Title Page

Protocol Title:		A Dose-Ranging, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Tezepelumab Alone or Combined With Topical Corticosteroids in Moderate-to-Severe Atopic Dermatitis
Short Protocol Title:		A Dose-Ranging, Placebo-Controlled, Double-Blind Study to Evaluate the Safety and Efficacy of Tezepelumab in Atopic Dermatitis
Protocol Number:		20170755
Investigational Product:		Tezepelumab
Trade Name:		
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Version/Date:		**Data Element Standards Version** / **Date** 5.0 / 15 March 2017

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled A Dose-Ranging, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Tezepelumab Alone or Combined With Topical Corticosteroids in Moderate-to-Severe Atopic Dermatitis, dated **25 August 2020**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my subinvestigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

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1. Protocol Synopsis

Protocol Title: A Dose-Ranging, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Tezepelumab Alone or Combined With Topical Corticosteroids in Moderate-to-Severe Atopic Dermatitis
Short Protocol Title: A Dose-Ranging, Placebo-Controlled, Double-Blind Study to Evaluate the Safety and Efficacy of Tezepelumab in Atopic Dermatitis

Study Phase: 2

Indication: Atopic Dermatitis (AD)

Rationale

Tezepelumab is being developed for the treatment of atopic dermatitis (AD). Thymic stromal lymphopoietin (TSLP) is an epithelial cytokine shown to be elevated in skin lesions of patients with AD. A previous phase 2a study (ALLEVIAD) demonstrated improvements in Investigator's Global Assessment (IGA) and Eczema Area and Severity Index (EASI) scoring, but did not meet statistical significance in the primary endpoint. A phase 1b study demonstrated improvement in IGA and EASI as secondary endpoints.

Three dose levels of tezepelumab (420 mg subcutaneous injection [SC] every 2 weeks [Q2W], 280 mg SC Q2W, and 210 mg SC every 4 weeks [Q4W]) were selected based on exposure-response analysis of tezepelumab concentration and IGA response from the ALLEVIAD study. These dose regimens will allow establishing exposure-response to aid in dose selection for future studies. A first dose of 420 mg will allow faster achievement of steady state for the lower dose regimens (210 mg SC Q4W and 280 mg SC Q2W), and is also anticipated to improve symptoms of AD (eg, sleep and pruritus).

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary – Part A	
• To evaluate the effect of tezepelumab compared with placebo, assessed using the Investigator's Global Assessment (IGA) and Eczema Area and Severity Index (EASI)	• IGA score of 0 (clear) or 1 (almost clear) (IGA 0/1) at week 16 • 75% reduction in EASI (EASI 75) at week 16
Secondary – Part A	
• To estimate the effect of tezepelumab compared with placebo on the efficacy measure of EASI	• 50% and 90% reduction in EASI (EASI 50/90) at week 16
• To estimate the time needed to reach EASI 50/75/90	• Time at which EASI 50/75/90 is achieved from day 1
• To estimate the effect of tezepelumab compared with placebo on the efficacy measure of Scoring Atopic Dermatitis (SCORAD)	• SCORAD at week 16
• To estimate the effect of tezepelumab compared with placebo on the patient-reported outcome (PRO) measure of pruritus assessed using a numeric rating scale (NRS)	• Pruritus NRS at week 16
• To characterize the pharmacokinetics (PK) of tezepelumab	• Serum trough concentrations of tezepelumab at scheduled visits
Safety – Part A and Part B	
• To establish the safety and tolerability of tezepelumab compared with placebo	• Subject incidence of adverse events (including serious adverse events)

Hypotheses

Part A

The primary hypothesis is that tezepelumab effectively increases the probability of an IGA 0/1 response and an EASI 75 response at week 16 in subjects with moderate-to-severe AD.

Part B

Part B is an estimation study; no hypotheses will be formally tested.

Overall Design

This phase 2b study is designed to evaluate the safety and efficacy of tezepelumab as a monotherapy and explore its efficacy as adjunct therapy in subjects with moderate-to-severe AD. This study consists of Part A (the main study evaluating tezepelumab as a monotherapy) and Part B (a study evaluating tezepelumab as

adjunctive therapy when combined with a topical corticosteroid [TCS] regimen). In Part A, two futility analyses are planned when the 80th and 160th subjects are projected to complete week 16, respectively. Upon a result of "not futile" for the first analysis and Part A has completed enrollment of 240 patients, enrollment of subjects in Part B of the study will commence. A result of "futile" for either analysis in Part A will result in termination of both Part A and Part B of the study.

Eligible subjects for both Part A and Part B will include adults with a clinical diagnosis of AD at least 2 years prior to screening, with AD that affects ≥ 10% of body surface area as assessed by EASI, an IGA score of ≥ 3, and an EASI score of ≥ 16.

Part A and Part B of this study will consist of a 28-day screening period, a 52-week treatment period, and a 20-week safety follow-up period. During the 28-day screening period, subjects must discontinue from all topical AD therapies, except for approved moisturizers (see Section 7.1.7), for at least the 7 consecutive days immediately prior to day 1. During the study, approved moisturizers are allowed to be applied, with the exception of 8 hours prior to any scheduled visit.

Part A is a dose-ranging, randomized, placebo-controlled, double-blind study designed to evaluate the safety and efficacy of tezepelumab as monotherapy in subjects with moderate-to-severe AD. Following the screening period, eligible subjects will be randomized 1:1:1:1 to receive 420 mg SC Q2W, 280 mg SC Q2W, 210 mg SC Q4W, or placebo. All subjects will receive a 420 mg SC dose (investigational product or placebo) as the first dose. Subjects will then receive the appropriate dose of investigational product at the week 2 visit, depending on which treatment group they are randomized to. Depending on if they are randomized to Q2W or Q4W dosing, the dose at week 2 could be placebo or tezepelumab. Non-responders are defined as those subjects who have not achieved at least a 50% improvement in EASI at week 16 compared to baseline (day 1). Subjects who are determined to be non-responders in Part A will receive tezepelumab 420 mg SC Q2W for the remainder of the study, beginning with the week 18 dose. The randomized treatment assignments for the non-responders will remain blinded until the end of study.

Part B is a randomized, placebo-controlled, double-blind study designed to evaluate the safety and efficacy of tezepelumab when administered with moderate class TCS in adults with moderate-to-severe AD. Enrollment of subjects in Part B of the study will only commence if there is a result of "not futile" for the first interim analysis in Part A and Part A has completed enrollment of 240 patients. Following the screening period,

eligible subjects will be randomized 2:1 to receive 420 mg SC Q2W or placebo; both groups in Part B will be allowed to use TCS after the day 1 visit. Non-responders in Part B will not be switched to 420 mg SC Q2W at week 18 and will remain on their initial dose for the duration of the study.

Number of Subjects

Approximately 240 subjects will be enrolled in Part A of the study. Approximately 60 subjects will be enrolled in Part B of the study.

Summary of Subject Eligibility Criteria

Eligible subjects for both Part A and Part B will include adults with a clinical diagnosis of AD at least 2 years prior to **s**creening, with AD that affects ≥ 10% of body surface area as assessed by EASI, an IGA score of ≥ 3, and an EASI score of ≥ 16.

For a full list of eligibility criteria, please refer to Section 6.1 to Section 6.2.

Treatments

Study treatment include tezepelumab or placebo as outlined in the table below.

Study Treatment Name	**Amgen Investigational Product:[a] Tezepelumab**	**Placebo**
Dosage Formulation	Each package will contain 3 vials.	Placebo will be presented in identical containers and stored/packaged the same way as tezepelumab.
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	Each subject will receive 3 injections per visit. For subjects randomized to 420 mg SC Q2W, 280 mg SC Q2W, and 210 mg SC Q4W: volumes for injections from vials provided will be detailed in the Investigational Product Instruction Manual (IPIM). Subjects randomized to Q4W dosing will receive placebo at intervening visits, such that all subjects receive an injection Q2W.	Each subject will receive 3 injections per visit. For subjects randomized to placebo: volumes for injections from vials provided will be detailed in the IPIM. Subjects will receive placebo dosing Q2W.
Route of Administration	SC injection	SC injection

IPIM = Investigational Product Instruction Manual; SC = subcutaneous; Q2W = every 2 weeks; Q4W = every 4 weeks

[a] Tezepelumab will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

In Part B of this study, subjects may commence TCS after day 1. Subjects who use TCS during the study should follow the dosing regimen outlined in Section 7.1.5.

Procedures

Key study procedures will include assessment of IGA, EASI, SCORAD, and other measures of AD disease severity. Samples will be collected for PK analysis and biomarker development. A safety follow-up will be conducted for 20 weeks after the final dose of study drug (18 weeks after the end of treatment [EOT] visit). All adverse events observed by the investigator or reported by the subject that occur after the first dose of investigational product through the end of study/safety follow-up visit or for 20 weeks after the last administration of investigational product are to be collected/reported. Disease-related adverse events for this study include AD. Serious adverse events observed by the investigator or reported by the subject after the signing of informed consent through the end of study/safety follow-up visit or for 20 weeks after the last administration of investigational product are reported using the Event CRF.

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Table 2-1 and Table 2-2.

Statistical Considerations

In Part A of this study, a total of 240 subjects will be randomized in a 1:1:1:1 ratio to tezepelumab 420 mg SC Q2W, 280 mg SC Q2W, 210 mg SC Q4W, and placebo (approximately 60 in each group). There is at least 85% power for each co-primary endpoint, assuming IGA 0/1 response rates of 10% and 40% for placebo and the highest tezepelumab dose group (420 mg SC Q2W), respectively, and assuming EASI response rates of 15% and 50%, respectively. These assumed treatment effects are based on the results of other new agents in this indication (DUPIXENT, 2017). These calculations used a 2-sided χ^2 test at a significance level of 0.025 (to reflect the Bonferonni-based gatekeeping procedure described in Section 10.3.2.1) and assumed a 10% dropout rate.

Part B of this study is exploratory. A sample size of 60 subjects (40 in the tezepelumab 420 mg SC Q2W group and 20 in the placebo group) was chosen as an adequate sample size to provide initial evidence of tezepelumab as a promising agent for adjunct therapy.

Subject disposition, demographics, and baseline disease characteristics will be summarized descriptively by randomized treatment group. For categorical endpoints, the descriptive statistics will contain frequency and percentage. For continuous endpoints, the descriptive statistics will include the number of observations, mean,

standard error, standard deviation, median, first quartile, third quartile, minimum, and maximum.

For Part A, the treatment effect for the primary analysis of the primary endpoints will be tested using a Bonferonni-based gatekeeping procedure to control the family-wise 2-sided type I error rate at 0.05. The procedure splits the α of 0.05 equally to test in parallel tezepelumab 420 mg SC Q2W versus placebo, and tezepelumab 280 mg SC Q2W versus placebo for IGA 0/1 and EASI 75 sequentially within each parallel path. If one of the parallel paths rejects the 2 hypotheses sequentially, and the other path has at least 1 hypothesis not rejected, then the unspent α of 0.025 from the successful path will be propagated to the unsuccessful path to retest the 2 hypotheses sequentially at a level of 0.05.

For the primary endpoints of IGA 0/1 and EASI 75 at week 16, the treatment effect will be tested using a logistic regression model adjusting for covariates specified in Section 10.2.2. From this model, odd ratios and 95% CIs will be reported comparing each tezepelumab dose group to placebo. In addition, the percentage of subjects in each treatment group with a response and the difference in the percentage of subjects responding between each tezepelumab dose group and placebo will be summarized with a 95% confidence interval.

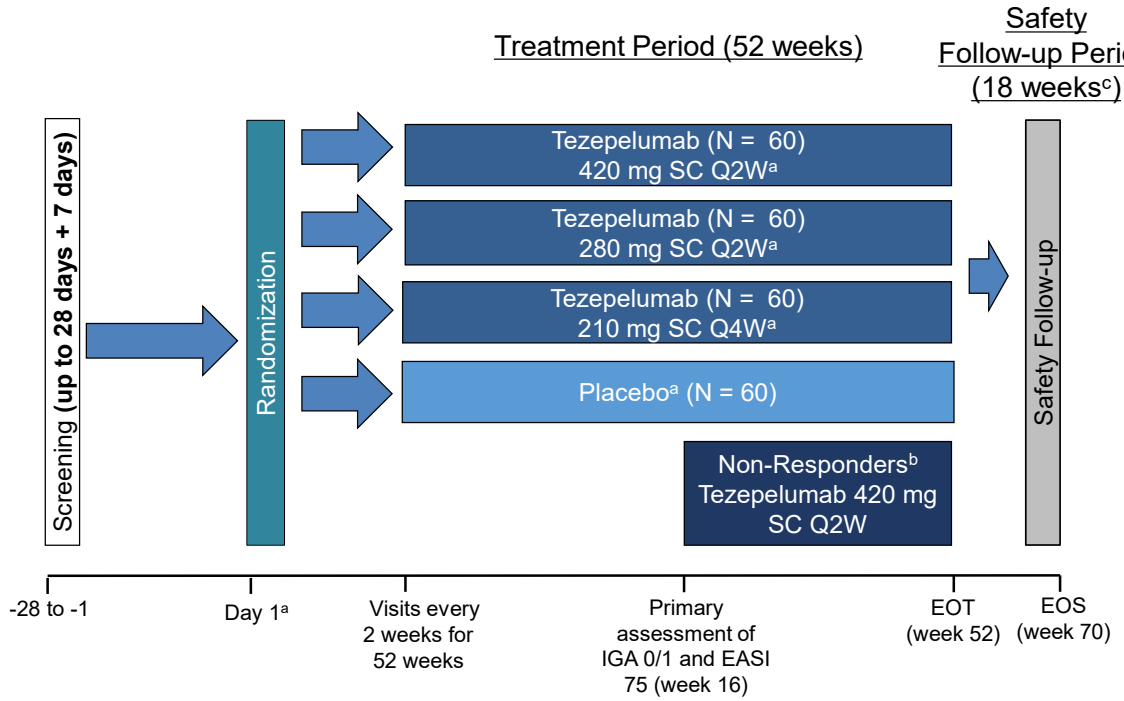
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen Inc.

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1 Study Schema for Part A

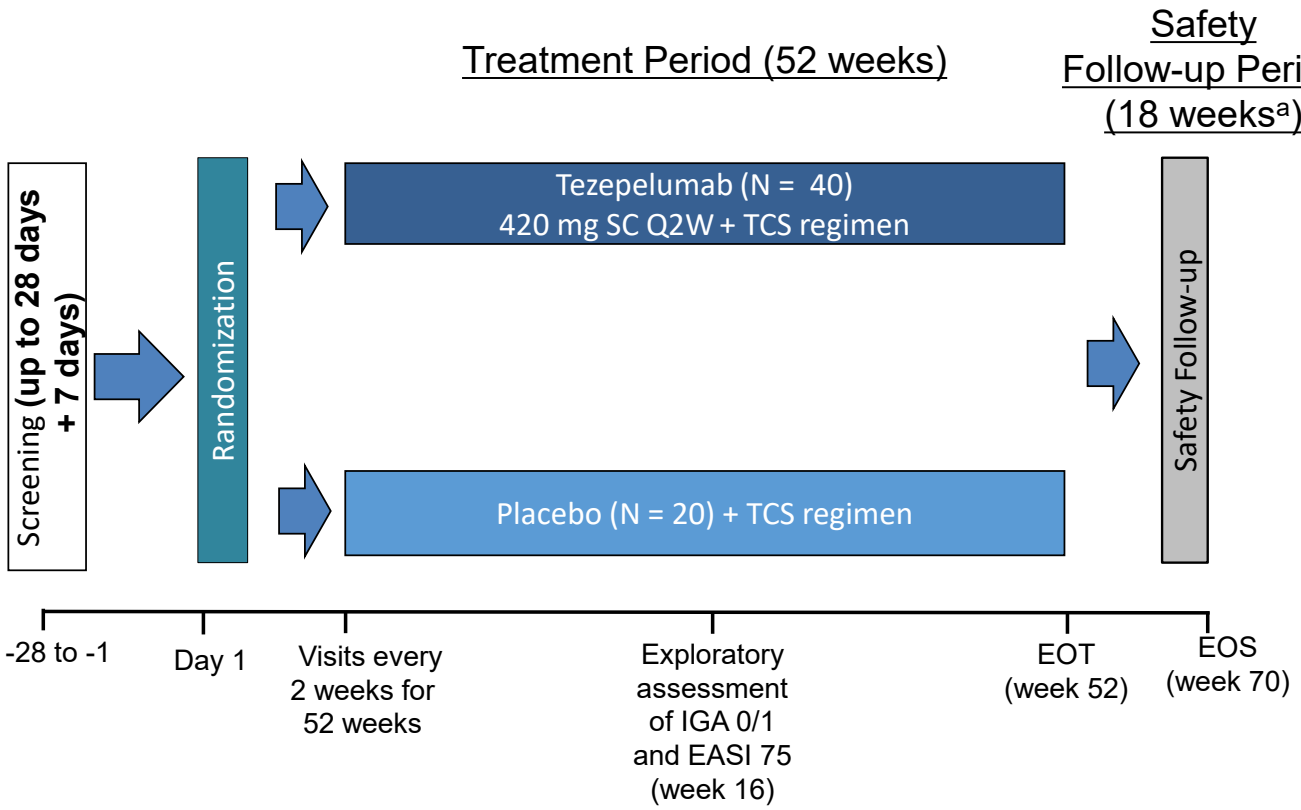


EA
Q2

a.

b.
No

c.



EASI = Eczema Area and Severity Index; EOS = End of Study; EOT = End of Treatment; IGA = Investigators' Global Assessment; SC = subcutaneous; TCS = topical corticosteroids; Q2W = every 2 weeks

a. Safety follow-up is 18 weeks after the EOT visit.

2.2 Schedule of Activities

Table 2-1. Schedule of Activities for Part A and Part B (Screening Through Week 24)

	Screening[a] (up to -28 d + 7 d)	Treatment Period (52 weeks)[b, p]												
		Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24
GENERAL AND SAFETY ASSESSMENTS														
Informed consent	X													
Informed consent for optional biomarker/pharmacogenetic assessments	X													
Verify eligibility criteria	X	X[o]												
Demographics	X													
Physical examination	X													
Physical measurements	X													
Medical and dermatology history	X													
Randomization		X												
Substance use	X													
12-lead ECG[c]	X													
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease-related events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapies review		X	X	X	X	X	X	X	X	X	X	X	X	X
LABORATORY ASSESSMENTS														
Serum or urine pregnancy test[e]	X	X		X		X		X		X		X		X
Coagulation	X	X							X					
Hematology	X	X						X						X
Chemistry	X	X						X						X
HIV, Hepatitis B and C screening	X													
Urinalysis (dipstick)	X	X						X						X
Anti-tezepelumab-antibody		X						X						X
Serum immunoglobulins[f]	X	X								X				

Footnotes defined on last page of the table

Table 2-1. Schedule of Activities for Part A and Part B (Screening Through Week 24)

	Screening[a] (up to -28 d + 7 d)	Treatment Period (52 weeks)[b, p]												
		Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24
PPD or Quantiferon GOLD	X													
STUDY-SPECIFIC ASSESSMENTS														
eDiary device distribution and training	X													
Electronic diary[g]	Completed in the morning at home on eDiary													
Assessment of EASI and IGA	X	X		X	X	X	X	X		X				X
SCORAD		X		X		X		X		X				X
EQ-5D-3L, POEM, DLQI, PGI-S		X		X		X		X		X				X
Tracking of TCS use (Part B subjects only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]														
PHARMACOKINETIC ASSESSMENTS														
PK sampling[k]		X	X[i]	X[i]				X		X				X[i]
PHARMACOGENETIC ASSESSMENTS														
Sample for DNA analysis (optional)[l]		X												
STUDY TREATMENT														
Administration of tezepelumab or placebo[m]		X[n]	X	X	X	X	X	X	X	X	X	X	X	X

AD = atopic dermatitis; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; Echo = echocardiogram; eCRF = electronic case report form; EOT = end of treatment; EQ-5D-3L = EuroQOL quality of life 5-dimensions 3-level version; HIV = human immunodeficiency virus; Ig = immunoglobulin; IGA = Investigator's Global Assessment; NRS = numeric rating scale; PD = pharmacodynamics; PGI-S = Patient's Global Impression of Severity; PK = pharmacokinetics; PPD = purified protein derivate; POEM = Patient Oriented Eczema Measure; *S.* aureus = *Staphylococcus* aureus; SCORAD = Scoring Atopic Dermatitis;
TCS = topical corticosteroids; Q4W = every 4 weeks; Wk = Week

[a] The screening visit can occur up to 28 days **+** 7 days before the first dose of investigational product on day 1.

[b] The window for visits is ± 3 days.

[c] ECG must be collected prior to any blood draws.

[d] Vital signs will be taken pre-dose prior to administration of investigational product. Subjects will be observed for 2 hours post-treatment at the day 1 and week 2 visits. For all other visits where investigational product is administered, subjects will be observed for a **period of time at the discretion of the Investigator**.
[e] Pregnancy testing applies to females of childbearing potential only, as defined in the protocol. The pregnancy test at screening must be a serum pregnancy test. All other scheduled pregnancy tests will be urine tests. Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations. If a urine pregnancy test is positive, a confirmatory serum pregnancy test will be performed by the study center and entered into the eCRF.
[f] This includes total serum IgE, IgA, IgG, and IgM. All immunoglobulin results will be redacted from laboratory reports.
[g] The eDiary includes Pruritus NRS.

[redacted]

[k] PK samples at day 1 and weeks 2, 4, 12, 16, 24, 32, 40, 48, and 50 should be collected before dosing with investigational product (trough).
[l] This is an optional assessment and requires an additional consent form. The sample for DNA analysis will be obtained at the day 1 visit using the cell pellet from a plasma sample taken on the same day.
[m] Administration of study drug is the final activity performed at a visit. Subjects randomized to Q4W dosing will receive placebo at the visits between dosing with tezepelumab. Subjects will be observed for 2 hours post-treatment at the day 1 and week 2 visits. For all other visits where investigational product is administered, subjects will be observed for a period of time at the discretion of the Investigator.
[n] All subjects will receive a 420 mg SC dose of either study drug or placebo as their first dose.
[o] Only certain inclusion criteria specified in the protocol will be re-evaluated at the day 1 visit. These criteria will be evaluated prior to any other day 1 study activities and are required to be met for dosing with investigational product.
[p] All subjects who terminate the study early will complete an early termination visit consisting of all assessments included in the EOT (week 52) visit. In addition, a safety follow-up visit will occur 18 weeks after the EOT visit.

Table 2-2. Schedule of Activities for Part A and Part B (Week 26 Through End of Study)

	Treatment Period (52 weeks)[a]													EOT[a]/ET[l]		EOS[a]	
	Wk 26	Wk 28	Wk 30	Wk 32	Wk 34	Wk 36	Wk 38	Wk 40	Wk 42	Wk 44	Wk 46	Wk 48	Wk 50	Wk 52	Wk 58	Wk 70	Unscheduled
GENERAL AND SAFETY ASSESSMENTS																	
Physical examination														X	X	X	X
12-lead ECG[b]																X	X
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease-related events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapies review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LABORATORY ASSESSMENTS																	
Urine pregnancy test[d]		X		X		X		X		X		X		X		X	X
Coagulation													X	X			X
Hematology						X						X		X	X	X	X
Chemistry						X						X		X	X	X	X
Urinalysis (dipstick)[e]						X						X		X	X	X	
Anti-tezepelumab-antibody						X						X				X	X
Serum immunoglobulins[f]					X							X		X			X
PPD or Quantiferon GOLD														X			
STUDY-SPECIFIC ASSESSMENTS																	
Electronic diary[g]	Completed in the morning at home on eDiary															X	X
Assessment of EASI and IGA						X						X	X	X		X	
SCORAD						X						X	X	X			
EQ-5D-3L, POEM, DLQI, PGI-S						X						X	X	X			
Tracking of TCS use (Part B subjects only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																	

Footnotes defined on last page of the table

Table 2-2. Schedule of Activities for Part A and Part B (Week 26 Through End of Study)

	Treatment Period (52 weeks)[a]													EOT[a]/ET[l]		EOS[a]	
	Wk 26	Wk 28	Wk 30	Wk 32	Wk 34	Wk 36	Wk 38	Wk 40	Wk 42	Wk 44	Wk 46	Wk 48	Wk 50	Wk 52	Wk 58	Wk 70	Unscheduled
[redacted]																	
PHARMACOKINETIC ASSESSMENTS																	
PK sampling[j]				X				X				X	X	X	X	X	
STUDY TREATMENT																	
Administration of tezepelumab or placebo[k]	X	X	X	X	X	X	X	X	X	X	X	X	X				

DLQI = Dermatology Quality of Life Index; EASI = Eczema Area and Severity Index;
ECG = electrocardiogram; Echo = echocardiogram; eCRF = electronic case report form; EOS = end of study; EOT = end of treatment; EQ-5D-3L = EuroQOL quality of life 5-dimensions 3-level version; ET = early termination; Ig = immunoglobulin; IGA = Investigator's Global Assessment; NRS = numeric rating scale; PGI-S = Patient's Global Impression of Severity; PK = pharmacokinetics; POEM = Patient Oriented Eczema Measure; PPD = purified protein derivate; SCORAD = Scoring Atopic Dermatitis; TCS = topical corticosteroids; Wk = Week

[a] The window for visits is ± 3 days.

[b] ECG must be collected prior to any blood draws.

[c] Vital signs will be taken pre-dose prior to administration of investigational product. Subjects will be observed for 2 hours post-treatment at the day 1 and week 2 visits. For all other visits where investigational product is administered, subjects will be observed for a period of time at the discretion of the Investigator.

[d] Pregnancy testing applies to females of childbearing potential only, as defined in the protocol. The pregnancy test at screening must be a serum pregnancy test. All other scheduled pregnancy tests will be urine tests. Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations. If a urine pregnancy test is positive, a confirmatory serum pregnancy test will be performed by the study center and entered into the eCRF.

[e] Urinalysis analyzed centrally only if dipstick locally is positive.

[f] This includes total serum IgE, IgA, IgG, and IgM. All immunoglobulin results will be redacted from laboratory reports.

[g] The eDiary includes Pruritus NRS.

[redacted]

[j] PK samples at day 1 and weeks 2, 4, 12, 16, 24, 32, 40, 48, and 50 should be collected before dosing with investigational product (trough).

[k] Administration of study drug is the final activity performed at a visit. Subjects randomized to Q4W dosing will receive placebo at the visits between dosing with tezepelumab. Subjects will be observed for 2 hours post-treatment at the day 1 and week 2 visits. For all other visits where investigational product is administered, subjects will be observed for a period of time at the discretion of the Investigator.

[l] All subjects who terminate the study early will complete an early termination visit consisting of all assessments included in the EOT (week 52) visit. In addition, a safety follow-up visit will occur 18 weeks after the EOT visit.

3. Introduction

3.1 Study Rationale

Tezepelumab is being developed for the treatment of atopic dermatitis (AD). Thymic stromal lymphopoietin (TSLP) is an epithelial cytokine shown to be elevated in skin lesions of patients with AD. A previous phase 2a study (ALLEVIAD) demonstrated improvements in Investigator's Global Assessment (IGA) and Eczema Area and Severity Index (EASI) scoring, but did not meet statistical significance in the primary endpoint. A phase 1b study demonstrated improvement in IGA and EASI as secondary endpoints.

In the ALLEVIAD study, not achieving statistical significance for the primary endpoint may have been due to the patient population selected, key study design elements surrounding topical corticosteroid (TCS) use, and length of treatment.

In the ALLEVIAD study, a small number of enrolled patients (20%) had severe disease and most had moderate AD (as determined by IGA score). The current study requires a minimum of a 2-year history of AD and a higher EASI minimum score of 16, which may lead to a greater treatment effect and is consistent with other studies of biologic therapies for AD (Simpson et al, 2016).

Patients were not required to be refractory to TCS at baseline (a requirement for the current study), and received TCS during the run-in and treatment periods. The study design did not exclude responders after the 2-week run-in period, which may have contributed to the large placebo response observed.

In the ALLEVIAD study, placebo-treated patients applied greater TCS amounts during treatment versus tezepelumab-treated patients. In addition, all patients liberally applied high-strength TCS during the 2-week run-in period. These 2 factors potentially decreased the differential effect due to tezepelumab treatment. In the monotherapy design for Part A of the current study, subjects will wash out from TCS and are required to abstain from TCS use for 16 weeks. This design has been used for other therapies and will allow for an evaluation of efficacy with less potential confounding (Simpson et al, 2016).

Second, the 12-week treatment period in ALLEVIAD may not have been of sufficient duration to demonstrate efficacy in the AD population. Dosing was through week 10, thus, steady-state exposures to tezepelumab were likely not attained. In the current study, the longer treatment duration evaluation of the primary endpoint at week 16 will ensure that tezepelumab reaches steady-state concentrations.

To explore whether clinical response continues to improve over time, treatment will continue up to 1 year, as tezepelumab is anticipated to be a chronic treatment regimen for a chronic disease. Also, given the mechanism of action of TSLP, a longer treatment period may reveal greater improvements in AD symptoms beyond week 16.

Part B of the current study is an exploratory study to investigate the clinical response of tezepelumab with TCS as adjunctive treatment. Inclusion of this cohort will allow for an evaluation of the effects of tezepelumab in a more real-life scenario. While TCS use was permitted in the ALLEVIAD study, the criteria for TCS use in Part B of the current study has been modified to provide guidance to the investigator for when and how to use TCS.

Three dose levels of tezepelumab (420 mg subcutaneous injection [SC] every 2 weeks [Q2W], 280 mg SC Q2W, and 210 mg SC every 4 weeks [Q4W]) were selected based on exposure-response analysis of tezepelumab concentration and IGA response from the ALLEVIAD study. These dose regimens will allow establishing exposure-response to aid in dose selection for future studies. A first dose of 420 mg will allow faster achievement of steady state for the lower dose regimens (210 mg SC Q4W and 280 mg SC Q2W), and is also anticipated to improve symptoms of AD (eg, sleep and pruritus).

3.2 Background

3.2.1 Disease

Atopic dermatitis is a chronic inflammatory skin disease (commonly referred to as eczema). In its severe form, AD is characterized by widespread skin lesions that manifest as red, itchy, swollen, cracked, weeping lesions with crusting and/or scaling. There is frequently intractable pruritus, as well as enhanced susceptibility to bacterial, viral, and fungal skin infections. Atopic dermatitis may affect up to 20% of children and up to 10% of adults (Hanifin and Reed, 2007; Silverberg and Hanifin, 2013; Silverberg et al, 2012). Atopic dermatitis is associated with a substantial patient burden that typically includes poor quality of life, sleep disturbance, and reductions in work productivity (Kiebert et al, 2002). Treatment recommendations for AD include liberal use of emollients, dry skin care protocols, and topical corticosteroids (TCS), which are commonly used in the clinical setting. Unfortunately, TCS have inadequate efficacy in many patients with moderate-to-severe disease, and their long-term use is associated with important side effects, such as thinning and discoloration of the skin, increased risk of skin infection, contact dermatitis, decreased bone density, and slowing of growth in

children depending on the extent of percutaneous administration (Chi et al, 2011; Ring et al, 2012).

The immunopathology of AD varies depending on the type of skin lesions. Acute lesions are characterized by a robust T helper 2 (Th2) immune response with production of interleukin (IL)-4, IL-5, and IL-13; and release of the epithelial cytokines IL-33, IL-25, and TSLP. Chronic lesions are characterized by a mixed Th1 and Th2 response (Beck and Leung, 2000; Soumelis et al, 2002).

Although TSLP is not detectable in the nonlesional skin of patients with AD, TSLP levels are elevated in both acute and chronic AD lesions (Soumelis et al, 2002). Thymic stromal lymphopoietin increases the number and maturation status of human migratory Langerhans cells and, through dendritic cells, induces a Th2 cytokine profile in cluster of differentiation (CD) 4+ helper T cells (Ebner et al, 2007). In a mouse model of AD, TSLP has been shown to directly stimulate antigen-specific CD4+ T cells to produce a Th2 cytokine profile following cutaneous allergen challenge (He et al, 2008). The role of TSLP in the development of fibrosis in AD is not well understood, but TSLP is detectable in lung fibroblasts (Soumelis et al, 2002), and a recent study suggests that TSLP directly promotes fibrocytes to produce collagen and that neutralization of TSLP significantly reduces skin fibrosis (Oh et al, 2011). As further evidence for the role of TSLP in the initiation and progression of AD, studies in mice overexpressing epidermal-specific TSLP demonstrate clinical and cellular features similar to human AD, including the development of eczematous lesions containing inflammatory cell infiltrates. Furthermore, in these studies, mice lacking T cells still develop AD-like disease, suggesting that TSLP can trigger AD-like skin inflammation in mice through direct activation of myeloid cells (Yoo et al, 2005).

Although most patients develop AD before the age of 5 years, up to 20% of patients may not develop AD until adulthood (Bieber et al, 2002; Kim et al, 2016). For many children, the onset of AD marks the beginning of a progression from AD to food allergy, allergic rhinitis, and eventually asthma, a phenomenon frequently described as the “atopic march” (Spergel and Paller, 2003). Indeed, up to 70% of patients with severe AD will develop asthma (Zheng et al, 2011). Numerous studies support a role for TSLP across the spectrum of atopic diseases and suggest that TSLP may function not only as an upstream regulator of inflammation in AD but as a modulator of disease progression within the atopic march. Zhang et al used a mouse model to demonstrate that induced expression of TSLP in mouse epidermal keratinocytes not only triggers AD but also

induces experimental allergic asthma (Zhang et al, 2009). In studies by Demehri and colleagues, mice overexpressing TSLP from skin keratinocytes not only developed AD-like skin inflammation but also were also susceptible to allergen-induced asthma. Furthermore, these authors demonstrated that epidermal-derived TSLP was sufficient to confer a severe asthma phenotype even in the absence of any skin defect (Demehri et al, 2009). Taken together, these studies suggest that TSLP is both necessary and sufficient to trigger the atopic march in a mouse model. In support of a key role for TSLP in the early development of AD, a prospective human birth cohort study revealed that high TSLP levels in skin at 2 months of age in addition to family history is a better predictor of AD development later in life compared to family history alone (Kim et al, 2016).

3.2.2 Amgen Investigational Product Background: Tezepelumab

Tezepelumab is a human recombinant monoclonal antibody of the immunoglobulin (Ig) G2 subclass that specifically binds human TSLP, blocking the interaction between TSLP and its high affinity receptor complex. Targeting TSLP may serve to inhibit multiple biologic pathways involved in AD.

A detailed description of the chemistry, pharmacology, pharmacokinetics (PK), efficacy, and safety of tezepelumab is provided in the Investigator's Brochure.

3.3 Benefit/Risk Assessment

In order to evaluate the clinical benefit-risk balance, preclinical and clinical data as well as a review of the available information for humanized monoclonal antibodies that are approved for and are in development for the treatment of AD have been considered. The ALLEVIAD study demonstrated improvements in EASI and IGA scoring, but did not meet statistical significance in its primary endpoint. A phase 1b study demonstrated improvement in IGA and EASI as secondary endpoints. In summary, the benefits for tezepelumab over placebo in AD include reduction of IGA, EASI, Scoring Atopic Dermatitis (SCORAD), and other markers of AD disease severity.

Tezepelumab has been well tolerated with no identified risks in studies to date.

[redacted]

[redacted]

The benefit/risk assessment for tezepelumab in AD based on the development through phase 2 is favorable. The future benefit/risk assessment will largely be defined by results from the phase 3 program.

More detailed information about the known and expected benefits and risks and safety profile of tezepelumab may be found in the Investigator's Brochure.

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary – Part A	
• To evaluate the effect of tezepelumab compared with placebo, assessed using the Investigator's Global Assessment (IGA) and Eczema Area and Severity Index (EASI)	• IGA score of 0 (clear) or 1 (almost clear) (IGA 0/1) at week 16 • 75% reduction in EASI (EASI 75) at week 16
Secondary – Part A	
• To estimate the effect of tezepelumab compared with placebo on the efficacy measure of EASI	• 50% and 90% reduction in EASI (EASI 50/90) at week 16
• To estimate the time needed to reach EASI 50/75/90	• Time at which EASI 50/75/90 is achieved from day 1
• To estimate the effect of tezepelumab compared with placebo on the efficacy measure of Scoring Atopic Dermatitis (SCORAD)	• SCORAD at week 16
• To estimate the effect of tezepelumab compared with placebo on the patient-reported outcome (PRO) measure of pruritus assessed using a numeric rating scale (NRS)	• Pruritus NRS at week 16
• To characterize the pharmacokinetics (PK) of tezepelumab	• Serum trough concentrations of tezepelumab at scheduled visits
Safety – Part A and Part B	
• To establish the safety and tolerability of tezepelumab compared with placebo	• Subject incidence of adverse events (including serious adverse events)
Exploratory – Part A and Part B	
• To estimate the long-term effect of tezepelumab on the efficacy measures of EASI, SCORAD, and Pruritus NRS	• IGA 0/1 at week 24, week 36, and week 52 • EASI 75 at week 24, week 36, and week 52 • EASI 50/90 at week 24, week 36, and week 52 • SCORAD at week 24, week 36, and week 52 • Pruritus NRS at week 24, week 36, and week 52
• To investigate potential biomarker development by biochemical analysis of blood or skin samples	• Serum biomarkers may include but are not limited to IgE, CCL17, and CCL22 • RNA transcriptional changes in blood and lesional versus nonlesional skin

Objectives	Endpoints
Exploratory – Part A and Part B (Continued)	
• To explore the effect of tezepelumab on Patient Global Impression of Severity (PGI-S)	• Change from baseline in PGI-S at scheduled visits
• To evaluate the effect of tezepelumab on health-related quality of life (HRQoL) assessed using the Dermatology Life Quality Index (DLQI)	• Change from baseline in DLQI at scheduled visits
• To evaluate the immunogenicity of tezepelumab	• Anti-tezepelumab antibodies
• To investigate the effects of drug target genes and AD genes and/or subject response to tezepelumab	• Gene polymorphisms that may influence clinical response to study drug, such as filaggrin and TSLP
Objectives	**Endpoints**
Exploratory – Part B	
• To evaluate the effect of tezepelumab compared with placebo, assessed using the IGA and EASI	• IGA score of 0 (clear) or 1 (almost clear) (IGA 0/1) at week 16 • EASI 75 at week 16
• To estimate the effect of tezepelumab compared with placebo on the efficacy measure of EASI	• EASI 50/90 at week 16
• To estimate the time needed to reach EASI 50/75/90	• Time at which EASI 50/75/90 is achieved from day 1
• To estimate the effect of tezepelumab compared with placebo on the efficacy measure of SCORAD	• SCORAD at week 16
• To estimate the effect of tezepelumab compared with placebo on the PRO measure of pruritus assessed using an NRS	• Pruritus NRS at week 16
• To characterize the PK of tezepelumab	• Serum trough concentrations of tezepelumab at scheduled visits
• To establish the safety and tolerability of tezepelumab compared with placebo	• Subject incidence of adverse events (including serious adverse events)

4.2 Hypotheses

Part A

The primary hypothesis is that tezepelumab effectively increases the probability of an IGA 0/1 response and an EASI 75 response at week 16 in subjects with moderate-to-severe AD.

Part B

Part B is an estimation study; no hypotheses will be formally tested.

5. Study Design

5.1 Overall Design

This phase 2b study is designed to evaluate the safety and efficacy of tezepelumab as a monotherapy and explore its efficacy as adjunct therapy in subjects with moderate-to-severe AD. This study consists of Part A (the main study evaluating tezepelumab as a monotherapy) and Part B (a study evaluating tezepelumab as adjunctive therapy when combined with a TCS regimen). In Part A, two futility analyses are planned when the 80th and 160th subjects are projected to complete week 16, respectively. Upon a result of "not futile" for the first analysis and Part A has completed enrollment of 240 patients, enrollment of subjects in Part B of the study will commence. A result of "futile" for either analysis in Part A will result in termination of both Part A and Part B of the study.

Eligible subjects for both Part A and Part B will include adults with a clinical diagnosis of AD at least 2 years prior to screening, with AD that affects ≥ 10% of body surface area as assessed by EASI, an IGA score of ≥ 3, and an EASI score of ≥ 16.

Part A and Part B of this study will consist of a 28-day screening period, a 52-week treatment period, and a 20-week safety follow-up period. During the 28-day screening period, subjects must discontinue from all topical AD therapies, except for approved moisturizers (see Section 7.1.7), for at least the 7 consecutive days immediately prior to day 1. During the study, approved moisturizers are allowed to be applied, with the exception of 8 hours prior to any scheduled visit.

Part A is a dose-ranging, randomized, placebo-controlled, double-blind study designed to evaluate the safety and efficacy of tezepelumab as monotherapy in subjects with moderate-to-severe AD. Following the screening period, eligible subjects will be randomized 1:1:1:1 to receive 420 mg SC Q2W, 280 mg SC Q2W, 210 mg SC Q4W, or placebo. All subjects will receive a 420 mg SC dose (investigational product or placebo) as the first dose. Subjects will then receive the appropriate dose of investigational product at the week 2 visit, depending on which treatment group they are randomized to. Depending on if they are randomized to Q2W or Q4W dosing, the dose at week 2 could be placebo or tezepelumab. Non-responders are defined as those subjects who have not achieved at least a 50% improvement in EASI at week 16 compared to baseline (day 1). Subjects who are determined to be non-responders in Part A will receive tezepelumab 420 mg SC Q2W for the remainder of the study, beginning with the

week 18 dose. The randomized treatment assignments for the non-responders will remain blinded until the end of study.

Part B is a randomized, placebo-controlled, double-blind study designed to evaluate the safety and efficacy of tezepelumab when administered with moderate class TCS in adults with moderate-to-severe AD. Enrollment of subjects in Part B of the study will only commence if there is a result of "not futile" for the first interim analysis in Part A and Part A has completed enrollment of 240 patients. Following the screening period, eligible subjects will be randomized 2:1 to receive 420 mg SC Q2W or placebo; both groups in Part B will be allowed to use TCS after the day 1 visit. Non-responders in Part B will not be switched to 420 mg SC Q2W at week 18 and will remain on their initial dose for the duration of the study.

The overall study design is described by a study schema in Section 2.1. The endpoints are defined in Section 4.1.

5.2 Number of Subjects

Approximately 240 subjects will be enrolled in Part A of the study. Approximately 60 subjects will be enrolled in Part B of the study.

Subjects in this clinical investigation shall be referred to as "subjects". For the sample size justification, see Section 10.1.

No groups/subgroups with specific needs are expected to be enrolled; no groups/subgroups are excluded from or underrepresented in the study.

5.2.1 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

5.2.2 Number of Sites

Approximately 100 investigative study centers in North America, Europe, and the Asia Pacific region will be included in the study. Study centers that do not enroll subjects within 6 months of site initiation may be closed.

5.3 End of Study

5.3.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), whether the study concluded as planned in the protocol or was terminated early.

The primary completion date is the date when the last subject has completed the assessments for week 16 in Part A of this study.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The end of study date is defined as the date when the last subject across all study centers is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.

5.3.2 Study Duration for Subjects

In Part A, for an individual subject, the length of participation includes a screening period of up to 28 days, a double-blind treatment period of 52 weeks, and a safety follow-up that occurs for 20 weeks after the final dose of study drug (18 weeks after the end of treatment [EOT] visit).

In Part B, for an individual subject, the length of participation includes a screening period of up to 28 days, a double-blind treatment period of 52 weeks, and a safety follow-up that occurs for 20 weeks after the final dose of study drug (18 weeks after the EOT visit).

5.4 Justification for Investigational Product Dose

[redacted]

[redacted]

6. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log may be completed and updated via an Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS).

Eligibility criteria will be evaluated during screening. Each subject should meet all the inclusion criteria and none of the exclusion criteria for this study in order to be enrolled. Under no circumstances can there be exceptions to this rule. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Subjects who do not meet the entry requirements for enrollment are screen failures.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Appendix 3).

6.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101 Subject has provided informed consent prior to initiation of any study specific activities/procedures

102 Age ≥ 18 to ≤ 75 years at screening

103 Clinical diagnosis of chronic AD (also known as atopic eczema) for at least 2 years prior to screening and has confirmed AD (Hanifin and Rajka criteria for AD; Hanifin and Rajka, 1980)

104 AD that affects ≥ 10% body surface area as assessed by EASI at screening and on day 1

105 An IGA score of ≥ 3 at screening and on day 1

106 An EASI score of ≥ 16 at screening and on day 1

107 Subject discontinued treatment with TCS, topical calcineurin inhibitors (TCI), and prescription moisturizers containing TCS or TCI for at least the 7 days immediately prior to the first dose of investigational product

108 Documented recent history (within 12 months before the screening visit) of inadequate response to treatment with topical TCS or subjects for whom topical treatments are otherwise medically inadvisable (ie, because of important side effects or safety risks)

- Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0 = clear to IGA 2 = mild) despite treatment with a daily regimen of TCS of medium or higher potency (with or without TCI as appropriate).

6.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Disease Related

201 Active dermatologic conditions, which might confound the diagnosis of AD or would interfere with the assessment of treatment, such as scabies, seborrheic dermatitis, cutaneous lymphoma, ichthyosis, psoriasis, allergic contact dermatitis, or irritant contact dermatitis

202 History of a clinically significant infection within 28 days prior to day 1 that, in the opinion of the investigator or medical monitor, might compromise the safety of the subject in the study, interfere with evaluation of the investigational product, or reduce the subject's ability to participate in the study. Clinically significant infections are defined as either of the following:

- 1) a systemic infection; or
- 2) a serious skin infection requiring parenteral antibiotic, antiviral, or antifungal medication

203 Diagnosis of a helminth parasitic infection within 6 months prior to screening that had not been treated with or had failed to respond to standard of care therapy

204 Documented medical history of chronic alcohol or drug abuse within 12 months prior to screening

205 History of anaphylaxis following any biologic therapy

206 Evidence of active liver disease at screening, including jaundice or aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase greater than twice the upper limit of normal (ULN)

207 Subjects who, in the opinion of the investigator, have evidence of active tuberculosis (TB), either treated or untreated, or a positive QuantiFERON-tuberculosis Gold (QFT-G) test for TB during screening. Subjects with an indeterminate QFT-G may be enrolled if they have ALL of the following:

- No symptoms of TB: productive, prolonged cough (> 3 weeks); coughing up blood; fever; night sweats; unexplained appetite loss; unintentional weight loss

- No evidence of active TB on chest radiograph within 3 months prior to the first dose of investigational product. Note: Chest radiograph is not part of screening procedure and will be the responsibility of the Investigator as this is outside the scope of this protocol

208 Positive hepatitis B surface antigen or hepatitis C antibody serology. Subjects with a history of hepatitis B vaccination without a history of hepatitis B are allowed to enroll in the study.

209 Positive human immunodeficiency virus (HIV) test at screening or the subject is taking antiretroviral medications, as determined by medical history, prior medications, and/or the subject's verbal report

Other Medical Conditions

210 History of malignancy, except for basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy ≥ 12 months prior to screening or other malignancies treated with apparent success with curative therapy ≥ 5 years prior to screening

211 History or evidence of severe depression, schizophrenia, previous suicide attempts, or suicidal ideation

Prior/Concomitant Therapy

212 Subjects who are unwilling to abstain from the use of TCS, TCI, and prescription moisturizers (those that contain TCS and TCI) from screening through week 16 (applies only to Part A subjects)

213 Subjects who have had side effects of topical medications including intolerance to treatment, hypersensitivity reactions, significant skin atrophy, or systemic effects as assessed by the investigator or by the subject's treating physician (applies only to Part B subjects)

214 More than or equal to 30% of the total lesional surface is located on areas of thin skin that cannot be safely treated with medium or higher potency TCS (eg, face, neck, intertriginous areas, areas of skin atrophy) (applies only to Part B subjects)

215 Receipt of any approved biologic agent (eg, dupilumab) within 4 months or 5 elimination half-lives (whichever is longer) prior to screening

216 Have used immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, interferon (IFN)-gamma, Janus kinase inhibitors, azathioprine, methotrexate) within 4 weeks prior to screening, or any condition that, in the opinion of the investigator, is likely to require such treatment(s) during the first 4 weeks of study treatment.

217 Have had phototherapy for AD in the 2 months prior to day 1, and subjects unwilling to avoid phototherapy during the first 16 weeks of the study

218 If on allergen-specific immunotherapy, subjects must be on a maintenance dose and schedule for ≥ 28 days prior to screening. Allergen-specific immunotherapy is defined as SC immunotherapy to aeroallergens and/or venom (Hymenoptera) as well as sublingual immunotherapy to aeroallergens

219 Vaccination with a live or attenuated vaccine within 28 days prior to day 1. Receipt of inactive/killed vaccinations (eg, inactive influenza) is allowed. Note

that receipt of the Th2 cytokine inhibitor suplatast within 15 days prior to randomization and during the study is not allowed.

220 Major surgery within 8 weeks prior to screening or planned inpatient surgery or hospitalization during the study period

Prior/Concurrent Clinical Study Experience

224 Currently receiving treatment in another investigational device or drug study, or less than 6 months since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

Other Exclusions

225 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional **16** weeks after the last dose of investigational product. (Females of childbearing potential should only be enrolled in the study after a negative highly sensitive serum pregnancy test).

226 Female subjects of childbearing potential who are sexually active with unsterilized male partners unwilling to use 1 highly effective method of contraception during treatment and for an additional **16** weeks after the last dose of investigational product. Cessation of contraception after this point must be discussed with a responsible physician. Females of childbearing potential are defined as those who are not surgically sterile (ie, had bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause). A highly effective method of contraception is defined as one that resulted in a low failure rate (ie, < 1% per year) when used consistently and correctly. Refer to Appendix 5 for additional contraceptive information.

230 Subject has known sensitivity to any of the products or components to be administered during dosing.

231 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.

6.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the study center's written institutional review board IRB/institutional ethics committee (IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Appendix 3).

The subject or the subject's legally acceptable representative must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (when informed consent is signed) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by IVRS/IWRS. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment.

This number will not necessarily be the same as the randomization number assigned for the study.

6.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) will not be rescreened.

7. Treatments

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Table 7-1 below.

7.1 Treatment Procedures

7.1.1 Investigational Products

The amount of investigational product, total volume, quantity, dose start date/time, and box number are to be recorded on each subject's CRF.

Table 7-1. Study Treatments

Study Treatment Name	Amgen Investigational Product:[a] Tezepelumab	Placebo
Dosage Formulation	Each package will contain 3 vials.	Placebo will be presented in identical containers, and stored/packaged the same as tezepelumab.
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	Each subject will receive 3 injections per visit. For subjects randomized to 420 mg SC Q2W, 280 mg SC Q2W, and 210 mg SC Q4W: volumes for injections from vials provided will be detailed in the Investigational Product Instruction Manual (IPIM). Subjects randomized to Q4W dosing will receive placebo at intervening visits, such that all subjects receive an injection Q2W.	Each subject will receive 3 injections per visit. For subjects randomized to placebo: volumes for injections from vials provided will be detailed in the IPIM. Subjects will receive placebo dosing Q2W.
Route of Administration	SC injection	SC injection
Accountability	The amount of investigational product, total volume, quantity, dose start date/time, and box number of investigational product are to be recorded on each subject's CRF(s).	The amount of investigational product, total volume, quantity, dose start date/time, and box number of investigational product are to be recorded on each subject's CRF(s).
Dosing Instructions	Investigational product will be administered by qualified study center personnel as the final activity for each study visit. The window for study visits is ± 3 days. Injection sites are to be rotated. Subjects will be observed for 2 hours post-treatment at the day 1 and week 2 visits. For all other visits where investigational product is administered, subjects will be observed for a period of time at the discretion of the Investigator.	Investigational product will be administered by qualified study center personnel as the final activity for each study visit. The window for study visits is ± 3 days. Injection sites are to be rotated. Subjects will be observed for 2 hours post-treatment at the day 1 and week 2 visits. For all other visits where investigational product is administered, subjects will be observed for a period of time at the discretion of the Investigator.

CRF = case report form; IPIM = Investigational Product Instruction Manual; SC = subcutaneous; Q2W = every 2 weeks; Q4W = every 4 weeks
[a] Tezepelumab will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

7.1.2 Non-investigational Products

Not applicable.

7.1.3 Medical Devices

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

7.1.4 Other Protocol-required Therapies

There are no other protocol-required therapies in this study.

7.1.5 Other Treatment Procedures

During the 28-day screening period, subjects must discontinue from all AD therapies, except for approved moisturizers (see Section 7.1.7), for at least the 7 consecutive days immediately prior to day 1. During the study, approved moisturizers are allowed to be applied, with the exception of 8 hours prior to any scheduled visit.

Medications and procedures permitted at any time during the study for subjects enrolled in Part A and Part B include:

- Basic skin care (cleansing and bathing), emollients, bleach baths, topical anesthetics, and antihistamines (all for any duration)
- Medications used to treat chronic diseases such as diabetes, hypertension, and asthma

Part A

In Part A of the study, if needed to control intolerable AD symptoms, rescue treatment for AD may be provided at the discretion of the investigator. Rescue is not allowed in the first 4 weeks of Part A. Topical calcineurin inhibitors may be used for rescue, but are to be reserved for problem areas only (eg, face, neck, intertriginous and genital areas). Investigators are to attempt to limit the first step of rescue therapy to topical medications, and escalate to systemic medications only for subjects who do not respond adequately following at least 7 days of topical treatment. If a subject receives rescue treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs

(eg, cyclosporine, mycophenolate-mofetil, azathioprine), study treatment is to be immediately discontinued.

All subjects are to complete the schedule of study visits and assessments whether or not they complete study treatment or receive rescue treatment for AD.

Part A Rescue Guidance

Subjects who use TCS are to apply medium potency TCS once daily to areas with active lesions. Low potency TCS should be used once daily on areas of thin skin (eg, face, neck, intertriginous, genital areas, areas of skin atrophy) or for areas where continued treatment with medium potency TCS is considered unsafe. Triamcinolone acetonide 0.1% cream or fluocinolone acetonide 0.025% ointment are recommended as medium potency TCS therapy; hydrocortisone 1% cream is recommended as low potency TCS therapy. After lesions are under control (clear or almost clear), subjects are to switch from medium potency to low potency TCS and treat once daily for 7 days, then cease TCS therapy.

If the lesions return, subjects are to resume treatment with medium potency TCS, and are to use the step-down approach to low potency TCS described above. For lesions that persist or worsen with once daily application of medium potency TCS, subjects may be treated (further rescued) with high or super-high potency TCS, unless higher potency TCS is considered unsafe.

Part B

Additionally, in Part B of the study, subjects are allowed to apply TCS following completion of all day 1 activities. Subjects should bring their containers of TCS to the site at every visit to have the container weighed and the amount of TCS used since the previous visit recorded.

Subjects who use TCS are to apply medium potency TCS once daily to areas with active lesions. Low potency TCS should be used once daily on areas of thin skin (eg, face, neck, intertriginous, genital areas, areas of skin atrophy) or for areas where continued treatment with medium potency TCS is considered unsafe. Triamcinolone acetonide 0.1% cream or fluocinolone acetonide 0.025% ointment are recommended as medium potency TCS therapy; hydrocortisone 1% cream is recommended as low potency TCS therapy. After lesions are under control (clear or almost clear), subjects are to switch from medium potency to low potency TCS and treat once daily for 7 days, then cease TCS therapy.

If the lesions return, subjects are to resume treatment with medium potency TCS, and are to use the step-down approach to low potency TCS described above. For lesions that persist or worsen with once daily application of medium potency TCS, subjects may be treated (rescued) with high or super-high potency TCS, unless higher potency TCS is considered unsafe.

In Part B, after all week 2 activities are completed, if needed to control intolerable symptoms, subjects may receive rescue treatment with any approved AD therapy (see Section 7.1.7 for excluded treatments). If rescue with TCS is necessary, mometasone 0.1% ointment is recommended as a high potency therapy; betamethasone dipropionate 0.05% optimized ointment or clobetasol propionate 0.05% cream are recommended as super-high potency therapy.

If a subject receives rescue treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (eg, cyclosporine, mycophenolate-mofetil, azathioprine) they must be discontinued from study treatment. All subjects are to complete the schedule of study visits and assessments whether or not they complete study treatment or receive rescue treatment for AD.

The use of TCI is to be reserved for problem areas (eg, face, neck, intertriginous and genital areas). TCS and TCI are not to be used concomitantly to treat the same affected areas.

7.1.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s), device(s) or combination product(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

Any product complaint(s) associated with an investigational product(s), non-investigational product(s), device(s), or combination product(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

7.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

The use of other investigational procedures and products while participating in this study is prohibited. The use of biologics, including dupilumab, is prohibited while participating in this study.

Treatment with systemic immunosuppressive/immunomodulating drugs (eg, methotrexate, cyclosporine, azathioprine, mycophenolate-mofetil, tacrolimus, and interferon gamma), Ig and or blood product during the study period is prohibited.

Vaccination with a live or attenuated vaccine is prohibited during the course of the study.

Planned inpatient surgery or hospitalization during the study period is prohibited.

Phototherapy is prohibited during the first 16 weeks of the study.

In Part A of the study, treatment with TCS, TCI, and prescription moisturizers that contain TCS or TCI is prohibited. Non-prescription moisturizers are allowed. Prescription moisturizers that have the same ingredients as available over-the-counter moisturizers are allowed for use.

In Part B of the study, treatment with TCI, and prescription moisturizers that contain TCS or TCI is prohibited until the week 2 assessments are completed. Non-prescription moisturizers are allowed. Prescription moisturizers that have the same ingredients as available over-the-counter moisturizers are allowed for use. Topical calcineurin inhibitors are only permitted for rescue. Topical corticosteroids are only permitted after the completion of all day 1 activities. After week 2, rescue with any approved AD therapy is allowed, however, study treatment will be discontinued for those subjects who use phototherapy, systemic corticosteroids, or injectable treatments as rescue therapy. Only those subjects using TCS and/or TCI as rescue will be permitted to continue concurrent therapy with study drug.

7.2 Method of Treatment Assignment

In Part A, subjects will be randomized in a 1:1:1:1 allocation ratio, to tezepelumab 420 mg SC Q2W, 280 mg SC Q2W, 210 mg SC Q4W, or placebo, respectively, in double-blind manner.

In Part B, subjects will be randomized in a 2:1 allocation ratio to 420 mg SC Q2W or placebo, respectively, in a double-blind manner.

The randomization will be performed by IVRS/IWRS.

The randomization date is to be documented in the subject's medical record and on the enrollment case report form.

7.3 Blinding

Both Part A and Part B of this study are double-blind. Treatment assignment will be blinded to all subjects, study center personnel, and Amgen as described below.

7.3.1 Study Center Personnel Access to Individual Treatment Assignments

A subject's treatment assignment is to only be unblinded when knowledge of the treatment is essential for further clinical management of the subject on this study. Unblinding at the study center for any other reason will be considered a protocol deviation. The Amgen Trial Manager must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the subject's condition. In this case, the Amgen Trial Manager must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.

A description of how responsible pharmacists and investigators will access treatment information (eg, via the IVR/IWR system), in the event that there is a need to break the blind, will be detailed in the IPIM.

7.3.2 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information is not to be distributed to the study team, investigators or subjects prior to the study being formally unblinded except as specified (eg, Section 7.3.1).

Staff from Clinical Supply Chain, Biological Sample Management, Clinical Pharmacology Modeling and Simulation, Computational Biology, Clinical Immunology, Clinical Biomarkers and Diagnostics, and Global Biostatistical Sciences departments who are responsible for tracking, assaying, or analyzing biological samples during the conduct of this study are considered unblinded to the treatment assignments in this study. These individuals will not to have access to subject level clinical data apart from the samples they are assaying and analyzing during the course of the study.

If exposure-response analysis is performed, the exposure-response analysis team, including Clinical Pharmacology Modeling and Simulation and Global Biostatistics

Sciences, who are independent of the study team, may be unblinded. The analysis plan and data integrity document for the exposure-response analysis will detail the analyses and describe the timing for unblinding according to Amgen's standard operating procedure.

7.4 Dose Modification

In Part A of this study, subjects who are determined to be non-responders will receive tezepelumab 420 mg SC Q2W for the remainder of the study, beginning with the week 18 dose. Non-responders are defined as those subjects who have not achieved at least a 50% improvement in EASI at week 16 compared to baseline (day 1). The randomized treatment assignments for the non-responders will remain blinded until the end of study.

In Part B, there will be no dose modification.

7.4.1 Dose-cohort Study Escalation/De-escalation and Stopping Rules

Not applicable.

7.4.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

7.4.2.1 Amgen Investigational Product: Tezepelumab

The reason for dose change of tezepelumab is to be recorded on each subject's CRF(s).

An individual subject may be discontinued at the discretion of the investigator and/or the sponsor due to clinically significant events.

In Part A of the study, subjects who are determined to be non-responders will receive tezepelumab 420 mg SC Q2W for the remainder of the study, beginning with the week 18 dose. Non-responders are defined as those subjects who have not achieved at least a 50% improvement in EASI at week 16 compared to baseline (day 1). The randomized treatment assignments for the non-responders will remain blinded until the end of study.

Subjects who receive rescue therapy with topical medications may continue treatment with study drug, per the instructions outlined in Section 7.1.5.

If a subject receives rescue treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (eg, cyclosporine, mycophenolate-mofetil, azathioprine), study treatment is to be immediately discontinued. All subjects are to complete the schedule of study visits and assessments whether or not they complete study treatment or receive rescue treatment for AD.

7.4.2.2 Non-Amgen/Amgen Non-Investigational Products

7.4.2.2.1 Topical Corticosteroids

Topical corticosteroid use is prohibited in Part A of this study. If topical corticosteroid use is required during Part A, refer to rescue guidance in Section 7.1.5.

In Part B of this study, subjects are allowed to initiate TCS use following completion of all day 1 activities. Subjects who apply TCS are to follow the dosing regimen described in Section 7.1.5.

Subjects will be monitored for signs of local or systemic TCS toxicity and will step down or stop treatment as directed by the Principal Investigator, who should direct the type and length of therapy. Signs of local toxicity include skin thinning; signs of systemic toxicity include hyperglycemia.

The reason for dose change of TCS is to be recorded on each subject's CRF(s).

7.4.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Appendix 7 for details regarding drug-induced liver injury (DILI) guidelines, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product during the study are provided in the IPIM.

7.6 Treatment Compliance

Subjects will receive the SC doses of investigational product at the study centers. The doses will be administered by qualified study personnel for the duration of the study. All efforts should be made to administer investigational product within the defined study windows. In the case of an out of window visit, investigational product can be administered within 1 week of the target visit day (ie, calculated from the day 1 visit). If investigational product cannot be administered within 1 week of the target visit date, the dose is considered missed.

7.7 Treatment of Overdose

A dose in excess of 420 mg tezepelumab administered within a 1-week period is considered an overdose. There is currently no specific treatment in the event of overdose of tezepelumab and the effects of overdose of this product are not known. An overdose with associated adverse events is recorded as the adverse event diagnosis/symptoms on the relevant adverse event modules in the Event CRF.

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

Prior therapies that were being taken from 5 years prior to screening through the first dose of investigational product should be collected.

For prior therapies being taken for the disease under study (eg, steroids, topical medications), collect therapy name, indication, dose, unit, frequency, route, start date and stop date. For all other prior therapies, collect therapy name, indication, dose, unit, frequency, route, and start date and stop date.

7.8.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.1.7.

Concomitant therapies are to be collected from the first dose of investigational product through the end of study safety follow-up.

For concomitant therapies being taken for the disease under study (eg, steroids, topical medications) collect therapy name, indication, dose, unit, frequency, route, start date and stop date. For all other concomitant therapies, collect therapy name, indication, dose, unit, frequency, route, start date and stop date.

Allowed concomitant treatments and directions pertaining to rescue therapy are outlined in Section 7.1.5.

8. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 8.1, 8.2.1, and 8.2.2.

8.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any

time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 2-1 and Table 2-2) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, disease-related events, and must document this decision in the subject's medical records. Subjects who receive systemic rescue therapies will be discontinued from study treatment but whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Appendix 3.

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- Decision by Sponsor
- Lost to follow-up
- Death
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Adverse event
- Subject request
- Pregnancy

8.2 Discontinuation From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data

can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Appendix 6 for further details). Refer to the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.2.1 Reasons for Removal From Washout, Run-in, or Invasive Procedures

Not applicable to this study.

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up

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 center.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The study center must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator can search publicly available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 2-1 and Table 2-2).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

9.1 General Study Periods

9.1.1 Screening, Enrollment, and Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the study center will register the subject in the IVRS/IWRS and screen the subject in order to assess eligibility for participation. The screening window for this study is up to 28 days (+ 7 days).

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects are not eligible for rescreening.

9.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 2-1 and Table 2-2). On-site study visits may be completed within a window of 3 days. The date of the first dose of tezepelumab or placebo is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of tezepelumab or placebo is to occur following completion of all other study activities for each visit.

9.1.3 Safety Follow-up

A safety follow-up visit will be conducted 20 weeks after the final dose of study drug (18 weeks after the EOT visit). All subjects who terminate the study early will complete an early termination visit consisting of all assessments included in the EOT (week 52)

visit and these subjects will complete a safety follow-up visit occur 18 weeks after the EOT visit.

9.1.4 End of Study

The EOS visit will occur 18 weeks after the EOT visit (20 weeks after the final dose of study drug) and is the same as the safety follow-up visit.

9.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

9.2.1 General Assessments

Study procedures and their timing are discussed in the Schedule of Activities (Table 2-1 and Table 2-2).

9.2.1.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

9.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on biomarker variability and PK of the protocol-required therapies.

9.2.1.3 Medical History

The Investigator or designee will collect a complete medical history that started within 5 years prior to enrollment through informed consent. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. In addition to the medical history above, AD history must date back to the original diagnosis. The current severity will be collected for each condition that has not resolved.

9.2.1.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

9.2.1.5 Physical Measurements

Height in centimeters should be measured without shoes. Weight in kilograms should be measured without shoes.

9.2.1.6 Substance Use

Obtain a detailed history of use of alcohol, tobacco, and caffeine.

9.2.2 Efficacy Assessments

9.2.2.1 Investigator's Global Assessment

The IGA allows investigators to assess overall disease severity at 1 given time point and consists of a 5-point severity scale from clear to severe disease (0 = clear; 1 = almost clear; 2 = mild disease; 3 = moderate disease; 4 = severe disease; 5 = very severe disease). The IGA uses clinical characteristics of erythema, infiltration, papulation, oozing, and crusting as guidelines for the overall severity assessment (Breuer et al, 2004). The IGA will be assessed at every visit according to the Schedule of Activities (Table 2-1 and Table 2-2). Whenever possible, the IGA should be assessed by the same investigator at each visit to reduce inter-rater variability.

9.2.2.2 Eczema Area and Severity Index

The EASI was designed by modifying the Psoriasis Area and Severity Index, which has been widely used in clinical trials and has been established as a well-accepted and standardized instrument for assessing therapeutic response in patients with psoriasis (Schmitt et al, 2007). The EASI evaluates 4 natural anatomical regions for severity and extent of key disease signs and focuses on key acute and chronic signs of inflammation (ie, erythema, induration/papulation, excoriation, and lichenification). The maximum score is 72, with higher values indicating more severe disease.

The EASI will be assessed at every visit according to the Schedule of Activities (Table 2-1 and Table 2-2). Whenever possible, the EASI should be assessed by the same investigator at each visit to reduce the inter-rater variability.

9.2.2.3 Scoring of Atopic Dermatitis

The SCORAD is a clinical tool for assessing the severity (ie, extent, intensity) of AD. The tool evaluates the extent and intensity of the AD lesions, along with subjective symptoms (Kunz et al, 1997). The maximum total score is 103, with higher values indicating more severe disease. The SCORAD should be assessed by the same investigator at each visit, whenever possible, to reduce inter-rater variability. The SCORAD will be conducted according to the Schedule of Activities (Table 2-1 and Table 2-2).

9.2.2.4 Patient-reported Outcomes

The electronic diary (eDiary), which includes the pruritus NRS, will be completed by the subject at home each morning during the treatment and follow-up periods. The remaining PROs will be conducted at the study center at the visits specified in the Schedule of Activities (Table 2-1 and Table 2-2) and should be completed prior to other study assessments to avoid the possibility of introducing bias to subject responses.

9.2.2.4.1 Electronic Diary

The electronic diary includes 1 item to capture subject-reported pruritus. The diary will be completed by the subject at home each morning using an electronic device according to the Schedule of Activities (Table 2-1 and Table 2-2).

9.2.2.4.1.1 Pruritus Numeric Rating Scale

Pruritus will be assessed using an NRS (0-10) with 0 = no itch and 10 = worst imaginable itch. Subjects will complete the NRS as part of the daily diary each day in the morning according to the Schedule of Activities (Table 2-1 and Table 2-2).

9.2.2.4.2 Patient Oriented Eczema Measure

The Patient Oriented Eczema Measure (POEM) is a 7-item validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults (Charman, 2004). It evaluates time spent in the past week with AD signs and symptoms: individual items of itching, bleeding, oozing, cracked, flaking, and dry/rough skin, and their impact on sleep. The POEM will be assessed at the study center, according to the Schedule of Activities (Table 2-1 and Table 2-2).

9.2.2.4.3 Dermatology Quality of Life Index

The DLQI is a 10-item, subject-completed, HRQoL assessment with content specific to those with dermatology conditions. The recall period is 1 week (Finlay and Kahn, 1994). The DLQI content captures respondent perceptions of dermatology-related symptoms and feelings (embracement), impacts on daily activities, leisure, work or school, personal relationships, and the side effects of treatment. Each item is scored on a 4-point Likert scale: 0 = not at all/not relevant; 1 = a little; 2 = a lot; and 3 = very much (Basra et al, 2008). The DLQI will be completed by the subject at the study center according to the Schedule of Activities (Table 2-1 and Table 2-2).

9.2.2.4.4 Patient Global Impression of Severity

The PGI-S is a single item designed to capture the subject's perception of overall symptom severity at the time of completion on a 5-point categorical response scale

(no symptoms to very severe symptoms. The PGI-S will be completed by the subject at the study center according to the Schedule of Activities (Table 2-1 and Table 2-2).

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities.

9.2.3.1 Adverse Events

All adverse events observed by the investigator or reported by the subject that occur after the first dose of investigational product through the end of study/safety follow-up visit or 20 weeks after the last administration of investigational product are to be collected/reported.

All adverse events related to any study procedure/activities will be collected/reported after signing the informed consent form through the end of study/safety follow-up visit or 20 weeks after the last dose of investigational product.

9.2.3.1.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

9.2.3.1.1.1 Disease-related Events

Disease-related events are defined in Appendix 4.

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after the first dose of investigational product(s)/study treatment/protocol-required therapies through the end of study are recorded using the Event CRF.

All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated serious disease-related event data to the sponsor within 24 hours of it being available.

Disease-related events assessed by the investigator to be more severe than expected and/or related to the investigational product(s)/study treatment/protocol-required therapies, and determined to be serious, must be reported on the Event CRF as serious adverse events and recorded and reported per Appendix 4 and Section 9.2.3.1.1.3.

Disease-related events pre-defined for this study include AD.

9.2.3.1.1.2 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 and is described in Appendix 4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product(s)/study treatment/protocol-required therapies through the end of study are reported using the Event CRF.

9.2.3.1.1.3 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 20 weeks after the last administration of investigational product are reported using the Event CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

9.2.3.1.1.4 Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. Per local requirements in some countries, investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

The method of recording, evaluating, and assessing causality of adverse events, adverse device effects, disease-related events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 4.

9.2.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

9.2.3.1.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC/IEC, if appropriate according to local requirements.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team (SAT) as appropriate. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

9.2.3.1.5 Events of Interest

An event of interest (EOI) is an event of scientific and medical interest towards improving the understanding of the investigational product. An EOI may be serious or non-serious. For this study, EOIs include:

9.2.3.1.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and female partners of male subjects will be collected after the start of study treatment and until **16** weeks after the final dose of study drug or the final study visit, whichever occurs later.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Appendix 5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Appendix 5.

9.2.3.2 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

9.2.3.3 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The ECG must include the following measurements: Heart Rate, QRS, QT, QTc, and PR intervals. The principal investigator (PI) (or designated study center physician or central reader) will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

9.2.3.4 Suicidal Risk Monitoring

Suicidal risk monitoring is not required for tezepelumab.

9.2.3.5 Other Safety

There are no other safety considerations for this study.

9.2.4 Clinical Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events.

Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities.

Laboratory/analyte results that could unblind the study will not be reported to investigative study centers or other blinded personnel until the study has been unblinded. Only eosinophils on complete blood count and differential are considered unblinding data for this study. Additional details regarding potentially unblinding data and study personnel are provided in Section 7.3.2.

9.2.4.1 Tuberculosis Testing

All subjects must receive either a purified protein derivate (PPD) or Quantiferon test at screening and ET/EOT.

The PPD test must be read by a trained healthcare professional 48 to 72 hours after the test is placed. PPD reader must be identified on the delegation of authority for this responsibility.

If a subject does not receive a PPD test, they must have Quantiferon testing. Refer to the central laboratory manual for instructions on sample collection, processing, and shipping of samples.

9.2.4.2 Pregnancy Testing

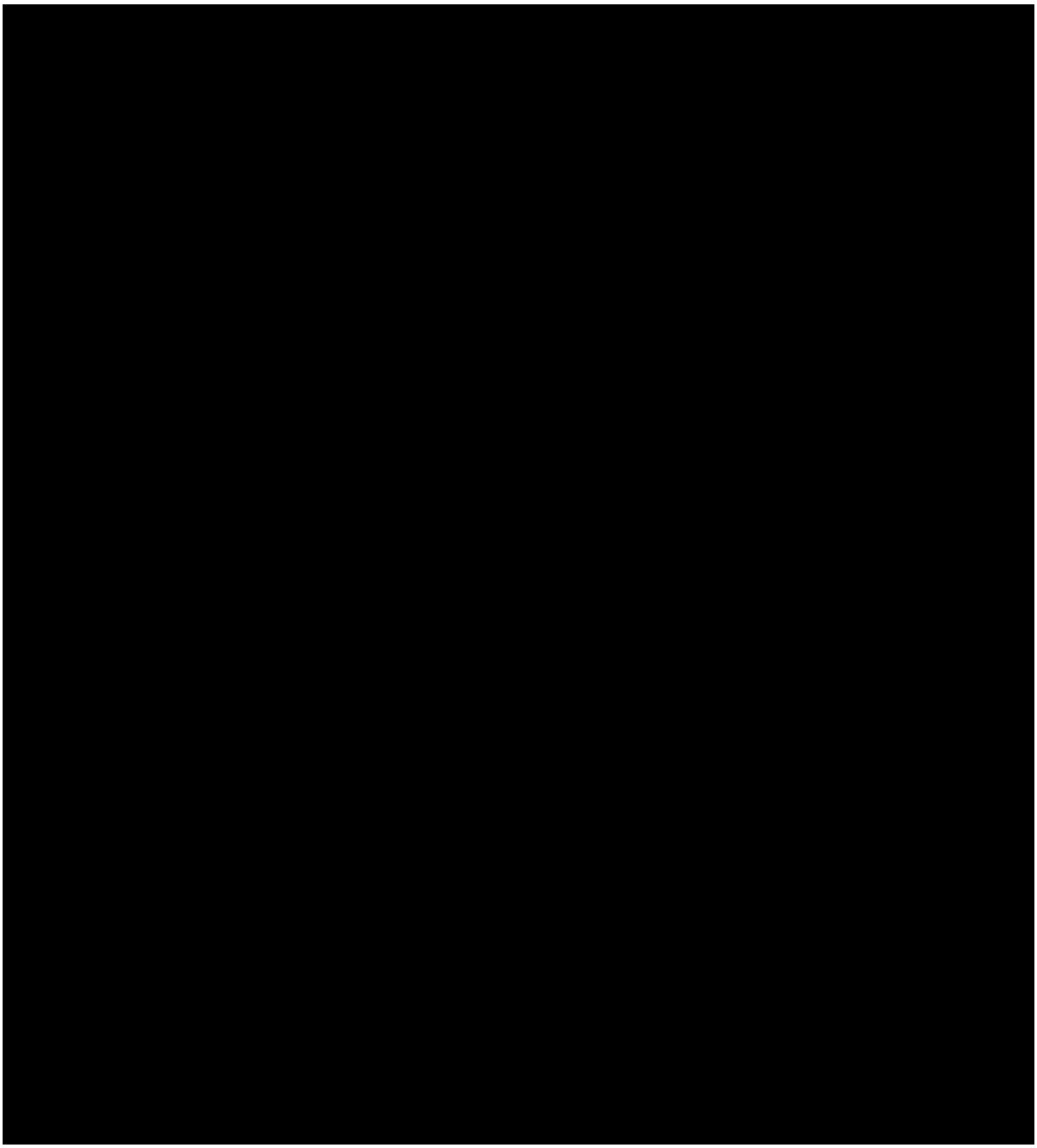
A high sensitive serum pregnancy test should be completed at screening and a high sensitive urine test should be completed within 7 days of initiation of investigational product for females of childbearing potential. Therefore, for this study, the initial pregnancy tests will occur at screening and at the day 1 visit (which is within 7 days of initiation of investigational product).

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Worksheet, see Figure 12-2). Refer to Appendix 5 for contraceptive requirements.

Additional pregnancy testing should be performed monthly during treatment with protocol-required therapies, then at week 52 and week 70 during the safety follow-up period.

If a urine pregnancy test is positive, a confirmatory serum pregnancy test will be performed and entered into the electronic case report form (eCRF).

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.



9.2.5 Pharmacokinetic Assessments

All subjects randomized to treatment with tezepelumab will have pharmacokinetic samples assessed.

Whole blood samples of approximately 5 mL will be collected for measurement of serum concentrations of tezepelumab as specified in the Schedule of Activities (Table 2-1 and Table 2-2). A maximum of 2 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

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

9.2.7 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of moderate-to-severe AD and/or to identify subjects who may have positive or negative response to investigational product or protocol-required therapies. Samples collected for this part of the study are described in Section 9.2.9.3. For subjects who consent to this/these analysis/analyses, DNA may be extracted. The final disposition of samples is described in Appendix 6.

9.2.8 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected according to the time points specified in the Schedule of Activities (Table 2-1 and Table 2-2). Bioanalytical testing for anti-tezepelumab antibodies will be conducted only if there are unexpected PK findings or safety-related concerns in the study population that warrant further investigation. Samples that test positive for anti-tezepelumab antibodies may be further characterized. Additional blood samples may be obtained to rule out the presence of anti-tezepelumab antibodies during the study.

Refer to the laboratory manual for detailed collection and handling instructions.

9.2.9 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to tezepelumab to investigate and further understand moderate-to-severe AD.

Blood samples and biopsies are to be collected according to the Schedule of Activities (Table 2-1 and Table 2-2). Refer to the Laboratory Manual for detailed collection and sample handling procedures for biomarker assessment.

9.2.9.1 Blood Biomarkers

Blood samples (serum/plasma and whole blood) will be collected as outlined in Table 2-1 and Table 2-2 for the assessment of changes in circulating biomarker levels that are elevated in subjects with AD. Additional assays which may be performed on blood samples include measuring changes in mRNA transcripts after tezepelumab treatment.

9.2.9.2 Skin RNA Transcript Profiling

Skin punch biopsy samples will be collected from a subset of consenting subjects according to the Schedule of Activities (Table 2-1 and Table 2-2) for RNA transcript analysis. The purpose of these analyses will be to retrospectively evaluate transcript biomarkers predictive of subject response at baseline, prior to investigational product administration, as well as to potentially identify additional AD biomarkers.

9.2.9.3 DNA

Whole blood will be collected at a single time point (day 1 visit) after subjects have been randomized into the study for extraction of DNA and analysis of polymorphisms associated with AD, TSLP, or tezepelumab response. The collection of blood for DNA analysis is optional and subjects who do not wish to have the DNA test done will still be eligible for the study. The completion of a separate Informed Consent Form (Pharmacogenetic ICF) related to DNA is required. Subjects who elect to have the DNA test done may, at any time before the end of the study, request that the blood collected for DNA analysis be destroyed.

9.2.10 Clinical Outcome Assessments

9.2.10.1 EQ-5D-3L

The EuroQOL quality of life 5-dimensions 3-level version (EQ-5D-3L) is a standardized instrument for use as a measure of health-related quality of life (HRQoL) and was developed by EuroQol (Brooks, 1996). It defines health in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 ordinal levels of severity: 1, no problem; 2, some problems; and 3, severe problems. Overall health state is defined as a 5-digit number. The EQ-5D-3L will be assessed at the study center, according to the Schedule of Activities (Table 2-1 and Table 2-2).

9.2.11 Optional Substudies

Optional substudies include skin punch biopsies (biomarker) and the sample for DNA analysis (pharmacogenetics). Obtain confirmation that the optional substudy ICF has been signed prior to performing any optional substudy procedures.

9.2.12 Other Assessments

Not applicable to this study.

10. Statistical Considerations

10.1 Sample Size Determination

In Part A of this study, a total of 240 subjects will be randomized in a 1:1:1:1 ratio to tezepelumab 420 mg SC Q2W, 280 mg SC Q2W, 210 mg SC Q4W, and placebo (approximately 60 in each group). There is at least 85% power for each co-primary endpoint, assuming IGA 0/1 response rates of 10% and 40% for placebo and the highest tezepelumab dose group (420 mg SC Q2W), respectively, and assuming EASI response rates of 15% and 50%, respectively. These assumed treatment effects are based on the results of other new agents in this indication (DUPIXENT, 2017). These calculations used a 2-sided χ^2 test at a significance level of 0.025 (to reflect the Bonferonni-based gatekeeping procedure described in Section 10.3.2.1) and assumed a 10% dropout rate.

Part B of this study is exploratory. A sample size of 60 subjects (40 in the tezepelumab 420 mg SC Q2W group and 20 in the placebo group) was chosen as an adequate sample size to provide initial evidence of tezepelumab as a promising agent for adjunct therapy.

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

Part A and Part B of the study will be analyzed separately, therefore, the analysis sets described below will be created for each study part.

10.2.1.1 Full Analysis Set

The full analysis set will include all randomized subjects. Subjects will be analyzed according to their randomized treatment group. Demographics, baseline disease characteristics, and efficacy analyses will be based on the full analysis set.

10.2.1.2 Safety Analysis Set

The safety analysis set will consist of all randomized subjects who receive at least 1 dose of investigational product. Subjects will be analyzed according to the actual treatment received. The safety analyses described in Section 10.3.2.3 will be based on the safety analysis set.

10.2.1.3 PK Analysis Set

Subjects who receive investigational product and have a sufficient number of serum concentration measurements for computing PK parameters will be included in the PK analysis set and subjects will be analyzed according to the treatment they actually receive.

10.2.2 Covariates

The analysis of the primary endpoints will be adjusted for the following baseline covariates:

- Baseline EASI (for EASI 75 at week 16)
- Baseline IGA (for IGA 0/1 at week 16)

Additional covariates may be considered in exploratory analyses and will be described in the Statistical Analysis Plan (SAP).

10.2.3 Subgroups

This study is not powered to draw conclusions from subgroup analyses. However, exploratory subgroup analyses based on the covariates above will be conducted to examine the consistency of the treatment effect for the primary endpoints for Part A. Additional subgroups for Part A will be specified in the SAP. Subgroup analyses are not planned for Part B.

10.2.4 Handling of Missing and Incomplete Data

Subjects missing data for the primary endpoints will be considered non-responders (ie, non-responder imputation). The last observation carried forward and multiple imputation methods may also be considered in sensitivity analyses. Similar methods will apply for the secondary endpoints EASI 50 and EASI 90 response. For the change from baseline to week 16 secondary endpoints, subjects missing week 16 will have their last observation carried forward; multiple imputation and a completers analysis may also be considered in sensitivity analyses.

10.3 Statistical Analyses

The SAP will be developed and finalized before database lock.

Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 5.3.1.

10.3.1 Planned Analyses

10.3.1.1 Interim Analysis and Early Stopping Guidelines

For Part A, two interim analyses are planned when approximately 80 and 160 subjects complete their week 16 assessments, respectively. [redacted]

The interim analyses will be performed by an independent statistician. The numerical results of the interim analyses will not be accessible to the study team. The study team will only know whether the study will continue or will be terminated based on the results.

For Part B, no interim analyses will be performed.

10.3.1.2 Primary Analysis

The primary analysis will occur when the primary completion date described in Section 5.3.1 has been observed, and the data have been entered, cleaned, and locked. The objective for the primary analysis is to assess safety and efficacy through week 16 for Part A only.

10.3.1.3 Exploratory Analysis for Part B

For Part B of this study, an exploratory analysis will occur when all subjects have completed the week 16 assessments, and the data have been entered, cleaned, and locked. The objective for this exploratory analysis is to assess safety and efficacy through week 16 for Part B only.

10.3.1.4 Final Analysis

The final analysis will occur when the end of study date described in Section 5.3.1 has been observed, and the data have been entered, cleaned, and locked. The final analysis will analyze efficacy and safety over the entire study period for Part A and Part B. For this analysis, Part A and Part B will be analyzed separately. However, some additional analyses (eg, adverse event summaries) may combine Part A and Part B; if performed, these analyses will be described in the SAP.

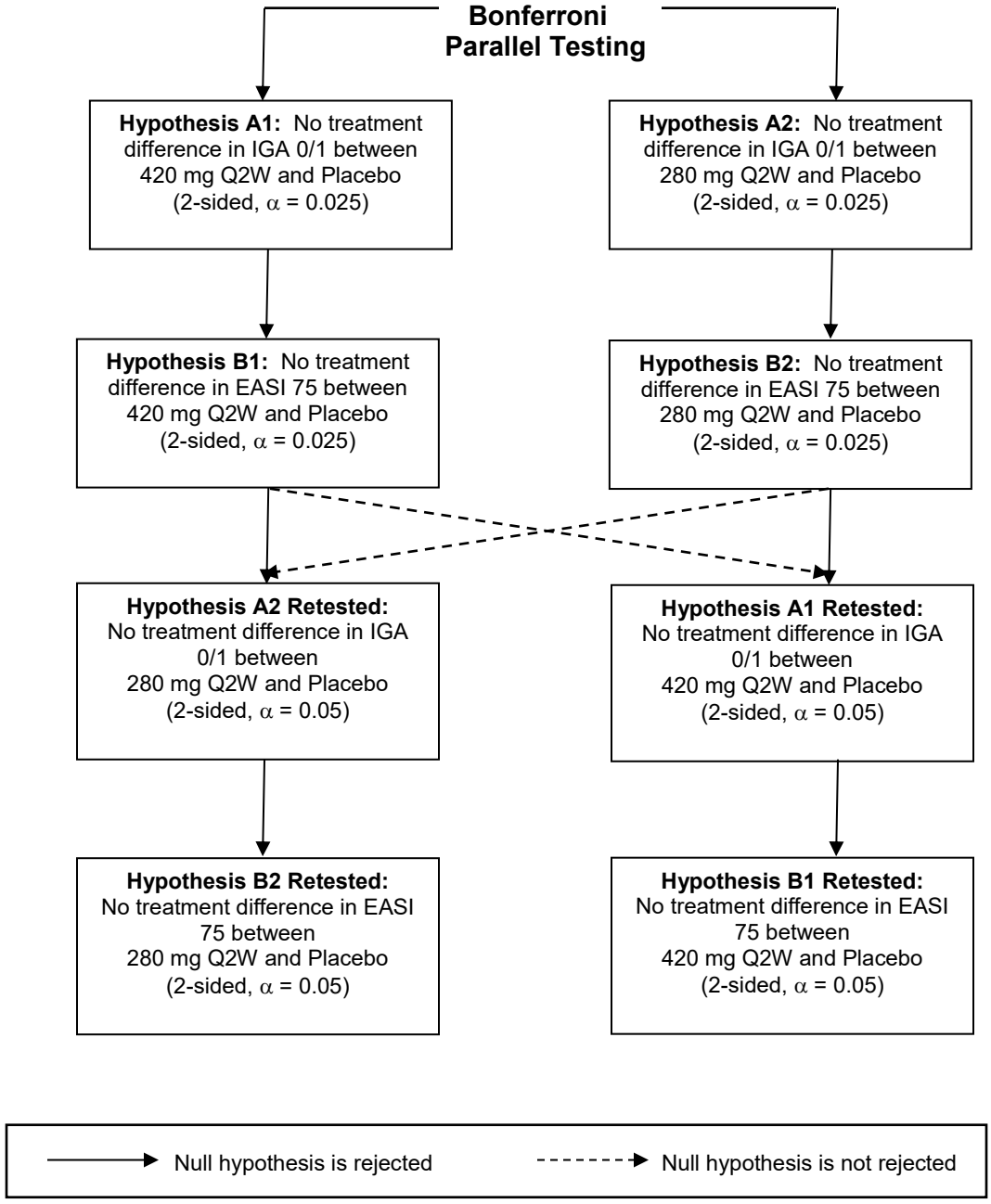
10.3.2 Methods of Analyses

10.3.2.1 General Considerations

Subject disposition, demographics, and baseline disease characteristics will be summarized descriptively by randomized treatment group. For categorical endpoints, the descriptive statistics will contain frequency and percentage. For continuous endpoints, the descriptive statistics will include the number of observations, mean, standard error, standard deviation, median, first quartile, third quartile, minimum, and maximum.

For Part A, the treatment effect for the primary analysis of the primary endpoints will be tested using a Bonferonni-based gatekeeping procedure to control the family-wise 2-sided type I error rate at 0.05. The procedure splits the α of 0.05 equally to test in parallel tezepelumab 420 mg SC Q2W versus placebo, and tezepelumab 280 mg SC Q2W versus placebo for IGA 0/1 and EASI 75 sequentially within each parallel path. If one of the parallel paths rejects the 2 hypotheses sequentially, and the other path has at least 1 hypothesis not rejected, then the unspent α of 0.025 from the successful path will be propagated to the unsuccessful path to retest the 2 hypotheses sequentially at a level of 0.05. This procedure is illustrated in Figure 10-1.

Figure 10-1. Alpha Split Between Two Doses of Interest



For all other endpoints in Part A and B, significance testing, if performed, will be considered descriptive.

10.3.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	For the primary endpoints of IGA 0/1 and EASI 75 at week 16, the treatment effect will be tested using a logistic regression model adjusting for covariates specified in Section 10.2.2. From this model, odd ratios and 95% CIs will be reported comparing each tezepelumab dose group to placebo. In addition, the percentage of subjects in each treatment group with a response and the difference in the percentage of subjects responding between each tezepelumab dose group and placebo will be summarized with a 95% confidence interval.
Secondary	The analysis of secondary endpoints will be descriptive and details will be provided in the SAP.
Exploratory	Details of the analysis of exploratory endpoints will be specified in the SAP.

10.3.2.3 Safety Analyses

10.3.2.3.1 Adverse Events and Disease-related Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment-emergent adverse events will also be provided. Subject incidence of disease-related events, if applicable, will be tabulated by system organ class and preferred term.

10.3.2.3.2 Laboratory Test Results

Laboratory parameters will be summarized descriptively by treatment group and visit**.** Grade 0 through 4 toxicities, as defined by the CTCAE, version 5.0 (or most recent version) will be presented for each laboratory parameter when available.

10.3.2.3.3 Vital Signs

Vital signs will be summarized by treatment group.

10.3.2.3.4 Exposure to Investigational Product

Exposure to investigational product will be summarized by treatment group. The summary of study drug exposure will include descriptive statistics for the number of study drug doses administered, total amount of study drug exposure. Additional details will be provided in the SAP.

10.3.2.3.5 Exposure to Other Protocol-required Therapy

Descriptive statistics will be produced to describe the exposure to TCS following day 1 to end of study.

10.3.2.3.6 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized for each treatment group as coded by the World Health Organization Drug (WHODRUG) dictionary.

10.3.2.4 Other Analyses

Not applicable.

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12. Appendices

Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
AD	atopic dermatitis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibody
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}7d}$	area under the curve from day 0 to day 7
$AUC_{0\text{-}28d}$	area under the curve from day 0 to day 28
CBC	complete blood count
CD	cluster of differentiation
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed serum concentration
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug induced liver injury
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI 50	50% reduction from baseline in EASI score
EASI 75	75% reduction from baseline in EASI score
EASI 90	90% reduction from baseline in EASI score
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
Enrollment	A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria at the screening visit
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), whether the study concluded as planned in the protocol or was terminated early
End of Study (end of trial)	defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable

Abbreviation or Term	Definition/Explanation
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EOI	event of interest
EOT	end of treatment
EQ-5D-3L	EuroQOL quality of life 5-dimensions 3-level version
eSAE	Electronic Serious Adverse Event
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRT	hormonal replacement therapy
HRQoL	Health-Related Quality of Life
ICF	informed consent form
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
ICH	International Council for Harmonisation
ID	identification
IFN	interferon
Ig	immunoglobulin
IGA	Investigator's Global Assessment
IGA 0/1	response of 0 (clear) or 1 (almost clear) skin on IGA scale
IL	interleukin
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Boards
INR	international normalized ratio
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
Interactive Voice Response System (IVRS)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information
Interactive Web Response System (IWRS)	web based technology that is linked to a central computer in real time as an interface to collect and process information
LDH	lactate dehydrogenase
LKM1	liver kidney microsomal type 1
NASH	nonalcoholic steatohepatitis
NRS	numerical rating scale
PD	pharmacodynamics
PGI-S	Patient Global Impression of Severity
PI	principal investigator

Abbreviation or Term	Definition/Explanation
PK	pharmacokinetics
PRO	patient-reported outcome
POEM	Patient Oriented Eczema Measure
POR	Proof of Receipts
PPD	purified protein derivate
Q2W	every 2 weeks
Q4W	every 4 weeks
QFT-G	QuantiFERON-tuberculosis Gold
Randomization	A subject will undergo randomization upon meeting all eligibility criteria at the day 1 randomization visit
S. aureus	*Staphylococcus aureus*
SAP	statistical analysis plan
SAT	safety assessment team
SC	subcutaneous
SCORAD	Scoring of Atopic Dermatitis
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
TBL	total bilirubin
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
TSLP	thymic stromal lymphopoietin
ULN	upper limit of normal
WHODRUG	World Health Organization Drug Dictionary

Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12-1 will be performed by the central laboratory and/or by the local laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 6.1 to 6.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12-1. Analyte Listing

Central Laboratory: Chemistry	Central Laboratory: Coagulation	Central Laboratory: Urinalysis	Central Laboratory: Hematology	Other Labs
Sodium	PT/INR	Specific gravity	RBC	Central Laboratory: Antibodies
Potassium	APTT	pH	Nucleated RBC	HLA typing
Chloride		Blood	Hemoglobin	Hep B surface antigen
Bicarbonate		Protein	Hematocrit	Hep C antibody
Total protein		Glucose	MCV	HIV[a]
Albumin		Bilirubin	MCH	Skin biopsy[b]
Calcium		WBC	MCHC	IgE
Adjusted calcium		RBC	RDW	IgA
Magnesium		Epithelial cells	Reticulocytes	IgG
Phosphorus		Bacteria	Platelets	IgM
Glucose		Casts	WBC	Serum Pregnancy
BUN or Urea		Crystals	Differential	PPD or Quantiferon Gold
Creatinine			• Total Neutrophils	Local Laboratory:
Uric acid			• Eosinophils	Urine Pregnancy
Total bilirubin			• Basophils	
Direct bilirubin			• Lymphocytes	
ALP			• Monocytes	
LDH			• Myeloblasts	
AST (SGOT)			• Promyelocytes	
ALT (SGPT)			• Myelocytes	
Cholesterol			•Metamyelocytes	
HDL			• Atypical lymphocytes	
LDL				
Triglycerides				

ALT = alanine aminotransferase; ALP = alkaline phosphatase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HDL = high density lipoprotein; Hep = hepatitis; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; I
NR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cell count; RDW = Red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count
[a] HIV assessment is recommended.
[b] Skin biopsy may be sent to a central lab for holding, then sent to a specialty lab for analysis.

Laboratory/analyte results that could unblind the study will not be reported to investigative study centers or other blinded personnel until the study has been unblinded. Only eosinophils on complete blood count and differential are considered unblinding data for this study and will not be reported to the site post-randomization.

Appendix 3. Study Governance Considerations

Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Institutional Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their study center.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the study center, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the study center and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Informed Consent Process

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her study center. Updates to the sample informed consent form are to be communicated formally in writing from the

Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative (defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study) will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject (or a legally acceptable representative) and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 8.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(ies), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above.

Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

All persons designated as authors must qualify for authorship, and all those who qualify are to be listed.

Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

- The coordinating investigator, identified by Amgen, will be any or all of the following:
- A recognized expert in the therapeutic area
- An Investigator who provided significant contributions to either the design or interpretation of the study
- An Investigator contributing a high number of eligible subjects

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being

protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research & Development Compliance and Audit function (or designees). Inspection of study center facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

CRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's study center.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs,

and correspondence. Source documents may also include data captured in the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) system (if used, such as subject identification (ID) and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable

Retention of study documents will be governed by the Clinical Trial Agreement.

Study and Site Closure

Amgen or its designee may stop the study or study center participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to

notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Disease-related Event

Disease-related Event Definition

• Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. See Section 9.2.3.1.1.1 for the list of disease-related events. All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours.
• Disease-related events that would qualify as an adverse event or serious adverse event:
  ○ An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event.
• Disease-related events that do not qualify as adverse events or serious adverse events:
  ○ An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a disease-related event.

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Events Meeting the Adverse Event Definition
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
"hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Adverse Device Effect

The detection and documentation procedures for adverse device effects described in this protocol apply to all Amgen medical devices provided for use in the study (see Section 7.1.3 for the list of Amgen medical devices).

Adverse Device Effect Definition
An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include adverse events resulting

Adverse Device Effect Definition
from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

Recording Adverse Events, Disease-related Events (if applicable), and Serious Adverse Events

Adverse Event, Disease-related Event (if applicable) and Serious Adverse Event Recording

- When an adverse event, disease-related event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/disease-related event/serious adverse event information in the Event case report form (CRF).
  - Additionally, the investigator is required to report a fatal disease-related event on the Event CRF.
- The investigator must assign the following adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Severity (or toxicity defined below);
  - Assessment of relatedness to investigational product, other protocol-required therapies, or devices; and
  - Action taken.
- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event CRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor/responsible contact research organization (CRO) in lieu of completion of the Event CRF page.
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on: The Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 which is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
Assessment of Causality
• The investigator is obligated to assess the relationship between investigational product, protocol-required therapies, device(s), and/or study-mandated procedures and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality. • There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data. • The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed Event CRF. • The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system via the Safety Report Form. • If the EDC system is unavailable for more than 24 hours, then the study center will report the information to Amgen using an Electronic Serious Adverse Event (eSAE) Contingency Form (paper form; see Figure 12-1) within 24 hours of the investigator's knowledge of the event. • The study center will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given study center, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a study center receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the study center can report this information on an Electronic Serious Adverse Event Contingency Form (paper form; see Figure 12-1).

Adverse Device Effects: Recording, Evaluating and Reporting

- Any adverse event resulting from an adverse device effect that occur during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the Event CRF page.
- It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by Amgen) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident.

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions
The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**
   Site Number* – Enter your assigned site number for this study
   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested
2. **Subject Information**
   Subject ID Number* – Enter the entire number assigned to the subject
   Age at event onset, Sex, and Race – Enter the subject's demographic information
   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**
   Provide the date the Investigator became aware of this Information
   Serious Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**
   Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.
   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.
   Is event serious?* – Indicate Yes or No. This is a mandatory field.
   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**
   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**
   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.
4. **Hospitalization**
   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

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Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. **IP Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**
    Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

AMGEN Study # 20170755 AMG 157	Electronic Serious Adverse Event Contingency Report Form **For Restricted Use**

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day _____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year_____

Serious Adverse Event diagnosis or syndrome **If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report** *List one event per line. If event is fatal, enter the cause of eeath. Entry of "death" is not acceptable, as this is an outcome.*	**Date Started** Day Month Year	**Date Ended** Day Month Year	Check only if event occurred before first dose of IP	**Is event serious?**	**If serious, enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP?								**Outcome of Event** -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
						<Pdevice> No✓	<Pdevice> Yes✓	<Pdevice> No✓	<Pdevice> Yes✓	<Pdevice> No✓	<Pdevice> Yes✓	<Pdevice> No✓	<Pdevice> Yes✓		
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

Serious Criteria:
01 Fatal
02 Immediately life-threatening
03 Required/prolonged hospitalization
04 Persistent or significant disability /incapacity
05 Congenital anomaly / birth defect
06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study # 20170755 AMG 157	Electronic Serious Adverse Event Contingency Report Form **For Restricted Use**

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Test / Unit											
	Test											
	Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20170755 AMG 157	Electronic Serious Adverse Event Contingency Report Form **For Restricted Use**

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - _____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for male and female subjects of childbearing potential are outlined in Section 6.2.

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and for **16** weeks after the last dose of protocol-required therapies.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception and for an increased length of time. In addition, male subjects may also be required to use contraception. The investigator must discuss these contraceptive changes with the subject.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.
- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

Note: Failure rate of < 1% per year when used consistently and correctly.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Unacceptable Methods of Birth Control for Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through **16** weeks following the final administration of study drug.
- Information will be recorded on the Pregnancy Notification Worksheet (see Figure 12-2). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.)
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through **16** weeks following the final dose of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 8.1 for details).

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional **16** weeks after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Figure 12-2) must be submitted to Amgen Global Patient Safety within 24 hours of the study center's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.)
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through **16** weeks following the final administration of study drug.
- Information will be recorded on the Lactation Notification Worksheet (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 225.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through **16** weeks after discontinuing protocol-required therapies.

Figure 12-2. Pregnancy and Lactation Notification Worksheet

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: _20170755_____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):**____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐ N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: _20170755_____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):**___(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Appendix 6. Sample Storage and Destruction

Any blood, biomarker, PK, DNA, or RNA sample collected according to the Schedule of Activities (Table 2-1 and Table 2-2) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the study center for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the moderate-to-severe atopic dermatitis (AD), the dose response and/or prediction of response to tezepelumab with or without TCS, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining (sample types [eg, blood, tumor]) samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the

request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Appendix 3 for subject confidentiality.

Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis (NASH)
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible drug-induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 12-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3 x ULN at any time	> 2 x ULN
		OR
INR	--	> 1.5 x ULN (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5 x ULN but < 8 x ULN for ≥ 2 weeks > 5 x ULN but < 8 x ULN and unable to adhere to enhanced monitoring schedule > 3 x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3 x ULN (when baseline was < ULN)
	OR	
ALP	> 8 x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then tezepelumab is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 12-2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified in the above, require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Appendix 4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 12-2 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2 x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count (CBC) with differential to assess for eosinophilia
- Serum total immunoglobulin G (IgG), anti-nuclear antibody (ANA), anti smooth muscle antibody, and liver kidney microsomal antibody -1 (LKM1) to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels

- A more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase (CPK), haptoglobin, lactate dehydrogenase (LDH), and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding CRFs.

Amendment no. 3

Protocol Title: A Dose-Ranging, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Tezepelumab Alone or Combined With Topical Corticosteroids in Moderate-to-Severe Atopic Dermatitis

Amgen Protocol Number Tezepelumab 20170755

Amendment Date: **25 August 2020**

Rationale:

The Protocol has been amended to update the safety language pertaining to the Pregnancy and Lactation information for female subjects and female partners.

- Female subjects and female partners of male subjects will now be required to refrain from becoming pregnant or breastfeeding until additional 16 weeks after the last dose of tezepelumab, instead of 14 weeks.
- Female subjects and female partners of male subjects' pregnancies must also be reported for an additional 16 weeks after the subject's last dose of tezepelumab, instead of 14 weeks.

Amendment 2

Protocol Title: A Dose-ranging, Double-blind, Placebo Controlled Study to Evaluate the Safety and Efficacy of Tezepelumab Alone or Combined with Topical Corticosteroids in Moderate-to-Severe Atopic Dermatitis

Amgen Protocol Number (Tezepelumab) 20170755

Amendment Date: 04 September 2019

Rationale:

The main purpose of this protocol amendment is two fold: 1) to address Amgen-mandated updates to the collection and reporting of disease-related events; and 2) align the male contraception language in the protocol with the updated contraception guidance in the Tezepelumab Investigator's Brochure.

Other minor, protocol clarifications and inconsistencies were updated during this amendment.

Amendment 1

Protocol Title: A Dose-Ranging, Double-Blind, Placebo Controlled Study to Evaluate the Safety and Efficacy of Tezepelumab Alone or Combined With Topical Corticosteroids in Moderate-to-Severe Atopic Dermatitis

Amgen Protocol Number (Tezepelumab) 20170755

Amendment Date: 20 November 2018

Rationale:

The main purpose of this protocol amendment is to address regulatory questions from EU VHP EU VHP-No: VHP1358 (VHP2018120) - RTQ submitted 06 Nov 2018 and to correct minor editorial changes and errors.

The major changes to the protocol are outlined below:

- Updated the safety follow-up period in response to RTQ Amended protocol from VHP to address GNA #55 by extending follow up period to 20 weeks after last dose.
- Added additional descriptive statistics for continuous endpoints in response to RTQ Amended protocol from VHP to address GNA #38.
- Added PPD or Quantiferon GOLD testing at screening and EOT/ET visits as requested by VHP RTQ #5, 19, and 20.
- Updated inclusion criterion 107 as a recommendation from study sites and KOLs as restriction of moisturizer type would impact recruitment and not influence efficacy.
- Updated exclusion criterion 215 in response to RTQ Amended protocol from VHP to address GNA #23.
- Removed language regarding receiving treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs after week 16 in response to RTQ Amended protocol from VHP to address GNA #26, 45, 52, 53.
- Updated interim analysis guidelines in response to RTQ Amended protocol from VHP to address GNA #54.
- Updated contraception guidance in response to RTQ Amended protocol from VHP to address GNA #46.