infiltrate and hyperproliferative keratinocytes, which retain intact nuclei (parakeratosis), elongation of rete ridges, and hyperconvoluted vasculature in the papillary dermis. The infiltrate consists of prominent T cells, dendritic cells (DCs), and neutrophils in the dermis. The dysregulation of the immune system, especially the activation of pathogenic T cells, has been well demonstrated to play an important role in psoriasis development.

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 DCs 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 (including LY3074828 in Study I6T-MC-AMAA [AMAA]) (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). LY3074828 is CCI [redacted] monoclonal antibody (molecular weight approximately 144,000 Da) that is directed against the p19 subunit of IL-23

and does not bind IL-12. LY3074828 is being developed for the treatment of autoimmune diseases in which the IL-23 pathway is thought to have a pathogenic role.

3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of LY3074828 are to be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

Table AMAF.1 shows the objectives and endpoints of the study.

Table AMAF.1. Objectives and Endpoints

Objectives	Endpoints
Primary To test the hypothesis that treatment with LY3074828 is superior to placebo in inducing PASI 90 response at Week 16 in subjects with moderate-to-severe plaque psoriasis	The proportion of subjects achieving PASI 90 at Week 16 (NRI)
Secondary • To evaluate the safety and tolerability of treatment with LY3074828 • To evaluate the efficacy of treatment with LY3074828 compared to placebo in inducing PASI 100 and PASI 75 at Week 16 • To evaluate the efficacy of treatment with LY3074828 compared to placebo in inducing sPGA 0 (clear) and sPGA 0/1 at Week 16 • To evaluate the effect of LY3074828 on patient reported outcome measures: Psoriasis Symptom Scale, Patient Global Assessment, DLQI, and SF-36 at Week 16 • To characterize the long-term efficacy of LY3074828 on the PASI 100, PASI 90, and PASI 75 responses at Week 52, 104, and 120 • To characterize the long-term efficacy of LY3074828 on patient reported outcome measures Psoriasis Symptom Scale, Patient Global Assessment, DLQI, and SF-36 at Weeks 52, 104, and 120 • To characterize the PK of LY3074828	• Adverse event and discontinuation rates • The proportion of subjects achieving PASI 100 and PASI 75 at Week 16 (NRI) • The proportion of subjects achieving sPGA 0 and sPGA 0/1 at Week 16 (NRI) • The mean change from baseline for Psoriasis Symptom Scale, Patient Global Assessment, DLQI, and SF-36 at Week 16 • The proportion of subjects achieving PASI 100, PASI 90, and PASI 75 at Weeks 52, 104, and 120 • The mean change from baseline for Psoriasis Symptom Scale, Patient Global Assessment, DLQI, and SF-36 at Weeks 52, 104, and 120 • Clearance and volume of distribution
Tertiary/Exploratory CCI [redacted]	[redacted] • CCI

Objectives	Endpoints
• CCI	
	• CCI

Abbreviations: BSA = Body Surface Area; DLQI = Dermatology Life Quality Index; EC_{50} = concentration of drug giving half maximal response; E_{max} = maximum response achievable; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PASI 75 = 75% improvement in PASI from baseline; PASI 90 = 90% improvement in PASI from baseline; PASI 100 = 100% improvement in PASI from baseline; PD = pharmacodynamics; PK = pharmacokinetics; PSSI = Psoriasis Scalp Severity Index; SF-36 = Short-Form Health Survey; sPGA = static Physician's Global Assessment.

5. Study Design

5.1. Overall Design

Study AMAF is a multicenter, randomized, parallel-arm, placebo-controlled trial with 4 study periods in subjects with moderate-to-severe plaque psoriasis.

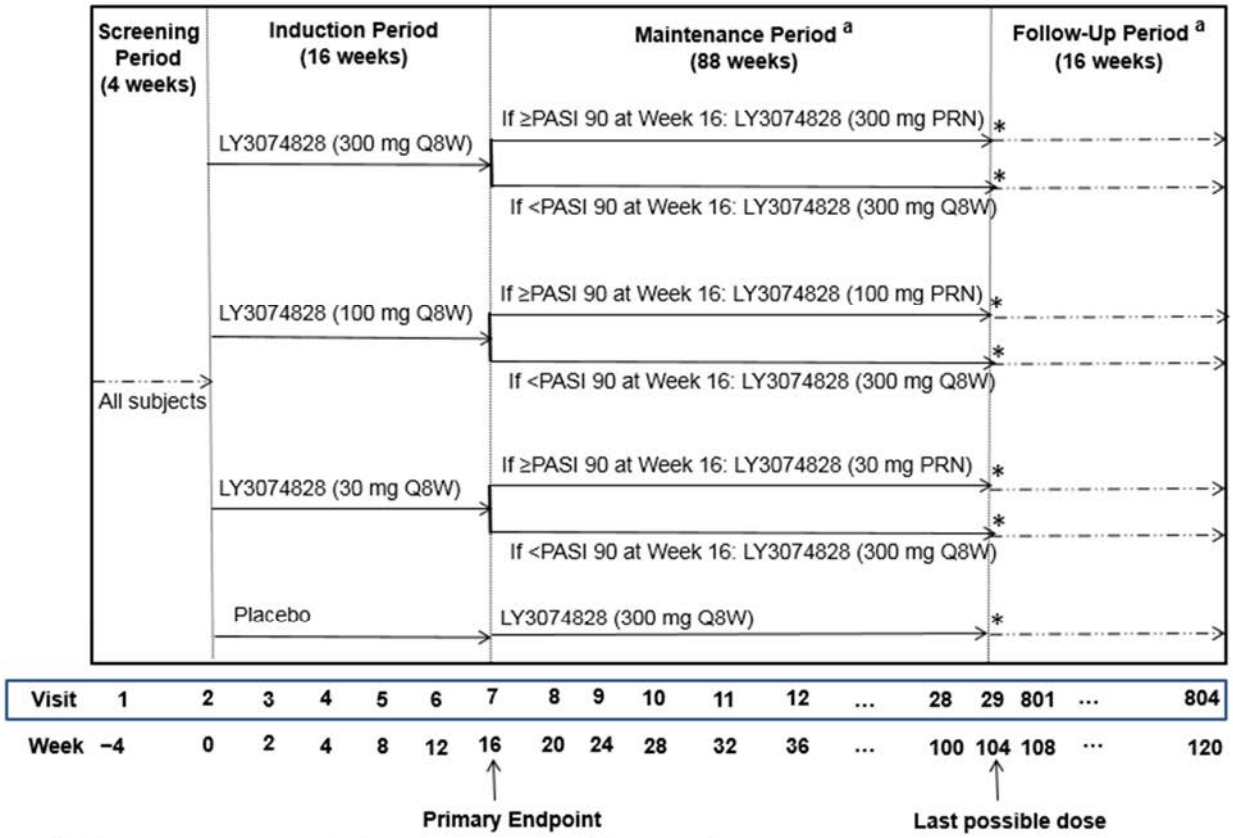
Screening Period (≤4 weeks): Subjects will be evaluated for study eligibility ≤28 days before the baseline visit (Visit 2/Week 0). At the baseline visit (Visit 2), subjects who fulfill the eligibility criteria will be randomized to 1 of 4 induction treatment arms.

Induction Period (16 weeks): A double-blind, 16-week induction period is designed to establish the efficacy and safety of LY3074828 administered at Visit 2 (Week 0) and Visit 5 (Week 8). Subjects will be randomized to 1 of 4 induction treatment arms (LY3074828 30 mg SC, LY3074828 100 mg SC, LY3074828 300 mg SC, and placebo every 8 weeks [Q8W]) stratified on the basis of previous exposure to biologic therapy for treatment of psoriasis.

Maintenance Period (88 weeks): The maintenance period consists of 88 weeks of treatment. At the end of the induction period (Week 16), subjects will continue treatment in the maintenance period which is intended to explore 1 of 2 treatment strategies through Week 104. All placebo subjects and subjects assigned to treatment with LY3074828 who have a <90% improvement in Psoriasis Area and Severity Index (PASI) from baseline (PASI 90) at Week 16 will receive LY3074828 300 mg SC Q8W during the entire maintenance period. Subjects with ≥PASI 90 (as needed [PRN] dosing group) at Week 16 will only be dosed with LY3074828 at the baseline dose level assignment no more frequently than Q8W when disease activity level is <PASI 90, and this will continue until ≥PASI 90 is regained. See Section 7.8.2 for maintenance period rescue treatment.

Subjects who complete Week 104 (Visit 29) of Study AMAF may be eligible to receive additional LY3074828 treatment by choosing to enroll in a separate long-term extension study, pending competent authority and/or ethical review board (ERB) approvals to conduct the separate long-term extension study.

Follow-up Period (16 weeks): Subjects who do not enroll in the separate long-term extension study will complete the follow-up period of Study AMAF. The follow-up period will include a visit every 4 weeks for a total of 16 weeks following Visit 29 to assess subject safety and study drug efficacy. Figure AMAF.1 illustrates the study design.



[a] Visits will occur every 4 weeks in the maintenance and follow-up periods.

* Option to enter the long-term extension study; patients who do not enter the long-term extension period will enter the Study AMAF Follow-Up Period.

Abbreviations: PASI = Psoriasis Area and Severity Index; PRN = as needed; Q8W = every 8 weeks.

Figure AMAF.1. Illustration of study design for Clinical Protocol I6T-MC-AMAF.

5.2. Number of Participants

Approximately 260 participants will be entered to achieve 200 randomized participants for an estimated total of 50 randomized participants per treatment group.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

This study will examine the effect of 16 weeks of induction dosing followed by evaluation of continuous dosing compared with PRN dosing in the maintenance period. All placebo subjects and subjects assigned to treatment with LY3074828 that have a <PASI 90 at Week 16 will receive LY3074828 300 mg SC Q8W during the entire maintenance treatment period. Subjects

with ≥PASI 90 (PRN dosing group) at Week 16 will only be dosed with LY3074828 at the baseline dose level assignment no more frequently than Q8W when disease activity level is <PASI 90, and this will continue until ≥PASI 90 is regained. The 2-year study duration will allow evaluation of the frequency of dosing a subject needs to maintain a high level PASI response.

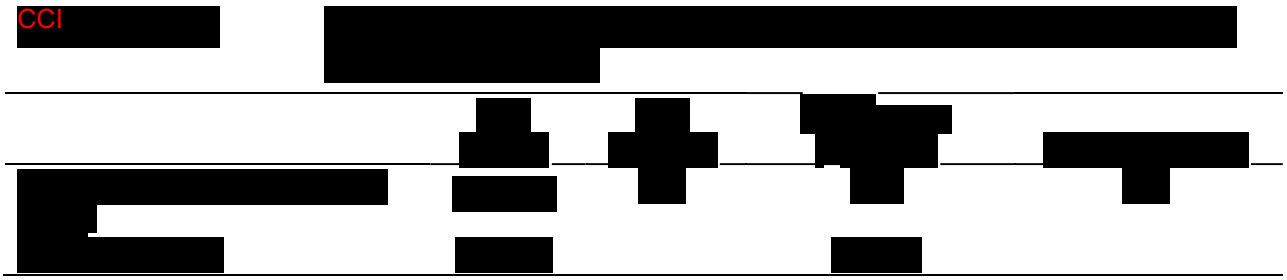
5.5. Justification for Dose

The dose levels and regimens planned for this study were selected based on analyses of PK, safety, and efficacy data from Study AMAA, literature information for other IL-23 antibodies, and nonclinical safety data.

The PK and efficacy data from Study AMAA in psoriasis subjects and literature information on psoriasis efficacy for other IL-23 antibodies (Gordon et al. 2015; Krueger et al. 2015; Papp et al. 2015) were used to develop a longitudinal model relating exposure of LY3074828 to PASI response rates. On the basis of simulations conducted with this model, doses of 30, 100, and 300 mg SC Q8W were chosen to cover a minimal-to-maximal effect range. At Week 16, the model projected PASI 90 response rates for 30, 100, or 300 mg Q8W during the induction period are (median [90% Projection Interval]) CCI [redacted] respectively.

At Week 104, the model projected PASI 90 response rates for subjects who achieved a PASI 90 response at Week 16 and received 30, 100, or 300 mg PRN maintenance dosing are CCI [redacted] respectively. At Week 104, the model projected PASI 90 response rates for subjects who received 30, 100, or 300 mg Q8W during the induction period and did not achieve a PASI 90 response at Week 16 and received 300 mg Q8W maintenance dosing are CCI [redacted], respectively.

The dose range and concentrations planned for this study were found to be safe in psoriasis subjects in the single-dose Study AMAA. The margin of safety for the high dose of 300 mg SC Q8W relative to the no-observed-adverse-effect level observed in the 6-month nonclinical toxicology study in cynomolgus monkeys is 26.7 based on dose and 31.4 based on area under the plasma concentration versus time curve (Table AMAF.2).



Abbreviations: AUC = area under the plasma concentration vs time curve; $AUC_{0–1344h,ss}$ = AUC over 1344 hours (8 weeks) at steady state; $AUC_{0–168}$ = AUC over 168 hours; IV = intravenous; NOAEL = no-observed-adverse-effect level; Q8W = every 8 weeks; SC = subcutaneous.

a Dose multiple is the dose in animals divided by dose in humans.

b Margin of safety is the calculated AUC in animals divided by predicted AUC in humans after adjusting for differences in dosing frequency.

c CCI

d NOAEL was determined in a 6-month repeat-dose toxicity study (Study 20043324).

e Monkey AUC value was based on average of male and female Day 176 means of AUC_{0-168} and has been multiplied by CCI AUC interval projected for humans and planned for this study.

6. Study Population

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

6.1. Inclusion Criteria

Subjects will be eligible for the study only if they meet all of the following criteria within the screening period, which is ≤28 days prior to the start of study treatment, unless specifically defined:

Type of Subject and Disease Characteristics

[1] 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 ≥10% body surface area (BSA) and absolute PASI score ≥12 in affected skin at screening (Visit 1) and baseline (Visit 2)
- sPGA score of ≥3 at screening (Visit 1) and baseline (Visit 2)
- are willing and able to undergo punch biopsies according to the Schedule of Activities (Section 2)

[2] candidate for biologic treatment for psoriasis

Subject Characteristics

[3] Male subjects must agree to use a reliable method of birth control during the study and for 3 months after the last dose of investigational product which is greater than 5 half-lives.

[4] Women of child-bearing potential must agree to either remain abstinent or use 2 effective methods of contraception for the entirety of the study. Abstinence or contraception must continue 3 months following completion of study drug administration which is greater than 5 half-lives.

A. Women of child bearing potential must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test at Visit 2 prior to exposure.

B. Two effective methods of contraception 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 (ie, 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.

[5] Women not of childbearing potential may participate and include those who are:

A. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or

B. postmenopausal – defined as either

i. A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either

a) cessation of menses for at least 1 year or

b) at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 mIU/mL; or

ii. A woman 55 years or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or

iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[6] are ≥18 and ≤ 75 years of age

[7] have an adequate organ function, including:

- hematologic: absolute neutrophil count ≥1.5 x 10^9/L (≥1.5x10^3/µL or ≥1.5 GI/L), platelet count ≥100 x 10^9/L (≥100 x 10^3/µL or ≥100 GI/L), hemoglobin level ≥10.0 g/dL (≥100 g/L), lymphocyte count >500 cells/µL (>0.50 x 10^3/µL or >0.50 GI/L), and total white blood cell count ≥3.0 x 10^9/L (≥3.0 x 10^3/µL or ≥3.0 GI/L)
- chemistry:
  - serum creatinine, aminotransferase (ALT), and aspartate aminotransferase (AST) levels ≤2 × upper limit of normal (ULN)
  - total bilirubin level (subjects with Gilbert's syndrome must have serum direct bilirubin <1.5 mg/dL) and alkaline phosphatase (ALP) <1.5 × ULN

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

Informed Consent

[9] have given written informed consent approved by Lilly, the ethics review board (ERB) governing the site, and any overseeing Regulatory Agency (if applicable)

6.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria within the screening period, which is ≤28 days prior to the start of study treatment, unless specifically defined:

Medical Conditions

[10] have an abnormality in the 12-lead electrocardiogram (ECG) that, in the opinion of the investigator, increases the risks associated with participating in the study

[11] Have presence or history within 12 months prior to screening of significant uncontrolled cerebrocardiovascular (for example, myocardial infarction, unstable angina, unstable arterial hypertension, moderate-to-severe heart failure [New York Heart Association class III/IV], or cerebrovascular accident); presence of 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

[12] use of known drugs of abuse or known alcohol abuse

[13] has Columbia Suicide Severity Rating Scale (C-SSRS) ideation within 1 month prior to screening or any suicidal behavior within 3 months prior to screening and either ideation or suicidal behavior during screening prior to Visit 2 treatment

[14] evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies

[15] have hepatitis C or test positive hepatitis C virus at screening, defined as: positive result for hepatitis C antibody and positive confirmatory polymerase chain reaction (PCR) test for hepatitis C virus

[16] have hepatitis B or test positive for hepatitis B virus (HBV) at screening, defined as: (1) positive for hepatitis B surface antigen (HBsAg+) or (2) positive for hepatitis B core antibody (HBcAb+) and positive confirmatory PCR for HBV, regardless of hepatitis B surface antibody status

[17] are women who are breastfeeding or plan to during study

[18] have donated blood of >500 mL within 14 days prior to baseline

[19] 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 treatment

[20] have received a systemic (including oral) anti-infective agent for an infection within 28 days of screening. Have had, according to the investigator, clinically significant symptomatic herpes zoster within 3 months of screening

[21] have evidence of active or latent tuberculosis (TB) (refer to Section 9.4.4.1 for details on full TB exclusion criteria)

[22] have received live vaccine(s) (included attenuated live vaccines) within 1 month of screening or intend to during the study

[23] have significant allergies to humanized monoclonal antibodies or any components of the LY3074828 product formulation

[24] have had lymphoma, leukemia, or any malignancy within the past 5 years, except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years and cervical carcinoma in situ, with no evidence of recurrence within the 5 years prior to baseline

[25] have any other skin conditions (excluding psoriasis) 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)

Prior/Concomitant Therapy

[26] 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 analogues) or phototherapy (including either oral and topical PUVA light therapy, ultraviolet B, excimer laser, or self-treatment with tanning beds or therapeutic sunbathing) within 28 days prior to baseline

[27] 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 nonprescription 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 analogues]) within 14 days prior to baseline

[28] have received anti-tumor necrosis factor (TNF) biologics or anti-IL-17 targeting biologics within 8 weeks prior to baseline

[29] have previous exposure to any biologic therapy targeting IL-23 (including ustekinumab), either licensed or investigational (previous briakinumab use is permitted)

[30] 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

Prior/Concurrent Clinical Trial Experience

[31] are currently enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study

[32] have participated, within the last 30 days in a clinical trial involving an investigational product. If the previous investigational product has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed prior to screening

[33] have previously completed or withdrawn from this study

Other Exclusions

[34] are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted

[35] are Lilly employees or employees of third-party organizations (TPOs) involved with the study that require exclusion of their employees

[36] are unsuitable for inclusion in the study in the opinion of the investigator or sponsor for any reason that may compromise the subject's safety or confound data interpretation

[37] have identifiable skin findings (for example, tattoos, birth marks, scars) that in the investigator's opinion could, if viewed in the photographs, reveal the subject's identity

6.3. Lifestyle Restrictions

Study participants should be instructed not to donate blood or blood products during the study or for 4 weeks following their last dose.

6.4. Screen Failures

Subjects who do not meet the criteria for participation in this study (screen failure) may be rescreened. Subjects may be rescreened only 1 time for failure due to criteria [1], [2], [4], [5], [7], [13], [17], [18], [19], [20], [22], [24], [26], [27], [28], [30], [31], [32], [34], or [35]. If a subject fails screening because of administrative reasons, rescreening can occur after sponsor approval. For each rescreening, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number. Subjects who have had previous screening chest radiography and TB tests as per protocol within 3 months of their rescreening date of consent do not need to repeat these procedures but may do so at the discretion of the investigator.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of SC administration of LY3074828 versus placebo during a 16-week induction period followed by a maintenance period designed to explore PRN maintenance treatment based upon disease activity at the end of the induction period. Table AMAF.3 shows the treatment regimens.

Table AMAF.3. Treatment Regimens

Treatment Group	Description
Induction Period	
LY Dose Arm 1	30 mg LY given SC Q8W
LY Dose Arm 2	100 mg LY given SC Q8W
LY Dose Arm 3	300 mg LY given SC Q8W
Comparator	Placebo given SC Q8W
Maintenance Period	
LY Dose Arm 1	If <PASI 90 at Week 16: 300 mg LY given SC Q8W
	If ≥PASI 90 at Week 16: 30 mg LY given SC PRN
LY Dose Arm 2	If <PASI 90 at Week 16: 300 mg LY given SC Q8W
	If ≥PASI 90 at Week 16: 100 mg LY given SC PRN
LY Dose Arm 3	If <PASI 90 at Week 16: 300 mg LY given SC Q8W
	If ≥PASI 90 at Week 16: 300 mg LY given SC PRN
Placebo	300 mg LY given SC Q8W

Abbreviations: LY = LY3074828; PASI = Psoriasis Area and Severity Index; PASI 90 = 90% improvement in PASI from baseline; PRN = as needed; Q8W = every 8 weeks; SC = subcutaneous.

SC administration of LY3074828 will be given in up to 4 injections (maximum volume 1.5 mL per injection). All subjects should be monitored after dosing according to investigator practice or local standard of care. Detailed instructions for investigational product administration will be provided separately by the sponsor.

Investigational product will be prepared at the site by unblinded pharmacists or other trained personnel. Investigational product will be administered at the site by blinded nurses or other trained personnel.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational agent(s) to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing
- at the end of the study returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law

7.1.1. Packaging and Labelling

LY3074828 will be supplied to the investigator by Lilly. Clinical trial materials are manufactured in accordance with good manufacturing practices. All investigational products will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

LY3074828 is supplied for clinical trial use as lyophilized powder in a glass vial and should be stored in refrigerated conditions (2ºC to 8ºC). The vial is manufactured to deliver CCI of LY3074828 and will be reconstituted with CCI [redacted] Placebo will be normal saline (0.9% sodium chloride).

When reconstituted and in a syringe, LY3074828 cannot be distinguished visually from placebo.

Detailed instructions regarding supplies and preparation and handling of LY3074828 will be provided by the sponsor.

Clinical trial materials will be labeled according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

Subjects who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS), and then the site will be responsible for administering the treatment to the subjects.

To achieve between-group comparability for exposure to previous biologic therapy, the randomization will be stratified by prior exposure to biologic therapy for psoriasis (yes/no).

7.2.1. Timing of Doses

The actual time of all dose administrations will be recorded in the subject's electronic case report form (eCRF).

7.3. Blinding

This is a double-blind study during the induction period. Baseline dose cohort assignment will remain blinded throughout the study; however, during the maintenance period, dosing strategy (PRN or Q8W) will be open label. To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. Only a study site pharmacist or other trained person will be unblinded at the site for investigational product preparation.

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option should be used ONLY if the subject's well-being requires knowledge of the subject's treatment assignment. All notifications resulting in an unblinding event are recorded and reported by the IWRS.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first

consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly clinical research physician (CRP) prior to unblinding a subject's treatment assignment unless this could delay emergency treatment of the patient. If a subject's treatment assignment is unblinded, Lilly must be notified immediately.

7.4. Dosage Modification

Dose adjustments are not permitted in this study, except for those for rescue therapy in the maintenance treatment period as described in Section 7.8.2.

7.5. Preparation/Handling/Storage/Accountability

Detailed instructions regarding supplies and preparation and handling of LY3074828 will be provided by the sponsor.

7.6. Treatment Compliance

Every attempt will be made to select subjects who have the ability to understand and comply with study instructions. The investigator is responsible for discussing methods to ensure high treatment compliance with the subject before randomization.

All doses of study medication will be administered at the study site. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

If a subject is noncompliant with study procedures and/or investigational product administration, the investigator should assess the subject to determine the reason for noncompliance and educate and/or manage the subject as appropriate to improve compliance. If, in consultation with Lilly or its designee, the noncompliance is deemed to be significant or if further noncompliance occurs, the subject should be discontinued from the study. A subject will be considered significantly noncompliant if he or she fails to attend for administration of study medication within the required treatment window as defined in the Schedule of Activities (Section 2).

7.7. Concomitant Therapy

All concomitant medication taken during the study must be recorded on the concomitant medication eCRF.

All subjects should maintain their usual medication regimens for concomitant conditions or diseases throughout the study unless those medications are specifically excluded in the protocol.

Subjects taking concomitant medications should be on stable dosages at the time of baseline and should remain at stable dosages throughout the study unless changes need to be made because of AEs. Additional systemic drugs are to be avoided during the study, unless required to treat AEs. Other medications may be allowed if they are approved by the sponsor or its designee.

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

Concomitant therapies for treatment of psoriasis during the study are permitted only as outlined in Table AMAF.4.

Table AMAF.4. CCI

[redacted]

7.8. Treatment after the End of the Study

7.8.1. Continued Access

LY3074828 will not be made available to subjects after conclusion of the study except by consenting and being eligible to participate in the separate long-term extension study, as described in Section 7.8.3.

7.8.2. Special Treatment Considerations

Subjects in the maintenance PRN dosing arm may receive blinded rescue treatment with 300 mg Q8W. Rescue treatment may occur if not regaining a PASI ≥90 after 3 consecutive doses of retreatment or if a subject is below a PASI 50 following 1 retreatment dose. A subject starting rescue treatment will remain on that regimen through the end of the study regardless of any subsequent changes in PASI score.

All biological agents carry the risk of an injection site and/or hypersensitivity general reaction. Therefore all subjects should be closely monitored for signs or symptoms that could result from such reactions. Sites should have appropriately trained medical staff and appropriate medical equipment available when subjects are receiving study drug. If a subject experiences an acute hypersensitivity reaction after an injection of study drug, he or she should receive appropriate supportive care.

7.8.3. Separate Long-Term Extension Study

Subjects who complete Study AMAF through the end of the maintenance period (Week 104 [Visit 29]) may be eligible to participate in a separate long-term extension study, which offers an additional treatment with LY3074828, pending competent authority and/or ERB approvals for the separate long-term extension study. To be eligible for the separate long-term extension study, subjects enrolled in Study AMAF must not have been permanently discontinued from the study treatment or from the study itself. Furthermore, subjects must meet the enrollment criteria specified in the protocol for the separate long-term extension study. Subjects who do not enroll into the separate long-term extension study will complete the follow-up period of Study AMAF.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Discontinuation of the investigational product for abnormal liver tests **should be considered** by the investigator when a subject meets one of the following conditions after consultation with the Lilly designated medical monitor and consideration of the clinical status of the subject (including patients with Gilbert's syndrome):

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

Subjects who discontinue the investigational product early will continue in the study according to the Schedule of Activities (Section 2).

Investigational product is to be discontinued for patients who experience clinically significant systemic hypersensitivity events (such as anaphylaxis) following administration of investigational product.

8.1.2. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor 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 sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product.

8.2. Discontinuation from the Study

Some possible reasons that may lead to permanent discontinuation include:

- enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study. **Note:** Enrollment in the separate long-term extension study shall be considered compatible with Study AMAF, provided that the subject is not permanently discontinued from treatment or from the study, and provided that the subject is deemed eligible for enrollment in the separate long-term extension 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 subject should be discontinued from the study
    - if the 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 subject requests to be withdrawn from the study
- AE
    - If the investigator decides that the subject should be withdrawn because of an AE/SAE or a clinically significant laboratory value, the investigational product is to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately. Refer to Safety Evaluations, Sections 9.2 and 9.2.1.
- subject experiences a systemic hypersensitivity event (such as anaphylaxis) following administration of investigational product.
- subject becomes pregnant

Subjects who discontinue the study early will have end-of-study procedures as outlined in Visit 804 in the Schedule of Activities (Section 2).

8.3. Lost to Follow-Up

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

Site personnel, or an independent third party, will attempt to collect the vital status of the subject within legal and ethical boundaries for all subjects randomized, including those who did not get

investigational product. Public sources may be searched for vital status information. If vital status is determined, this will be documented and the subject will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect vital status information.

9. Study Assessments and Procedures

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

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

Unless otherwise stated in the 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

9.1.1. Primary Efficacy Assessments

The primary efficacy endpoint is the proportion of subjects achieving PASI 90 at Week 16 (nonresponder imputation [NRI]). PASI 90 indicates 90% improvement from baseline in PASI.

The PASI is an accepted primary efficacy measurement for this phase of development of psoriasis treatments (EMA 2004). The PASI combines assessments of the extent of body-surface involvement in 4 anatomical regions (head, trunk, arms, and legs) and the severity of desquamation (scaling), erythema, and plaque induration/infiltration (thickness) in each region, yielding an overall score from 0 for no psoriasis up to 72 for the most severe disease (Fredriksson and Pettersson 1978). The PASI has been the most frequently used endpoint and measure of psoriasis severity in clinical trials (EMA 2004; Menter et al. 2008). A clinically meaningful response is a PASI 75, which represents at least a 75% decrease (improvement) from the baseline PASI score. Higher levels of clearance (PASI 90), as well as complete resolution of psoriasis (PASI 100), have become additional endpoints because of the increasing recognition of the association of higher clearance with greater health-related quality of life (Puig 2015).

9.1.2. Secondary Efficacy Assessments

Secondary efficacy endpoints are PASI 100 and PASI 75 at Week 16, sPGA at Week 16, and PASI 100, PASI 90, and PASI 75 at Weeks 52, 104, and 120.

PASI 100, 90, and 75 are percentage improvements in PASI (100%, 90%, and 75%, respectively).

The sPGA provides the physician's determination of the subject'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 subject's psoriasis is assessed as clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).

9.1.3. Additional Efficacy Assessments/Disease Activity Measures

Percent BSA will be evaluated as the percent involvement of psoriasis on each subject's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), where 1% corresponds to the size of the subject's hand (including the palm, fingers, and thumb) (National Psoriasis Foundation 2009).

Psoriasis Scalp Severity Index (PSSI) measures the affected scalp area and the severity of clinical symptoms. If the subject has scalp psoriasis at any time during the study, the PSSI will be used for all remaining visits. The PSSI is a composite score derived from the sum of scores for erythema, induration, and desquamation multiplied by a score for the extent of scalp area involved (range 0 to 72). Higher scores indicate worse severity (Thaci et al. 2015).

Clinical whole body photographs will be collected at the times shown in the Schedule of Activities (Section 2) for patients who have given their consent to have photographs taken. Detailed instructions for obtaining clinical photographs will be provided in a study manual. Documentation of the clinical improvement will be permitted through sequential whole body photography before and after study treatment.

9.1.4. Health Outcomes Assessments

The following patient-reported questionnaires will be administered according to the Schedule of Activities (Section 2) in countries where the questionnaires have been translated into the native language of the region and linguistically validated. They should be completed before administration of study drug; before the subject's clinical examination; before the subject receives any tests or results; and before the subject's health, health data, or emotions are discussed.

9.1.4.1. Psoriasis Symptom Scale

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 (NRS) 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 past 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.

9.1.4.2. Patient's Global Assessment of Psoriasis

The Patient's Global Assessment of Psoriasis (PatGA) is a patient-reported, single-item scale on which subjects are asked to rank, by selecting a number on a 0-to-5 NRS, the severity of their psoriasis "today" from 0 (clear), no psoriasis, to 5 (severe).

9.1.4.3. Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is a patient-reported, 10-question, validated, health-related quality of life (HRQOL) questionnaire that covers 6 domains: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment (Basra et al. 2008; Finlay and Khan 1994). Responses to each question include "Not at all," "A little," "A lot," and "Very much," with corresponding numerical scores of 0, 1, 2, and 3 respectively. A "Not relevant" option provided for Items 3 to 10 is scored as 0. Item 7 (work or studying) comprises 2 parts, with the first part being scored as 0 for a "No" response and 3 for a "Yes" response. If one answers "No" to the first part of the question, the response options for the second part are "A lot," "A little," and "Not at all" which correspond to the numerical scores of 2, 1, and 0, respectively. If any one question is left unanswered, it is scored 0; however, if 2 or more questions are left unanswered, the DLQI is not scored. The DLQI total score is the sum of all responses to its 10 questions. The DLQI sum score has a range of 0 to 30 with lower scores indicating less impairment and higher scores indicating more dermatology-specific HRQOL impairment. A DLQI total score of 0 to 1 is considered as having no effect on a subject's HRQOL (Hongbo et al. 2005).

9.1.4.4. Medical Outcomes Study 36-Item Short-Form Health Survey

The Short-Form Health Survey (SF-36) is a 36-item, patient-reported measure designed to be a short, multipurpose assessment of health (Ware and Sherbourne 1992). Items are answered on Likert scales of varying lengths. The SF-36 acute version will be used, which has a 1-week recall period. The SF-36 has 8 domains: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. Two overall summary scores can be obtained: physical component summary (PCS) and mental component summary (MCS) scores. Individual domains are scored from 0 to 100 with higher scores indicating better HRQOL. The PCS and MCS summary scores are normalized and transformed to calculate the PCS and MCS summary scores with normative values of 50 and standard deviation of 10 (Ware et al. 2001). Minimal clinically important differences (MCID) have been defined as ≥2.5-point increases from baseline for SF-36 PCS and MCS and ≥5.0-point increases from baseline for individual domain scores (Strand et al. 2013).

9.1.5. Appropriateness of Assessments

The clinical safety parameters in this study are routine elements of clinical health assessment and Phase 2 drug development. The disease activity and health outcome measurements are used both in clinical practice and psoriasis clinical trials. Psoriasis is associated with numerous skin based symptoms and HRQOL impairment, which justifies the use of psoriasis symptom severity as well as dermatologic and generic HRQOL assessments used in this study (Kimball et al. 2005; EMA 2004).

9.2. Adverse Events

Investigators are responsible for monitoring the safety of 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 subject.

The investigator is responsible for the appropriate medical care of 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 investigational product or the study, or that caused the subject to discontinue the investigational product before completing the study. The 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.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure or investigational product via eCRF.

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

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

The investigator answers yes/no when making this assessment.

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

If a subject's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.2.1. Serious Adverse Events

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

- 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 one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Although all AEs occurring after signing the ICF are recorded in the eCRF, SAE reporting begins after the subject has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly 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.

Pregnancy (during maternal or paternal exposure to investigational product) 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.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the 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.

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 identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. 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.

9.2.1.2. Adverse Event Monitoring with a Systematic Questionnaire

The C-SSRS (Posner et al. 2007; Columbia University Medical Center [WWW]) is a scale that captures the occurrence, severity, and frequency of suicide-related ideations and behaviors during the assessment period. The C-SSRS must be administered by appropriately trained site personnel. The tool was developed by the National Institute of Mental Health Treatment of

Adolescent Suicide Attempters trial group for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categorization of suicidal events. Subjects will be assessed according to the Schedule of Activities (Section 2).

CCI [redacted]

9.2.2. Complaint Handling

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

Subjects will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

- Complaints must be reported by site staff within 24 hours of study/site personnel becoming aware of a product issue, regardless of the availability of the complaint sample.
- Retain the investigational product under appropriate storage conditions, if available or when obtained, until instructed to return it to Lilly.
- Product complaints for Non-Lilly Products (including concomitant drugs) that do not have a Lilly Product Batch or Control number are reported directly to the manufacturer per product label.
- Follow the instructions outlined in the Product Complaint Form for other reporting requirements.

9.3. Treatment of Overdose

In case of suspected overdose, hematology, chemistry, vital signs, and oxygen saturation should be monitored and supportive care provided as necessary. There is no known antidote for LY3074828.

9.4. Safety

9.4.1. Electrocardiograms

For each subject, ECGs should be collected according to the Schedule of Activities (Section 2). ECGs should be recorded according to the study specific recommendations included in the Schedule of Activities.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the subject receives the first dose of the investigational treatment should be reported to Lilly or its designee as an AE via eCRF.

9.4.2. Vital Signs

For each subject, vital signs measurements should be conducted according to the Schedule of Activities (Section 2).

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the subject receives the first dose of study treatment should be reported to Lilly or its designee as an AE via eCRF.

9.4.3. Laboratory Tests

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

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the subject receives the first dose of investigational product should be reported to Lilly or its designee as an AE via eCRF.

9.4.4. Other Tests

9.4.4.1. Chest Radiography and Tuberculosis Testing

Posterior-anterior view and lateral view (unless local standards dictate 1 view) chest radiography will be obtained at screening (Visit 1), unless the radiographs or medical report from chest radiography performed within 3 months before initial screening (per local standard of care for TB evaluation) are available to the investigator for review.

In addition, subjects will be tested as indicated in the Schedule of Activities (Section 2) for evidence of active or latent TB. A positive TB test result is indicated by a purified protein derivative (PPD) skin test response ≥5 mm induration documented approximately 48 to 72 hours after test application (regardless of Bacillus Calmette-Guerin vaccination history). In countries where the QuantiFERON-TB Gold test (or equivalent) is available and is preferred (in the judgment of the investigator) as an alternative to the PPD skin test for the evaluation of TB infection in a subject, that test may be used instead of the PPD test. If the QuantiFERON-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the subject is excluded from the study.

Subjects with documentation of negative TB test results within 3 months before initial screening may not need to repeat TB testing at screening (Visit 1) based on judgment of the investigator. Documentation of this previous test result must include a record of the size (in millimeters) of the induration response. A PPD test recorded as “negative” without documenting the size of induration (in millimeters) will not be acceptable and will require a retest.

However, subjects with a PPD skin test response ≥5 mm induration or a positive QuantiFERON-TB Gold test result at screening and no other evidence of active TB may be rescreened once and enrolled according to the following requirements:

- after receiving at least 4 weeks of appropriate ongoing prophylactic therapy for latent TB as per local standard of care

- no evidence of treatment hepatotoxicity (ALT and AST levels must remain ≤2X ULN) upon retesting of serum ALT and AST levels before randomization

Such subjects must continue and complete appropriate latent TB therapy during the course of the study to remain eligible and must continue to meet all other inclusion and exclusion criteria for participation.

Subjects who have a documented history of completing an appropriate TB prophylaxis regimen with no history of reexposure since their treatments were completed and no evidence of active TB are eligible to participate in the study; these subjects should not undergo PPD or QuantiFERON-TB Gold (or other approved interferon-gamma release assay) testing.

Subjects who have had household contact with a person with active TB must be excluded unless appropriate and documented prophylaxis for TB has been given, as described above.

Subjects with any history of **active** TB are excluded from the study, regardless of previous or current TB treatments.

9.4.5. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

If a study subject experiences elevated ALT ≥3X ULN, ALP ≥3X ULN, or elevated TBL ≥2X ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure subject safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See Appendix 4.

Any enrolled subject who is HBcAb+ will undergo periodic monitoring of HBV deoxyribonucleic acid (DNA) per the Schedule of Activities.

In addition to the above, any enrolled subject who is HBcAb+ and who experiences an elevated ALT or AST level >3X ULN must undergo HBV DNA testing. If the HBV DNA PCR test is negative, the investigator should consult with the Lilly-designated medical monitor regarding further management of the subject.

If the result of any HBV DNA PCR test is positive at any time, the subject must be discontinued from the study and should receive appropriate follow-up medical care, including consideration for antiviral therapy. A specialist physician in the care of patients with hepatitis (for example, infectious disease or hepatologist subspecialists) should be consulted and potentially start antiviral therapy.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of a sponsor assessment committee (an advisory group for this study formed to protect the integrity of data; refer to Section 10.3.7) should conduct additional analyses of the safety data.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine the serum concentrations of LY3074828.

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last patient visit for the study.

9.6. Pharmacodynamics

Not applicable.

9.7. Pharmacogenomics

9.7.1. Whole Blood Sample for Pharmacogenetic Research

A whole 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 response to LY3074828 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 subject number. These samples and any data generated can be linked back to the subject only by the investigator site personnel.

Samples will be retained for a maximum of 15 years after the last subject visit for the study, or for a shorter period if local regulations and/or ERBs/investigational review boards (IRBs) impose shorter time limits, 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 LY3074828 or after LY3074828 becomes 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, and candidate gene studies. Regardless of technology utilized genotyping data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics (PD), mechanism of action, variability of subject response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

CCI [redacted] will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to LY3074828, pathways associated with psoriasis, mechanism of action of LY3074828, and/or research method or in validating diagnostic tools or assay(s) related to psoriasis.

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

Samples will be retained for a maximum 15 years after the last subject visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits, 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 LY3074828 or after LY3074828 becomes commercially available.

Skin biopsies from lesional skin at baseline will be required of all subjects according to the Schedule of Activities (Section 2). A local anesthetic will be applied, and 4-mm punch skin biopsies will be obtained from where a psoriatic lesion was in existence at baseline according to the Schedule of Activities. Detailed instructions for handling the biopsies at the study site will be provided by the sponsor. Skin biopsies will be used to understand the mechanism of action of the test drug. Exploratory analysis of biomarker data that comes from testing of the biopsies may be analyzed in relation to the clinical outcome, with a view to possible identification of baseline markers that predict response and to investigate the observed long lasting response to treatment.

9.8.1. Samples for Immunogenicity Research

Blood samples for immunogenicity testing will be collected to determine antibody production against the investigational product as specified in the Schedule of Activities (Section 2). Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of the investigational product (drug-tolerant ADA assay). Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the investigational product (neutralizing ADA assay).

Samples will be retained for a maximum of 15 years after the last subject visit for the study, or for a shorter period if regulations and ERBs impose shorter time limits, at a facility selected by

Lilly or its designee. The duration allows the sponsor to respond to future regulatory requests related to the investigational product.

9.9. Health Economics

Health economics and medical resource utilization parameters will not be evaluated in this study.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 200 subjects will be randomized at a 1:1:1:1 ratio in the blinded induction dosing period to LY3074828 30 mg, 100 mg, 300 mg, and placebo (50 subjects per dosing regimen, respectively). Randomization will be stratified by prior exposure to biologic therapy for psoriasis (yes/no).

CCI [redacted]

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Intent-to-treat (ITT)	All randomized subjects, even if the subject does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Subjects will be analyzed according to the treatment to which they were assigned. Unless otherwise noted, efficacy and health outcomes analyses for the induction period will be conducted on this population.
Safety	All randomized subjects who received at least 1 dose of study treatment. Subjects will be analyzed according to the treatment to which they were assigned. Safety analyses for the induction period will be conducted on this population.
Maintenance period	All ITT subjects who received at least 1 dose of study treatment and have entered the maintenance period at Week 16 (Visit 7). Efficacy, health outcomes, and safety analyses for the maintenance period will be conducted on this population.
Follow-up	All ITT subjects who received at least 1 dose of study treatment and have entered the post-treatment follow-up period. Subjects will be analyzed according to the last treatment they received before entering the post-treatment follow-up period. Efficacy, health outcomes, and safety analyses for the post-treatment follow-up period will be conducted on this population.

Abbreviation: ITT = intent-to-treat.

Additional analysis populations will be described in the statistical analysis plan (SAP) as deemed appropriate.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

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

Geographic regions will include United States (US) and other (Non-US). Unless otherwise specified, the statistical analysis models will adjust for geographic region and prior exposure to biologic therapy use (yes/no).

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

10.3.1.1. General Considerations for Analyses in the Induction Period

Continuous data will be summarized in terms of the mean, standard deviation, minimum, maximum, median, and number of observations. Categorical data will be summarized as frequency counts and percentages. Comparisons between each LY3074828 dose regimen (30 mg, 100 mg, 300 mg) and placebo will be performed for all analyses in the induction period with no adjustment for multiple comparisons.

For the induction period efficacy, health outcomes, and safety analyses, baseline is defined as the last available value before the initial randomization, which in most cases will be the measure recorded at Week 0 (Visit 2). Change from baseline will be calculated as the visit value of interest minus the baseline value.

Treatment comparisons of categorical efficacy variables will be conducted using a logistic regression analysis with treatment, geographic region (US/Non-US), and prior exposure to biologic therapy use (yes/no) in the model. The proportions and 95% confidence intervals will be reported.

Treatment comparisons of continuous efficacy and health outcome variables will be made using mixed-effects for repeated measures (MMRM).

When MMRM is used, the model includes treatment, geographic region (US/Non-US), prior exposure to biologic therapy use (yes/no), baseline value, visit, and the interaction of treatment-by-visit as fixed factors. The covariance structure to model the within-subject errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III sums of squares for the least squares means will be used for the statistical comparison; the 95% confidence interval will also be reported. Treatment group comparisons with placebo at Week 16 (Visit 7) and all other visits will be tested.

Fisher's exact test will be used for categorical safety data including AE, baseline, and discontinuations. Continuous vital sign and laboratory values will be analyzed by analysis of covariance (ANCOVA) with treatment and baseline value in the model. Other continuous safety variables will be analyzed by t-tests, unless otherwise stated.

10.3.1.2. General Considerations for Analyses in the Maintenance Period

For maintenance period efficacy analysis, unless otherwise stated, baseline is defined as the last available value before the initial randomization in the induction period which in most cases will be the value recorded at Week 0 (Visit 2).

For maintenance period safety analysis, for subjects

- randomized to placebo in the induction period and for subjects who did not achieve PASI 90, baseline is defined as the last available value before the treatment reassignment in the maintenance period (Week 16, Visit 7)
- who did achieve PASI 90, baseline is defined as the last available value before the initial randomization which in most cases will be the measure recorded at Week 0 (Visit 2)

Change from baseline and 95% confidence interval will be calculated by treatment as the visit value of interest minus the baseline value for continuous variables. The proportion and 95% confidence interval will be reported by treatment for categorical variables.

The Kaplan-Meier product limit method will be used to estimate the survival curves for time-to-event variables; median time to loss of response will be summarized by treatment.

10.3.1.3. Missing Data Imputation

Analysis of categorical efficacy and health outcome variables will be assessed using a NRI method. Subjects will be considered a nonresponder for the NRI analysis if they do not meet the clinical response criteria or have missing clinical response data at the analysis time point. Randomized subjects without at least 1 postbaseline observation will also be defined as nonresponders for the NRI analysis.

10.3.2. Treatment Group Comparability

10.3.2.1. Subject Disposition

Subject disposition will be summarized for each treatment period. Reasons for discontinuation from the study will be summarized. Treatment comparisons of reasons for discontinuation during induction will be made using Fisher's exact test.

10.3.2.2. Subject Characteristics

Subject characteristics and baseline clinical measures will be summarized for each treatment period. Baseline characteristics will include gender, age, age category, weight, race, geographic region (US/Non-US), baseline disease severity, duration of disease, prior exposure to biologic therapy, previous nonbiologic systemic therapy, and previous biologic therapy. Baseline clinical measurements will include sPGA score, PASI total score, BSA, PSSI, PSS total score, PatGA, DLQI total score, SF-36 (PCS), and SF-36 (MCS).

Treatment group comparisons for induction will be conducted using Fisher's exact test for categorical data and a 1-way analysis of variance (ANOVA) for continuous data.

10.3.2.3. Concomitant Therapy

Previous and concomitant medications will be summarized for subjects who enter each treatment period and will be presented by anatomical therapeutic chemical (ATC) drug classes using the latest version of the World Health Organization (WHO) drug dictionary. Treatment group comparisons for induction will be conducted using Fisher's exact test.

10.3.2.4. Treatment Compliance

Treatment compliance with investigational product will be summarized for subjects who enter the induction and maintenance periods. A subject will be considered significantly noncompliant if he or she fails to attend for administration of study medication within the required treatment window as defined in the Schedule of Activities (Section 2). Overall compliance with therapy is defined to be missing no more than 20% of the expected doses and not missing 2 consecutive doses. Proportions of subjects who demonstrate overall compliance during the induction period will be compared between treatment groups using Fisher's exact test.

10.3.3. Efficacy Analyses

Primary and secondary analyses will be based on the intent-to-treat (ITT) population.

10.3.3.1. Primary Analyses

Treatment comparisons between each LY3074828 dose regimen (30 mg, 100 mg, 300 mg) and placebo in the proportion of subjects achieving PASI 90 at Week 16 will be analyzed using logistic regression with NRI as described in Section 10.3.1.1.

10.3.3.2. Secondary Analyses

Treatment comparisons between each LY3074828 dose regimen (30 mg, 100 mg, 300 mg) and placebo at Week 16 in the proportion of subjects achieving PASI 100, PASI 75, sPGA 0 (clear), and sPGA 0/1 will be analyzed using logistic regression with NRI as described in Section 10.3.1.1. The proportion and 95% confidence interval of subjects achieving PASI 100, PASI 90, and PASI 75 at Weeks 52, 104, and 120 will be summarized by treatment.

Treatment comparisons between each LY3074828 dose regimen (30 mg, 100 mg, 300 mg) and placebo in the change from baseline to Week 16 in health outcome measures DLQI, SF-36, CCI [redacted] will be analyzed using the MMRM model as described in Section 10.3.1.1. The change from baseline and 95% confidence interval for health outcome measures DLQI, SF-36, and PatGA at Weeks 52, 104, and 120 will be summarized by treatment.

The Week 120 (Visit 804) data will be summarized by including only subjects who both enter and complete the post-treatment follow-up period of Study AMAF.

CCI [redacted]

10.3.4. Safety Analyses

Safety will be assessed by evaluating AE, laboratory analytes, vital signs, ECGs, and C-SSRS.

The induction period safety analyses will compare LY3074828 to placebo for which treatment group comparisons will be analyzed using the methods described in Section 10.3.1.1. The maintenance period safety analyses will summarize safety measures by treatment. Summaries of safety data collected during the follow-up period will be presented separately.

AEs will be coded according to the *Medical Dictionary for Regulatory Activities* and summarized by system organ class, preferred term, severity, and relationship to investigational product. A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after baseline. For each event classification term, the number of subjects experiencing a TEAE with that classification term will be tabulated.

Treatment-related TEAEs are defined as events that are indicated by the investigator on the eCRF to be related to treatment. If a subject reports the occurrence of a particular event more than once, the most severe of those events will be included in the summary tables of TEAEs, and the most severe of the most related of those events will be included in the summary tables of

treatment-related events. For events that are gender specific, the denominator and computation of the percentage will only include subjects from the given gender.

Additional safety parameters include laboratory analytes, vital signs, ECGs, and C-SSRS. Laboratory analytes and vital signs will be presented as mean changes from baseline and as incidence of abnormal values. ECG and C-SSRS data will be listed by subject. Other covariate data, including body weight, will be summarized by treatment group.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Analyses of data will be performed using a nonlinear mixed-effect modeling approach as implemented in NONMEM software on a computer that meets or exceeds the minimum system requirements for this program. It is possible that other validated equivalent software programs may be used if appropriate. The version of any software used for the analysis will be documented.

Population PK analyses will be performed to characterize the PK of LY3074828. These analyses will include model-based and graphical evaluations of the data. Estimates of PK model parameters and covariate effects and corresponding 90% confidence intervals will be reported.

Analyses of exposure-response relationships will be conducted using both exploratory graphical approaches and model based approaches. Exploratory graphical analysis approaches for categorical clinical endpoints (eg, PASI 90, sPGA 0, etc.) may consist of graphs showing the percentage of subjects that achieve the clinical endpoint at different percentiles (eg, quartiles) of exposure of LY3074828 at Week 16 and Week 104. Measures of exposure may include population PK estimated average concentrations (Css, avg) or observed trough concentrations at the time of the clinical endpoint. Model based analyses of the categorical clinical endpoints will utilize population exposure-response logistic regression models, where maximum effect (E_{max}) or other model structures may be used to relate exposure to the probability of achieving the endpoint. These models may be used to evaluate subject factors that may impact the relationship between exposure and the probability of achieving the endpoint. Longitudinal exposure-response models for PASI scores or response rates may be developed, which relate the time course and magnitude of LY3074828 exposure to the time course and magnitude of PASI response.

Additional analyses may be conducted if they are deemed appropriate. Further details on PK and PK/PD analyses will be provided in the PK/PD analysis plan.

10.3.6. Other Analyses

10.3.6.1. Subgroup Analyses

Subgroup analyses will be conducted for PASI 100 and PASI 90 at Week 16 (NRI) using the ITT population.

Subgroups to be evaluated may include gender, age, body weight, race, geographic region, baseline disease severity, duration of disease, prior exposure to biologic therapy, previous

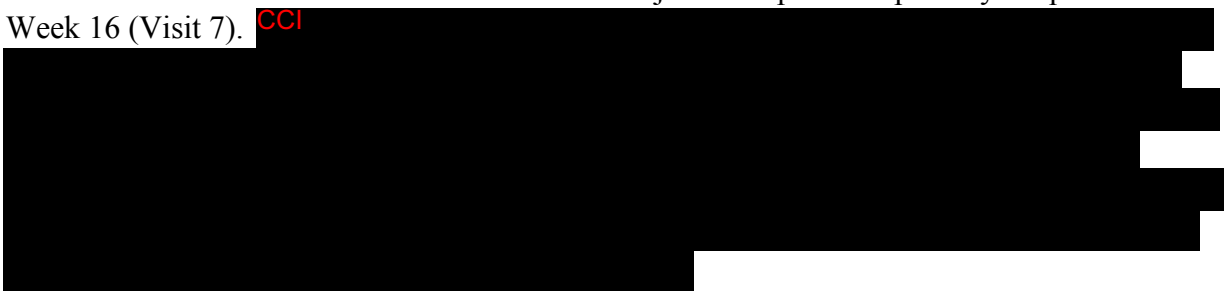
nonbiologic systemic therapy, and previous biologic therapy. A detailed description of the subgroup variables will be provided in the SAP.

A logistic regression model with treatment, subgroup, and the interaction of subgroup-by-treatment included as factors will be used. The subgroup-by-treatment interaction will be tested at the significance level of 0.10. Treatment group differences will be evaluated within each category of the subgroup using Fisher's exact test, regardless of whether the interaction is statistically significant. Missing data will be imputed using NRI as described in Section 10.3.1.3. If any group within the subgroup is less than 10% of the total population, only summaries of the efficacy data will be provided (that is, no inferential testing).

Additional subgroup analyses may be performed as deemed appropriate and necessary.

10.3.7. Interim Analyses

There will be an interim database lock after all subjects complete the primary endpoint at Week 16 (Visit 7). CCI



Interim analyses will not impact the current study design or implementation. The interim efficacy results will be used for internal decision making to trigger planning activities associated with the investigational product and to aid development of PK/PD modeling. No adjustment of Type I error will be performed.

Given that the additional interim database locks are post-primary, these additional analyses will not impact the primary analysis and outcomes. All post-primary interim analyses are exploratory and supportive in nature, and do not impact the integrity or scientific value of this study.

To minimize any bias being introduced into the analysis of the study results, the SAP and PK/PD analysis plan will be finalized and approved before the first efficacy interim analysis begins. Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.

Ongoing monitoring of safety data (including AEs, SAEs, and selected laboratory measurements) will continue throughout the study using blinded data. Interim safety analyses may be conducted to review unblinded safety data; the analyses will be conducted and reviewed by an internal assessment committee composed of personnel who do not have direct site contact, data entry responsibilities, or data validation responsibilities. Details regarding safety reviews will be specified in the trial level safety review plan or a separate document.

11. References

Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol*. 2008;159(5):997-1035.

Boniface K, Guignouard E, Pedretti N, Garcia M, Delwail A, Bernard FX, Nau F, Guillet G, Dagregorio G, Yssel H, Lecron JC, Morel F. A role for T cell-derived interleukin 22 in psoriatic skin inflammation. *Clin Exp Immunol*. 2007;150(3):407–415.

Caruso R, Botti E, Sarra M, Esposito M, Stolfi C, Diluvio L, Giustizieri ML, Pacciani V, Mazzotta A, Campione E, Macdonald TT, Chimenti S, Pallone F, Costanzo A, Monteleone G. Involvement of interleukin-21 in the epidermal hyperplasia of psoriasis. *Nat Med*. 2009;15(9):1013–1015.

Columbia University Medical Center. Columbia–Suicide Severity Rating Scale (C-SSRS) web site. Available at: http://www.cssrs.columbia.edu. Accessed April 1, 2016.

Crow JM. Therapeutics: silencing psoriasis. *Nature.* 2012;492(7429):S58-S59.

Di Cesare A, Di Meglio P, Nestle FO. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. *J Invest Dermatol.* 2009;129(6):1339–1350.

[EMA] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. November 2004. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003329.pdf. Accessed March 31, 2016.

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol.* 1994;19(3):210-216.

Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. *Dermatologica*. 1978;157(4):238-244.

Gordon KB, Callis Duffin K, Bissonnette R, Prinz JC, Wasfi Y, Li S, Shen Y-K, Szapary P, Randazzo B, Reich K. A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. *N Engl J Med* 2015;373(2):136-144.

Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? *J Invest Dermatol*. 2005;125(4):659-664.

[IFPA] International Federation of Psoriasis Associations. Profile of psoriasis page. International Federation of Psoriasis Associations web site. Available at: http://www.ifpa-pso.org/web/page.aspx?refid=42 . Accessed November 2014.

Kagami S, Rizzo HL, Lee JJ, Koguchi Y, Blauvelt A. Circulating Th17, Th22, and Th1 cells are increased in psoriasis. *J Invest Dermatol*. 2010;130(5):1373–1383.

Kimball AM, Jacobson C, Weiss S, Vreeland MG, Wu Y. The psychosocial burden of psoriasis. *Am J Clin Dermatol.* 2005;6(6):383–392.

Kopp T, Riedl E, Bangert C, Bowman EP, Greisenegger E, Horowitz A, Kittler H, Blumenschein WM, McClanahan TK, Marbury T, Zachariae C, Xu D, Hou XS, Mehta A, Zandvliet AS, Montgomery D, van Aarle F, Khalilieh S. Clinical improvement in psoriasis with specific targeting of interleukin-23. *Nature*. 2015;521(7551):222-226.

Krueger JG, Ferris LK, Menter A, Wagner F, White A, Visvanathan S, Lalovic B, Aslanyan S, Wang EEL, Hall D, Solinger A, Padula S, Scholl P. Anti–IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: Safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol*. 2015;136(1):116-124.

Lee E, Trepicchio WL, Oestreicher JL, Pittman D, Wang F, Chamian F, Dhodapkar M, Krueger JG. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. *J Exp Med*. 2004;199(1):125–130.

Lew W, Bowcock AM, Krueger JG. Psoriasis vulgaris: cutaneous lymphoid tissue supports T-cell activation and "Type 1" inflammatory gene expression. *Trends Immunol*. 2004;25(6):295-305.

Lowes MA, Kikuchi T, Fuentes-Duculan J, Cardinale I, Zaba LC, Haider AS, Bowman EP, Krueger JG. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. *J Invest Dermatol*. 2008;128(5):1207–1211.

Menter A, Gottlieb A, Feldman SR, VanVoorhees AS, Leonardi CL, Gordon KB, Lebwohl M, Koo JY, Elmets CA, Korman NJ, Beutner KR, Bhushan R. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2008;58(5):826-850.

National Psoriasis Foundation. The psoriasis and psoriatic arthritis pocket guide. 2009. Available at: https://www.psoriasis.org/sites/default/files/accessing-health-care/FY10_Pocket_Guide_WEB.pdf . Accessed 13 May 2016.

Papp K, Thaci D, Reich K, Riedl E, Langley RG, Krueger JG, Gottlieb AB, Nakagawa H, Bowman EP, Mehta A, Li Q, Zhou Y, Shames R. Tildrakizumab (MK-3222) an anti-interleukin -23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. *Br J Dermatol.* 2015;173(4):930-939.

Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Identification and Management of Psoriasis and Associated ComorbidiTy (IMPACT) project team. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol.* 2013;133(2):377-385.

Piskin G, Tursen U, Sylva-Steenland RM, Bos JD, Teunissen MB. Clinical improvement in chronic plaque-type psoriasis lesions after narrow-band UVB therapy is accompanied by a decrease in the expression of IFN-gamma inducers -- IL-12, IL-18 and IL-23. *Exp Dermatol.* 2004;13(12):764–772.

Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Pyschiatry.* 2007;164(7):1035-1043.

Puig L. PASI90 response: the new standard in therapeutic efficacy for psoriasis. *J Eur Acad Dermatol Venereol*. 2015;29(4):645-648.

Sands BE, Chen J, Penney M, Newhold P, Faggioni R, van der Merwe R, Patra K, Klekotka P, Pulkstenis E, Drappa J, Gasser RA. A randomized, double-blind placebo-controlled phase 2a induction study of MEDI2070 (anti-p19 antibody) in patients with active Crohn's disease who have failed anti-TNF antibody therapy. *J Crohns Colitis*. 2015;9(suppl 1):S15-S16. Abstract OP025.

Sofen H, Smith S, Matheson RT, Leonardi CL, Calderon C, Brodmerkel C, Li K, Campbell K, Marciniak SJ Jr, Wasfi Y, Wang Y, Szapary P, Krueger JG. Guselkumab (an IL-23-specific mAb) demonstrates clinical and molecular response in patients with moderate-to-severe psoriasis. *J Allergy Clin Immunol*. 2014;133(4):1032-1040.

Steinman L. A brief history of T(H)17, the first major revision in the T(H)1/T(H)2 hypothesis of T cell-mediated tissue damage. *Nat Med.* 2007;13(2):139–145.

Strand V, Fiorentino D, Hu C, Day RM, Stevens RM, Papp KA. Improvements in patient-reported outcomes with apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of moderate to severe psoriasis: results from a phase IIb randomized, controlled study. *Health Qual Life Outcomes* 2013;11:82.

Thaci D, Unnebrink K, Sundaram M, Sood S, Yamaguchi Y. Adalimumab for the treatment of moderate to severe psoriasis: subanalysis of effects on scalp and nails in the BELIEVE study. *J Eur Acad of Derm and Vener* 2015;29(2):353-360.

Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-483.

Ware JE, Kosinski M, Dewey JE. How to score version 2 of the SF-36 health survey. Lincoln, RI: QualityMetric, Incorporated; 2001.

Weaver CT, Hatton RD, Mangan PR, Harrington LE. IL-17 family cytokines and the expanding diversity of effector T cell lineages. *Annu Rev Immunol*. 2007;25:821–852.

12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	anti-drug 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 adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the subject are not. A double-blind study is one in which neither the 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.
BSA	body surface area
CIOMS	Council for International Organizations of Medical Sciences
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.
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.
CSR	clinical study report
DC	dendritic cell
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
ERB/IRB	ethical review board/investigational review board

Term	Definition
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the trial are those who have been assigned to a treatment.
enter	Subjects entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IL	interleukin
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.
IV	intravenous
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, 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.
ITT	intention-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
MCS	mental component summary
MMRM	mixed-effects for repeated measures
NRI	nonresponder imputation

Term	Definition
NRS	numeric rating scale
PASI	Psoriasis Area and Severity Index
PASI 50	50% improvement in PASI from baseline
PASI 75	75% improvement in PASI from baseline
PASI 90	90% improvement in PASI from baseline
PASI 100	100% improvement in PASI from baseline
PatGA	Patient's Global Assessment of Psoriasis
PCR	polymerase chain reaction
PCS	physical component summary
PK/PD	pharmacokinetics/pharmacodynamics
PPD	purified protein derivative
PRN	as needed
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcome
PSS	Psoriasis Symptom Scale
PSSI	Psoriasis Scalp Severity Index
PUVA	psoralen plus ultraviolet A light therapy
Q8W	every 8 weeks
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
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.
SC	subcutaneous
SF-36	Short-Form Health Survey
SUSARs	suspected unexpected serious adverse reactions
TB	tuberculosis
TBL	total bilirubin level

Term	Definition
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, which and does not necessarily have to have a causal relationship with this treatment.
Th	T helper
ULN	upper limit of normal
US	United States

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology:	**Clinical Chemistry:**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin	Total protein
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Cell morphology	Alanine aminotransferase (ALT)
Neutrophils, segmented	Aspartate aminotransferase (AST)
Lymphocytes	Blood urea nitrogen (BUN)
Monocytes	Creatinine
Eosinophils	Uric acid
Basophils	Calcium
Platelets	Glucose, nonfasting
	Albumin
	Cholesterol
Urinalysis:	Fasting lipid profile[c]
Specific gravity	Creatine kinase (CK)
pH	
Protein	**Other:**
Glucose	Hepatitis B surface antigen[a]
Ketones	Hepatitis C antibody[a,b]
Bilirubin	HIV[a]
Urobilinogen	Hepatitis B core antibody[a]
Blood	Hepatitis B surface antibody[a]
Nitrite	Pregnancy test (serum[a] and urine)
Urine leukocyte esterase	FSH[a]
Microscopic examination of sediment	QuantiFERON®-TB Gold test[a]
	Exploratory storage samples (DNA)
	Exploratory storage samples (serum, plasma, whole blood, RNA, and tissue RNA)
	Anti-LY3074828 antibodies (immunogenicity)
	Serum LY3074828 concentration (PK)
	C-reactive protein, high-sensitivity
	HBV PCR
	Lymphocyte subsets

Abbreviations: DNA = deoxyribonucleic acid; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HIV = human immunodeficiency virus; PCR = polymerase chain reaction; PK = pharmacokinetic; RBC = red blood cell; RNA = ribonucleic acid; WBC = white blood cell.

[a] Performed at screening only.

[b] A positive hepatitis C antibody laboratory assessment will be confirmed with an additional test method.

[c] Fasting lipid profile: patients should not eat or drink anything except water for 12 hours prior to sample collection. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation.

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for ensuring:

- that the subject understands the potential risks and benefits of participating in the study
- that informed consent is given by each 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 investigational product.
- answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the trial.

Appendix 3.1.2. Ethical Review

The investigator must give assurance that the ERB was properly constituted and convened as required by International Conference on 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, including any changes made by the ERBs, 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

Appendix 3.1.3. Regulatory Considerations

This study will be conducted in accordance with:

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

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

Appendix 3.1.4. Investigator Information

Physicians with a specialty in dermatology or other specialties with appropriate experience (private practice, university, psoriasis research centers) will participate as investigators in this clinical trial.

Appendix 3.1.5. 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.

Appendix 3.1.6. Final Report Signature

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The CSR coordinating investigator will be selected by the sponsor. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

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

Appendix 3.2. 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
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, 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 eCRF data and 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 subject data recorded against source documents at the study site. The study may be audited by Lilly or its

representatives, 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 original source documents.

Appendix 3.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Electronic patient-reported outcome (ePRO) measures (for example, a rating scale) or other data reported directly by the subject (for example, event diary) are entered into an ePRO instrument (for example, personal digital assistant) at the time that the information is obtained. In these instances where there is no prior written or electronic source data at the site, the ePRO instrument record will serve as the source.

Any data for which the ePRO instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

eCRF data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Any data for which paper documentation provided by the subject will serve as the source document will be identified and documented by each site in that site's study file.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, 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.

Appendix 3.3.2. Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with subjects in consultation with the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
Red blood cells	Prothrombin Time
White blood cells	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a]**
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
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
Alanine aminotransferase (ALT)	**Anti-nuclear antibody[a]**
Aspartate aminotransferase (AST)	
Gamma-Glutamyl Transferase (GGT)	**Anti-smooth muscle antibody[a]**
Creatine phosphokinase (CPK)	

Abbreviations: IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio.

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

Appendix 5. Protocol Amendment I6T-MC-AMAF(b) Summary: A Phase 2, Multicenter, Randomized, Parallel-Arm, Placebo-Controlled Study of LY3074828 in Subjects with Moderate-to-Severe Plaque Psoriasis

Overview

Protocol I6T-MC-AMAF A Phase 2, Multicenter, Randomized, Parallel-Arm, Placebo Controlled Study of LY3074828 in Subjects with Moderate to Severe Plaque 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 described in the following table:

Amendment Summary for Protocol I6T-MC-AMAF Amendment (b)

Section # and Name	Description of Change	Brief Rationale
2. Schedule of Activities: row for "Day with Visit Tolerance Interval" in Maintenance Dosing Period	Changed Day 523 to Day 532.	Typographical error related to the number of days associated with timing of Visit 22 was corrected.
7.8.2. Special Treatment Considerations	Text deleted that implied patients could receive more study drug after developing clinically significant systemic hypersensitivity events.	Text on how to manage hypersensitivity events has been updated to align with approach used across other mirikizumab studies per most recent IB update.
8.1.1. Permanent Discontinuation from Study Treatment	Text added that investigational product is to be discontinued for patients who experience clinically significant systemic hypersensitivity events (such as anaphylaxis) following administration of investigational product.	Direction given to discontinue investigational product if a patient experiences a clinically significant hypersensitivity event is consistent with most recent IB update.
8.2. Discontinuation from Study	Text added to permanently discontinue investigational product for patients who experience clinically significant systemic hypersensitivity events.	Direction given to discontinue investigational product if a patient experiences a clinically significant hypersensitivity event is consistent with most recent IB update.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

2. Schedule of Activities

Maintenance Dosing Period (Visits 19-29)												
Visit No.:	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**Comments**
Week Relative to Study Drug Start	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	All activities should be completed prior to any study dose administration unless otherwise stated below.
Day with Visit Tolerance Interval	**448 ± 5**	**476 ± 5**	**504 ± 5**	**~~523~~ 532 ± 5**	**560 ± 5**	**588 ± 5**	**616 ± 5**	**644 ± 5**	**672 ± 5**	**700 ± 5**	**728 ± 5**	

7.8.2. Special Treatment Considerations

Subjects in the maintenance PRN dosing arm may receive blinded rescue treatment with 300 mg Q8W. Rescue treatment may occur if not regaining a PASI ≥90 after 3 consecutive doses of retreatment or if a subject is below a PASI 50 following 1 retreatment dose. A subject starting rescue treatment will remain on that regimen through the end of the study regardless of any subsequent changes in PASI score.

All biological agents carry the risk of an injection site and/or hypersensitivity general reaction. Therefore all subjects should be closely monitored for signs or symptoms that could result from such reactions. Sites should have appropriately trained medical staff and appropriate medical equipment available when subjects are receiving study drug. If a subject experiences an acute hypersensitivity reaction after an injection of study drug, he or she should receive appropriate supportive care. ~~and consideration for any premedication for future injections will be agreed between the investigator and sponsor.~~

8.1.1. Permanent Discontinuation from Study Treatment

Subjects who discontinue the investigational product early will continue in the study according to the Schedule of Activities (Section 2).

Investigational product is to be discontinued for patients who experience clinically significant systemic hypersensitivity events (such as anaphylaxis) following administration of investigational product.

8.2. Discontinuation from Study

Some possible reasons that may lead to permanent discontinuation include:

- AE
    - If the investigator decides that the subject should be withdrawn because of an AE/SAE or a clinically significant laboratory value, the investigational product is to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately. Refer to Safety Evaluations, Sections 9.2 and 9.2.1.
- subject experiences a systemic hypersensitivity event (such as anaphylaxis) following administration of investigational product.
- subject becomes pregnant

Leo Document ID = 723d17a2-8adb-4d94-8c62-013049e7ef78

Approver: [redacted]
Approval Date & Time: 21-Aug-2018 12:34:29 GMT
Signature meaning: Approved

Approver: [redacted]
Approval Date & Time: 21-Aug-2018 17:32:39 GMT
Signature meaning: Approved