Janssen Research & Development*

Clinical Protocol

A Phase 3, Multicenter, Randomized, Double-blind Study Evaluating the Comparative Efficacy of CNTO 1959 (Guselkumab) and Secukinumab for the Treatment of Moderate to Severe Plaque-type Psoriasis

ECLIPSE

Protocol CNTO1959PSO3009; Phase 3
AMENDMENT 1

CNTO 1959 (guselkumab)

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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Prepared by: Janssen Research & Development, LLC
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	6 December 2016
Amendment 1	5 October 2017

Amendments below are listed beginning with the most recent amendment.

Amendment 1 (5 October 2017)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The overall reason for the amendment is to delete the reference to the Week 48 database lock (DBL) as detailed in the original study design. The study will have a singular database lock (DBL) at Week 56.

Applicable Section(s)	Description of Change(s)
Rationale: To delete the reference to the database lock (DBL) at Week 48 from the Study Design, and clarify that only one database lock (DBL) will occur at Week 56.	
Synopsis, Overview of Study Design; 3.1. Overview of Study Design, After Week 44 through Week 56 (Follow-up Period)	There ~~are 2~~**is 1** DBL in this study~~, 1 at Week 48, and 1~~ at Week 56. ~~The sponsor will be unblinded after the last subject has completed the Week 48 visit and the Week 48 DBL has occurred.~~ The **sponsor, the** investigators and subjects will be unblinded after the Week 56 DBL has occurred.
Figure 1: Schematic Overview of the Study	*The reference to the DBL at Week 48 has been deleted from the study schematic timeline.*
Rationale: To clarify that subjects who complete their final study visit prior to Week 48 are not to have blood samples drawn for analysis of serum biomarkers.	
Time and Events Schedule Footnote b and j.	b: All Week 48 study procedures should be performed on any subject who terminates the study prior to Week 48**, except for collection of serum for biomarkers**. j: Serum biomarker measurements will include but are not limited to: serum IL-17A, IL-17F, and IL-22. **For subjects who discontinue from the study prior to Week 48, serum is not to be collected for measurement of biomarkers.**
10.2 Discontinuation of Study Treatment/Withdrawal from the Study	**Discontinuation of Study Treatment** *[last paragraph]* If **the** subject discontinues study treatment before his or her last scheduled injection, he or she should return for the remaining regularly scheduled study visits for at least 12 weeks after receiving the last administration of study drug. For subjects who complete their final study visit prior to Week 48, every effort should be made to conduct the Week 48 assessments as indicated in the Time and Events Schedule. **For subjects who discontinue from the study prior to Week 48, serum is not to be collected for measurement of biomarkers.**
Rationale: To correct Exclusion Criterion #23 to specify that Exclusion Criterion #24 and not #28 applies to BCG vaccination.	
4.2. Exclusion Criteria Criterion #23	23. Has received, or is expected to receive, any live virus or bacterial vaccination within 3 months before the first administration of study drug. For BCG vaccine, see Exclusion Criterion ~~28~~**24**.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify the subject study visits at which each version of the Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) is to be conducted.	
9.6.1. Electronic Columbia-Suicide Severity Rating Scale	The 'Baseline/Screening' version of the eC-SSRS will be conducted during the screening visit followed by the 'Since Last Visit' version of the eC-SSRS at **Week 0, and** all visits ~~from baseline/Week 0~~**starting at Week 4** through Week 56.
Rationale: To replace X-ray with ECG Manual since an x-ray manual was not provided to the sites.	
15. Study-Specific Materials	• ~~X-ray~~**ECG** Manual.
Rationale: Minor errors were noted.	
Throughout the protocol.	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Phase 3, Multicenter, Randomized, Double-blind Study Evaluating the Comparative Efficacy of CNTO 1959 (Guselkumab) and Secukinumab for the Treatment of Moderate to Severe Plaque-type Psoriasis

Protocol Number: CNTO1959PSO3009

OBJECTIVES, ENDPOINTS, AND HYPOTHESES

Primary Objective

The primary objective is to evaluate the efficacy of guselkumab compared with secukinumab for the treatment of subjects with moderate to severe plaque-type psoriasis.

Secondary Objective

The secondary objectives are to assess:

- The safety and tolerability of guselkumab in subjects with moderate to severe plaque-type psoriasis.
- The PK and immunogenicity of guselkumab after subcutaneous (SC) administrations in subjects with moderate to severe plaque-type psoriasis.

Primary Endpoint

The primary endpoint in this study is the proportion of subjects who achieve a Psoriasis Area and Severity Index (PASI) 90 response at Week 48, comparing the guselkumab group and the secukinumab group.

Major Secondary Endpoints

The major secondary endpoints to compare the guselkumab group and the secukinumab group are listed below and are the proportion of subjects who achieve:

- A PASI 75 response at both Week 12 and Week 48.
- A PASI 90 response at Week 12.
- A PASI 75 response at Week 12.
- A PASI 100 response at Week 48.
- An Investigator's Global Assessment (IGA) score of cleared (0) at Week 48.

Other Secondary Endpoints

- The other secondary endpoints to compare the guselkumab group and the secukinumab group are listed below and are the proportion of subjects who achieve:
  - A PASI 90 response at both Week 16 and Week 48.
  - A PASI 75 response at Week 16.
  - A PASI 90 response at Week 16.
  - A PASI 90 response at all 7 visits from Week 24 through Week 48.
  - An IGA score of cleared (0) or minimal (1) at Week 16.
  - An IGA score of cleared (0) or minimal (1) at Week 12.

- The proportions of subjects who achieve a PASI 75 response at Week 48 among PASI 75 responders at Week 12.
- The proportions of subjects who achieve a PASI 90 response at Week 48 among PASI 90 responders at Week 16.
- The proportions of subjects who achieve a PASI 50/75/90/100 response over time through Week 48.
- The proportions of subjects who achieve an IGA score of cleared (0) response, IGA score of cleared (0) or minimal (1) response, and IGA of cleared (0), minimal (1), or mild (2) response over time through Week 48.
- Percentages of improvement from baseline in PASI over time through Week 48.

Hypotheses

The proposed randomized, blinded, two-active-arm trial will evaluate the relative performance of guselkumab and secukinumab utilizing a comprehensive battery of endpoints (eg, PASI 75, 90, and 100) at various timepoints (eg, Week 12 and Week 48) using rigorous statistical methodology to control for multiplicity.

While the ultimate goal of the trial is to demonstrate that the efficacy of guselkumab is superior to secukinumab for PASI 90 at Week 48, an initial test for non-inferiority is included for this endpoint because the overall profile of guselkumab will likely be favorable compared with secukinumab (in terms of potential for increased compliance and lesser patient burden), even if final results only indicate the relative efficacy is no worse for this endpoint.

The primary hypotheses are that guselkumab treatment is non-inferior to secukinumab as assessed by the proportion of subjects achieving a PASI 90 response at Week 48 with a non-inferiority margin of 10% and, once non-inferiority is established, that guselkumab is superior to secukinumab as assessed by the proportion of subjects achieving a PASI 90 response at Week 48.

The major secondary hypotheses are that guselkumab treatment is:

- Non-inferior to secukinumab for the maintenance of a PASI 75 response as assessed by the proportion of subjects who achieve a PASI 75 response at both Week 12 and Week 48 with a non-inferiority margin of 10% and, once non-inferiority is established, that guselkumab is superior to secukinumab as assessed by the proportion of subjects who achieve a PASI 75 response at both Week 12 and Week 48.
- Non-inferior to secukinumab at Week 12 as assessed by the proportion of subjects who achieve PASI 90 at Week 12 with a non-inferiority margin of 10%.
- Non-inferior to secukinumab at Week 12 as assessed by the proportion of subjects who achieve PASI 75 at Week 12 with a non-inferiority margin of 10%.
- Non-inferior to secukinumab at Week 48 as assessed by the proportion of subjects who achieve PASI 100 at Week 48 with a non-inferiority margin of 10% and, once non-inferiority is established, that guselkumab is superior to secukinumab as assessed by the proportion of subjects who achieve a PASI 100 response at Week 48.
- Non-inferior to secukinumab at Week 48 as assessed by the proportion of subjects who achieve an IGA score of cleared (0) at Week 48 with a non-inferiority margin of 10% and, once non-inferiority is established, that guselkumab is superior to secukinumab as assessed by the proportion of subjects who achieve an IGA score of cleared (0) at Week 48.

OVERVIEW OF STUDY DESIGN

This is a Phase 3, randomized, double-blind, multicenter, active-controlled study evaluating the comparative efficacy of CNTO 1959 (guselkumab) and secukinumab in subjects with moderate to severe plaque-type psoriasis.

There is 1 database lock (DBL) in this study at Week 56. The sponsor, the investigators and subjects will be unblinded after the Week 56 DBL has occurred. The end of the study is defined as the timepoint when the last subject completes the Week 56 visit.

SUBJECT POPULATION

The target population is adult men or women with a diagnosis of plaque-type psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug. Subjects must have moderate to severe plaque-type psoriasis defined by PASI ≥12, IGA ≥3, and involved body surface area ≥10%. Subjects must be candidates for either systemic therapy or phototherapy for psoriasis, may have previously received some systemic therapies or phototherapy for psoriasis, and be considered, in the opinion of the investigator, suitable candidates for secukinumab (Cosentyx®) therapy according to their country's approved secukinumab product labeling.

DOSAGE AND ADMINISTRATION

For those subjects randomized to guselkumab, a 100 mg/mL solution of guselkumab in a single-use prefilled syringe (PFS) assembled with the UltraSafe PLUS™ Passive Needle Guard (PFS-U) device will be used. Subjects who are randomized to the guselkumab treatment arm will receive 2 injections: 1 injection of active guselkumab and 1 injection of placebo when guselkumab is scheduled to be administered (Weeks 0, 4, 12, 20, 28, 36, and 44) or 2 injections of placebo when no guselkumab is scheduled to be administered (Weeks 1, 2, 3, 8, 16, 24, 32, and 40), to mimic the secukinumab 300 mg dosing schedule consisting of 2 injections and to maintain the blind. For those subjects randomized to Cosentyx, commercially available secukinumab (Cosentyx) will be supplied as a single-use PFS and administered according to the manufacturer's directions. Each 300 mg dose is given as 2 subcutaneous injections of 150 mg each. An appropriately qualified, unblinded member of the study staff will administer the drug and will have no other role in the conduct of the study.

All study drug injections will be administered at the investigational site. With the exception of the unblinded site personnel who dispense and/or administer the investigational product, all other site personnel and subjects will remain blinded to the treatment assignments until the last subject completes Week 56 evaluations and the database has been locked. Sites must ensure that they have the ability to physically blind and/or separate the blinded subject from the unblinded administrator. A physical barrier must be used such that the study drug can be administered by the unblinded site personnel, and the subject and other site personnel remain blinded.

EFFICACY EVALUATIONS

Efficacy evaluations chosen for this study are consistent with those utilized to evaluate other therapies for psoriasis. Efficacy evaluations include:

- IGA
- PASI

BIOMARKER EVALUATIONS

Biomarker sample collections will be conducted to measure serum markers, gene expression and cellular profiles in skin biopsies, [redacted] and genetic associations with psoriasis or response to treatment. Data collected from these samples will be used for exploratory research that will include the following objectives:

1. To understand the molecular effects of guselkumab and secukinumab.
2. To understand psoriasis pathogenesis.
3. To understand why individuals differ in their responses to guselkumab or secukinumab.
4. [redacted]

GENETIC (DNA) EVALUATIONS

Genetic (DNA) research may consist of the analysis of one or more candidate genes or analysis of the entire genome (as appropriate) in relation to guselkumab, secukinumab or psoriasis clinical endpoints. Whole blood samples will be collected for genetic analyses. Epigenetic evaluation may be conducted on skin samples obtained in the biopsy substudy. Only subjects who sign the consent form to participate in the genetic (DNA) assessment will have whole blood DNA or skin samples collected.

SAFETY EVALUATIONS

Safety evaluations include assessments of the following: adverse events (AEs; including injection-site and allergic reactions), clinical laboratory tests (hematology, chemistry, and pregnancy testing), physical examinations, vital sign measurements, electrocardiograms, concomitant medication review, electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) questionnaires, and early detection of tuberculosis (TB).

STATISTICAL METHODS

Approximately 1,040 subjects will be randomized in a 1:1 ratio to guselkumab 100 mg (n=520) or secukinumab 300 mg (n=520). With a non-inferiority margin of 10% and assumed treatment difference of 10 percentage point difference favoring guselkumab for the proportion of subjects achieving a PASI 90 response at Week 48, this study will have > 99% power to demonstrate the non-inferiority for the primary endpoint of PASI 90 at Week 48 and at least 90% power to detect a treatment difference (ie, superiority of guselkumab over secukinumab) for the primary endpoint of PASI 90 at Week 48.

In order to compare the proportion of subjects responding to the two treatments, the Cochran-Mantel-Haenszel chi-square test stratified by investigator site will be used. To test the non-inferiority of guselkumab to secukinumab, a 1-sided (α=0.025) Z-test with Mantel-Haenszel weights adjusted by investigator site will be used. A longitudinal modeling approach will also be used as a sensitivity analysis to compare the proportion of subjects responding to treatment. All statistical testing will be performed 2-sided at a significance level of 0.05 for superiority and 1-sided at a significance level of 0.025 for non-inferiority.

Subjects who discontinue study agent due to lack of efficacy or an AE of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could improve psoriasis are considered treatment failures. The baseline values will be assigned regardless of the observed data for continuous endpoints, zero will be assigned to improvement and percent improvement, and nonresponder status will be assigned to binary response variables. After applying the treatment failure rules, the remaining missing data will be assigned nonresponder status for binary variables. For the longitudinal analyses, treatment failure rules or missing data handling rules will not be applied.

Primary Analysis

The primary endpoint in this study is the proportion of subjects who achieve a PASI 90 response at Week 48. To address the primary efficacy objective, the proportion of subjects achieving a PASI 90 response at Week 48 will be evaluated with a non-inferiority test followed by a superiority test. The following stepwise comparisons will be made to compare the efficacy of guselkumab to that of secukinumab at Week 48:

a. A non-inferiority margin of 10% was chosen based on a minimal clinically meaningful difference. This margin was also used as the non-inferiority margin for the ustekinumab psoriasis study C0743T12 and the guselkumab psoriasis CNTO1959PSO3001 and CNTO1959PSO3002 studies. To claim the non-inferiority of guselkumab to secukinumab, the lower bound of the 2-sided 95% confidence interval of P1 – P2 must be $\geq -10\%$, where P1 and P2 are the proportions of subjects achieving a PASI 90 response at Week 48 in the guselkumab and the secukinumab groups, respectively. If non-inferiority is not established, no further test will be conducted and Step b will be skipped.

b. If non-inferiority is established in Step a, the superiority test of guselkumab to secukinumab will be performed at 2-sided (α=0.05).

If both the non-inferiority test and the superiority test are positive, the major secondary hypotheses comparing the guselkumab group and the secukinumab group will be tested sequentially. Otherwise, all remaining p-values will be considered nominal.

Major Secondary Analyses

For the major secondary analysis, all non-inferiority tests will be performed at 1-sided (α=0.025) with a non-inferiority margin of 10%. The major secondary analyses are:

- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving a PASI 75 response at both Week 12 and Week 48 will be performed. If non-inferiority is established, the superiority test on this endpoint will be performed.
- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving a PASI 90 response at Week 12 will be performed.
- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving a PASI 75 response at Week 12 will be performed.
- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving a PASI 100 response at Week 48 will be performed. If non-inferiority is established, the superiority test on this endpoint will be performed.
- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving an IGA score of cleared (0) at Week 48 will be performed. If non-inferiority is established, the superiority test on this endpoint will be performed.

In order to control the overall Type 1 error rate, the primary analysis and major secondary analyses will be tested in a fixed sequence as ordered above. That is, the first major secondary analysis will be performed only if the primary endpoint is positive for both non-inferiority and superiority, and the subsequent analysis will be performed only if the preceding analysis in the sequence is positive.

Other Efficacy Analyses

In addition to the primary and major secondary analyses, the analyses for other efficacy endpoints will be performed.

- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving a PASI 90 response at both Week 16 and Week 48 will be performed. If non-inferiority is established, the superiority test on this endpoint will be performed.
- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving a PASI 75 response at Week 16 will be performed.
- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving a PASI 90 response at Week 16 will be performed.
- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving a PASI 90 response at all 7 visits from Week 24 through Week 48 will be performed. If non-inferiority is established, the superiority test on this endpoint will be performed.
- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving an IGA score of cleared (0) or minimal (1) at Week 16 will be performed.
- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving an IGA score of cleared (0) or minimal (1) at Week 12 will be performed.
- The proportions of subjects who achieve a PASI 75 response at Week 48 among PASI 75 responders at Week 12 will be summarized by treatment group.
- The proportions of subjects who achieve a PASI 90 response at Week 48 among PASI 90 responders at Week 16 will be summarized by treatment group.
- The proportions of subjects who achieve a PASI 50/75/90/100 response over time through Week 48 will be summarized by treatment group.
- The proportions of subjects who achieve an IGA score of cleared (0) response, IGA score of cleared (0) or minimal (1) response, and IGA of cleared (0), minimal (1), or mild (2) response over time through Week 48 will be summarized by treatment group.
- The percentages of improvement from baseline in PASI over time through Week 48 will be summarized by treatment group.

Safety such as AEs, vital signs, eC-SSRS, laboratory values and ECG parameters will be summarized statistics.

TIME AND EVENTS SCHEDULE

Phase	Screening[a]	Active Treatment															Follow-up	
Week		0	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48[b]	56
Study Procedures																		
Screening/Administrative																		
Informed consent	X																	
Medical history and demographics	X																	
Inclusion/ exclusion criteria	X	X																
Study Drug Administration																		
Randomization		X																
Administration[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Safety Assessments																		
Physical examination (including skin exam)	X																X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG		X							X								X	
Tuberculosis evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest radiograph	X																	
Urine pregnancy test[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X																
Weight		X																
Concomitant therapy	X	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	X
eC-SSRS[e]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X

TIME AND EVENTS SCHEDULE

Phase	Screening[a]	Active Treatment														Follow-up	
Week		0	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48[b]	56
Study Procedures																		
Efficacy Assessments																		
IGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Surface Area (BSA)%	X	X																
Clinical Laboratory Assessment																		
QuantiFERON-TB test[f]	X																	
Hepatitis B and C serology	X																	
HIV antibody test	X																	
Hematology	X	X				X		X			X			X			X	X
Chemistry[g]	X	X				X		X			X			X			X	X
Lipid panel[h]		X																
Hs-CRP		X																
Pharmacokinetics and Immunogenicity[i]																		
Serum guselkumab concentration		X				X		X		X		X				X		X
Antibodies to guselkumab		X				X		X		X		X				X		X
Biomarkers																		
Serum biomarkers[j]		X				X					X						X	
Skin biopsy (RNA)[k]		X				X					X							
[redacted]		[redacted]									[redacted]						[redacted]	

TIME AND EVENTS SCHEDULE

Phase	Screening[a]	Active Treatment															Follow-up	
Week		0	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48[b]	56
Study Procedures																		
Genetic (DNA) evaluations																		
Genetic (DNA) analyses[m]		X																

FOOTNOTES:

a: The screening visit should occur within approximately 4 weeks before the Week 0 visit.

b: All Week 48 study procedures should be performed on any subject who terminates the study prior to Week 48, except for collection of serum for biomarkers. If a subject terminates post-Week 48, sites should make every effort to conduct the Week 56 assessments.

c: All study procedures and evaluations should be completed before administration of study drug. Assessments for subjects who discontinue study agent administration or withdraw from the study are discussed in Section 10.2.

d: Women of childbearing potential must have a negative urine pregnancy test before randomization, before study drug administration, and at all study visits.

e: The eC-SSRS should be completed by the subject before any tests, procedures, or other consultations to prevent influencing subject perceptions,

f: A tuberculin skin test is additionally required if the QuantiFERON-TB Gold test is not approved/registered in the country in which this study is being conducted.

g: Laboratory tests are listed in Section 9.6.

h: Subjects must fast (ie, no food or beverages [except water]) for at least 8 hours before blood is drawn for lipid panel. All other visits can be nonfasting.

i: All blood samples must be collected before study agent administration at visits when a study agent administration is scheduled. Details will be provided in the Laboratory Manual.

j Serum biomarker measurements will include but are not limited to: serum IL-17A, IL-17F, and IL-22. For subjects who discontinue from the study prior to Week 48, serum is not to be collected for measurement of biomarkers.

k Biopsy samples for RNA and tissue histology will be collected only from subjects who consent to participate in the optional biopsy substudy. Biopsy samples will be used to assess the cellular and molecular profiles of psoriatic skin lesions at baseline and during treatment.

[redacted]

m: Blood samples for genetic (DNA) analyses will be collected only from subjects who sign a separate consent form to participate in the genetic (DNA) evaluations.

ABBREVIATIONS

BCG	Bacille Calmette-Guérin
BSA	body surface area
CSR	clinical study report
DBL	database lock
ECG	electrocardiogram
eCRF	electronic case report form
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
eDC	electronic data capture
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IL	interleukin
IL-23R	interleukin-23 receptor
IM	intramuscular
IRB	Institutional Review Board
IWRS	interactive web response system
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NAb	neutralizing antibodies
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PASI	Psoriasis Area and Severity Index
PD	pharmacodynamic(s)
PFS	prefilled syringe
PFS-U	prefilled syringe assembled with the UltraSafe PLUS™ Passive Needle Guard
PK	pharmacokinetic
PQC	Product Quality Complaint
PsA	psoriatic arthritis
SAP	Statistical Analysis Plan
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
Tc17	CD8+ T cells
Th17	T helper 17
ULN	upper limit of normal

1. INTRODUCTION

Guselkumab (CNTO 1959) is a fully human immunoglobulin G1 lambda monoclonal antibody (mAb) that binds to human interleukin (IL)-23 with high specificity and affinity. The binding of guselkumab to IL- blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor (IL-23R), inhibiting IL-23-specific intracellular signaling and subsequent activation and cytokine production. In this manner, guselkumab inhibits the biological activity of IL-23 in all in vitro assays examined.

For the most comprehensive nonclinical and clinical information regarding guselkumab, refer to the latest version of the Investigator's Brochure and Addenda for guselkumab.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

The clinical development program to support use of guselkumab in the treatment of moderate to severe plaque-type psoriasis includes two Phase 1 studies, one Phase 2 study, and three Phase 3 global studies. The two Phase 1 studies and the Phase 2 study have been completed, and formed the basis to proceed to Phase 3. Details about these 3 individual studies are provided in the Investigator's Brochure. Results from two of the Phase 3 studies (CNTO1959PSO3001 and CNTO1959PSO3002) are presented below. Specifically, these two Phase 3 studies were both conducted using placebo and an active comparator, adalimumab (HUMIRA®). In these studies, guselkumab demonstrated superior efficacy to both placebo and adalimumab. The results of these 2 studies provide valuable benchmark data to assess the comparative efficacy of guselkumab and secukinumab.

Phase 3 Study (CNTO1959PSO3001, VOYAGE 1)

Study CNTO1959PSO3001 (VOYAGE 1) was a multicenter, Phase 3, randomized, double-blind, placebo- and active-comparator-controlled study in subjects with moderate to severe plaque-type psoriasis with 3 parallel treatment groups: placebo, guselkumab 100 mg, and adalimumab. Subjects in the placebo group crossed over to guselkumab 100 mg beginning at Week 16. In that study, 837 adult subjects were randomized to receive guselkumab (n=329) or adalimumab (n=334) or placebo (n=174).

At Week 16, a significantly greater proportion of subjects randomized to guselkumab achieved the co-primary endpoints of an Investigator's Global Assessment (IGA) score of cleared (0) or minimal (1) and Psoriasis Area and Severity Index (PASI) 90 response (85.1% and 73.3%, respectively; $p<0.001$ for both endpoints) compared with placebo (6.9% and 2.9%, respectively). At Week 24, a significantly higher proportion of subjects achieved IGA score of cleared (0), IGA score of cleared (0) or minimal (1), and PASI 90 response in the guselkumab group than in the adalimumab group. Similar to the observations at Week 24, a significantly higher proportion of subjects achieved an IGA score of cleared (0), an IGA score of cleared (0) or minimal (1), and a PASI 90 response in the guselkumab group than in the adalimumab group at Week 48.

Treatment with guselkumab was well-tolerated through Week 48. The frequency of AEs was comparable between the guselkumab, placebo, and adalimumab groups through Week 16 and between the guselkumab and adalimumab groups through Week 48. The most common AEs were nasopharyngitis and upper respiratory tract infection. Through Week 16, the percentage of subjects with 1 or more serious adverse events (SAEs) was 1.7% (n=3) in the placebo group, 2.4% (n=8) in the guselkumab group and 1.8% (n=6) in the adalimumab group, and was comparable between the guselkumab (4.9% [n=16]) and adalimumab (4.5% [n=15]) groups through Week 48. The incidence of infections was comparable between placebo, guselkumab and adalimumab groups through Week 16, and between the guselkumab group (52.3%) and the adalimumab group (50.2%) through Week 48. No opportunistic infections or active tuberculosis (TB) were reported. No anaphylactic or serum-sickness reactions were reported in the guselkumab group, and the incidence of injection site reactions was lower in the guselkumab group than the adalimumab group.

Phase 3 Study (CNTO1959PSO3002, VOYAGE 2)

Study CNTO1959PSO3002 (VOYAGE 2) was a multicenter, Phase 3, randomized, double-blind, placebo- and active-comparator-controlled study in subjects with moderate to severe plaque-type psoriasis with 3 treatment groups: placebo, guselkumab 100 mg, and adalimumab. In that study, 992 adult subjects were randomized to either the placebo (n=248), guselkumab (n=496), or adalimumab (n=248) treatment groups at Week 0. Subjects in the placebo group crossed over to guselkumab 100 mg beginning at Week 16. This study evaluated the benefit of maintenance therapy using a randomized withdrawal design starting at Week 28.

At Week 16, a significantly greater proportion of subjects randomized to guselkumab achieved the co-primary endpoints of an IGA score of cleared (0) or minimal (1) and a PASI 90 response (84.1% and 70.0%, respectively; $p<0.001$ for both endpoints) compared with placebo (8.5% and 2.4%, respectively). In addition, a significantly greater proportion of subjects achieved IGA score of cleared (0), IGA score of cleared (0) or minimal (1), and PASI 90 response in the guselkumab group than in the adalimumab group at Week 24.

Treatment with guselkumab was well tolerated. Through Week 16, the proportion of subjects experiencing 1 or more AEs was comparable between treatment groups. Nasopharyngitis and upper respiratory tract infection were the most common AEs. The percentage of subjects with 1 or more SAEs was comparable between the placebo and guselkumab groups, and slightly higher in the adalimumab group. The incidence of infections was comparable between placebo, guselkumab, and adalimumab groups through Week 16. Through Week 28, the proportion of subjects experiencing 1 or more AEs was comparable between the guselkumab and adalimumab groups. Two adalimumab-treated subjects reported active TB. No opportunistic infections were reported. No anaphylactic or serum-sickness reactions were reported.

1.2. Comparator

Cosentyx® (secukinumab)

Secukinumab (Cosentyx, Novartis Pharmaceuticals Corporation), a recombinant, high affinity, fully human mAb that selectively targets IL17A, is the first approved anti-IL-17 mAb for the treatment of moderate to severe plaque psoriasis. Secukinumab was selected as the active comparator because it is one of the newer, subcutaneously (SC) self-administered agents shown to achieve very high levels of efficacy in moderate to severe plaque psoriasis, and therefore provides a valuable and relevant benchmark for comparison with guselkumab. Subjects randomized to secukinumab must be dosed according to the labeled dose regimen for plaque psoriasis: 300 mg at Weeks 0, 1, 2, 3, and 4 followed by 300 mg q4w (through Week 44 in this study).

For further information regarding secukinumab, refer to the current prescribing information.

1.3. Overall Rationale for the Study

1.3.1. Role of IL-23 in the Treatment of Psoriasis

Psoriasis pathogenesis involves the dysregulation of IL-23- and IL-17-mediated immune responses. IL-23 is a key regulatory cytokine produced by activated antigen presenting cells that affects the differentiation, expansion and maintenance of $CD4^+$ IL-17 producing T helper 17 (Th17) cells, IL-22 producing T helper 22 cells, and CD8+ T cells (Tc17).[9] Th17 cells secrete several inflammatory mediators including IL-17A, IL-17F, and IL-22. In addition to being produced by Th17 cells, IL-17A is also produced by γδ-T cells and Tc17 cells, which are also regulated to some extent by IL-23.[12] Th17 and Tc17 cells have been shown to be elevated in psoriatic plaques and antagonism of either IL-23 or IL-17 has demonstrated clinical benefit in psoriasis.[1] Inhibition of IL-23 may impact the differentiation, expansion, and maintenance of Th17 and Tc17 cells providing sustained disruption of Th17 and Tc17 cell involvement in psoriasis lesions. Antagonism of soluble IL-17 inhibits local IL-17-mediated pathology in psoriasis lesions in addition to soluble IL-17 produced by non-Th17 cells. Selective inhibition of IL-23R-expressing Th17 and Tc17 cells, the source of IL-17 in psoriasis lesions, by blocking IL-23, may yield sustained clinical benefit in psoriasis.

Guselkumab, a human mAb specifically targets IL-23. A rapidly growing body of literature suggests that the IL-23/IL-17 pathway contributes to the chronic inflammation underlying the pathophysiology of many immune-mediated diseases,[14,19] including psoriasis.[8] In addition, susceptibility to psoriasis, psoriatic arthritis (PsA), and inflammatory bowel disease has been shown to be associated with genetic polymorphisms in IL-23/IL-23R components.[2,4,7,11,13] Finally, the clinical response to guselkumab observed in Phase 1, 2, and 3 psoriasis studies demonstrates the specific importance of IL-23 in the pathogenesis of plaque-type psoriasis and supports further investigation of the clinical benefit of guselkumab compared to secukinumab.

1.3.2. Dose Rationale

A dose regimen of guselkumab 100 mg at Weeks 0 and 4 and q8w thereafter was selected for the global Phase 3 studies of guselkumab for the treatment of moderate to severe plaque-type psoriasis. This dose regimen was chosen based on results of the guselkumab dose-ranging study (CNTO1959PSO2001) in subjects with moderate to severe plaque-type psoriasis and pharmacokinetic (PK)/pharmacodynamic (PD) modeling based on the data from that study. The same dose regimen studied in the global phase 3 program will be used in this study.

1.3.3. Rationale for Trial Design and Efficacy Analyses

The proposed randomized, blinded, two-active-arm trial will evaluate the relative performance of guselkumab and secukinumab utilizing a comprehensive battery of endpoints (eg, PASI 75, 90, and 100) at various timepoints (eg, Week 12 and Week 48) using rigorous statistical methodology to control for multiplicity.

The statistical analyses will employ a sequential testing approach to control for multiplicity that includes both superiority and non-inferiority testing for specified endpoints.

While the ultimate goal of the trial is to demonstrate that the efficacy of guselkumab is superior to secukinumab for PASI 90 at Week 48, initial testing for non-inferiority is included for this endpoint because the overall profile of guselkumab will likely be favorable compared with secukinumab (in terms of potential for increased compliance and lesser patient burden), even if relative efficacy is no worse for this endpoint.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESES

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

The primary objective is to evaluate the efficacy of guselkumab compared with secukinumab for the treatment of subjects with moderate to severe plaque-type psoriasis.

Secondary Objectives

The secondary objectives are to assess:

- The safety and tolerability of guselkumab in subjects with moderate to severe plaque-type psoriasis.
- The PK and immunogenicity of guselkumab after subcutaneous (SC) administrations in subjects with moderate to severe plaque-type psoriasis.

Exploratory Objectives

The exploratory objectives are to explore:

- The PD effects (biomarkers) of treatment with guselkumab or secukinumab in subjects with moderate to severe plaque-type psoriasis.
- The impact of treatment with guselkumab or secukinumab on psoriasis skin lesion gene expression profiles and cellular content in subjects with moderate to severe plaque-type psoriasis.
- [redacted]
- The association between genetic factors and 1) the efficacy of guselkumab or secukinumab and 2) psoriasis.

2.1.2. Endpoints

Primary Endpoint

The primary endpoint in this study is the proportion of subjects who achieve a PASI 90 response at Week 48, comparing the guselkumab group and the secukinumab group.

Major Secondary Endpoints

The major secondary endpoints to compare the guselkumab group and the secukinumab group are listed below and are the proportion of subjects who achieve:

- A PASI 75 response at both Week 12 and Week 48.
- A PASI 90 response at Week 12.
- A PASI 75 response at Week 12.
- A PASI 100 response at Week 48.
- An IGA score of cleared (0) at Week 48.

Other Secondary Endpoints

- The other secondary endpoints to compare the guselkumab group and the secukinumab group are listed below and are the proportion of subjects who achieve:
  - A PASI 90 response at both Week 16 and Week 48.
  - A PASI 75 response at Week 16.
  - A PASI 90 response at Week 16.
  - A PASI 90 response at all 7 visits from Week 24 through Week 48.
  - An IGA score of cleared (0) or minimal (1) at Week 16.
  - An IGA score of cleared (0) or minimal (1) at Week 12.

- The proportions of subjects who achieve a PASI 75 response at Week 48 among PASI 75 responders at Week 12.
- The proportions of subjects who achieve a PASI 90 response at Week 48 among PASI 90 responders at Week 16.
- The proportions of subjects who achieve a PASI 50/75/90/100 response over time through Week 48.
- The proportions of subjects who achieve an IGA score of cleared (0) response, IGA score of cleared (0) or minimal (1) response, and IGA of cleared (0), minimal (1), or mild (2) response over time through Week 48.
- Percentages of improvement in PASI over time through Week 48.

2.2. Hypotheses

The proposed randomized, blinded, two-active-arm trial will evaluate the relative performance of guselkumab and secukinumab utilizing a comprehensive battery of endpoints (eg, PASI 75, 90, and 100) at various timepoints (eg, Week 12 and Week 48) using rigorous statistical methodology to control for multiplicity.

While the ultimate goal of the trial is to demonstrate that the efficacy of guselkumab is superior to secukinumab for PASI 90 at Week 48, initial testing for non-inferiority is included for this endpoint because the overall profile of guselkumab will likely be favorable compared with secukinumab (in terms of potential for increased compliance and lesser patient burden), even if final results only indicate the relative efficacy is no worse for this endpoint.

The primary hypotheses are that guselkumab treatment is non-inferior to secukinumab as assessed by the proportion of subjects achieving a PASI 90 response at Week 48 with a non-inferiority margin of 10% and, once non-inferiority is established, that guselkumab is superior to secukinumab as assessed by the proportion of subjects achieving a PASI 90 response at Week 48.

The major secondary hypotheses are that guselkumab treatment is:

- Non-inferior to secukinumab for the maintenance of a PASI 75 response as assessed by the proportion of subjects who achieve a PASI 75 response at both Week 12 and Week 48 with a non-inferiority margin of 10% and, once non-inferiority is established, that guselkumab is superior to secukinumab as assessed by the proportion of subjects who achieve a PASI 75 response at both Week 12 and Week 48.
- Non-inferior to secukinumab at Week 12 as assessed by the proportion of subjects who achieve PASI 90 at Week 12 with a non-inferiority margin of 10%.
- Non-inferior to secukinumab at Week 12 as assessed by the proportion of subjects who achieve PASI 75 at Week 12 with a non-inferiority margin of 10%.

- Non-inferior to secukinumab at Week 48 as assessed by the proportion of subjects who achieve PASI 100 at Week 48 with a non-inferiority margin of 10% and, once non-inferiority is established, that guselkumab is superior to secukinumab as assessed by the proportion of subjects who achieve a PASI 100 response at Week 48.
- Non-inferior to secukinumab at Week 48 as assessed by the proportion of subjects who achieve an IGA score of cleared (0) at Week 48 with a non-inferiority margin of 10% and, once non-inferiority if established, that guselkumab is superior to secukinumab as assessed by the proportion of subjects who achieve an IGA score of cleared (0) at Week 48.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a Phase 3, randomized, double-blind, multicenter, active-comparator-controlled study in subjects with moderate to severe plaque-type psoriasis. The target population is adult men or women, with a diagnosis of plaque-type psoriasis (with or without PsA) for at least 6 months before the first administration of study drug. Subjects must have moderate to severe plaque-type psoriasis defined by IGA ≥3, PASI ≥12, and involved body surface area (BSA) ≥10%. Subjects must be candidates for either systemic therapy or phototherapy for psoriasis, and may have previously received some systemic therapies or phototherapy for psoriasis. Subjects with nonplaque forms of psoriasis (eg, erythrodermic, guttate, or pustular) or with drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium) are excluded. Subjects who have ever received guselkumab or secukinumab are also excluded.

Key features of study drug administration for each treatment group are outlined below; for details regarding concomitant placebo administrations to maintain the blind, see Section 6.

Week 0 through Week 44 (Blinded Treatment Period)

As depicted in Figure 1, approximately 1,040 subjects who satisfy all inclusion and exclusion criteria will be randomized in a 1:1 ratio to 1 of 2 treatment arms:

- **Group I** (n=520): guselkumab 100 mg SC at Weeks 0, 4, 12, and q8w thereafter through Week 44.
- **Group II** (n=520): secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4 and q4w thereafter through Week 44.

After Week 44 through Week 56 (Follow-up Period)

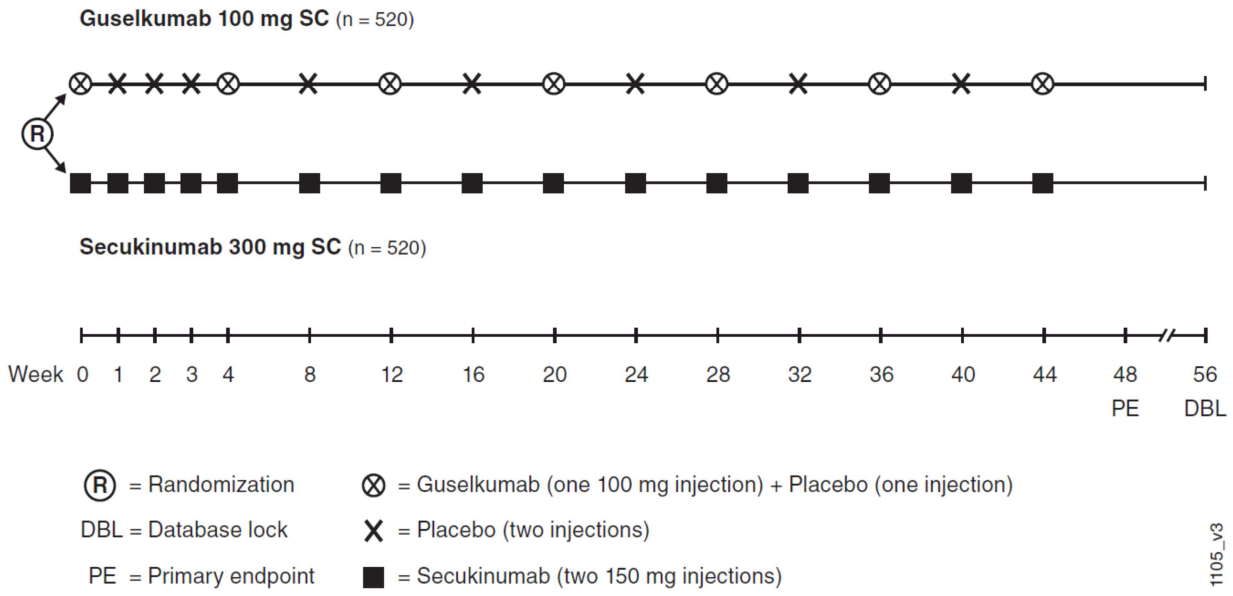
The follow-up period will begin after Week 44 and extend through Week 56.

There is 1 database lock (DBL) in this study at Week 56. The sponsor, the investigators, subjects, and site monitors will be unblinded after the Week 56 DBL has occurred. The end of the study is defined as the timepoint when the last subject completes the Week 56 visit.

A pharmacogenomic blood sample will be collected from subjects who consent separately to this component of the study (where local regulations permit). Subject participation in pharmacogenomic research is optional.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



3.2. Study Design Rationale

This Phase 3, randomized, double-blind, multicenter study will evaluate the comparative efficacy and assess the safety of guselkumab, compared with secukinumab for the treatment of subjects with moderate to severe plaque-type psoriasis.

Multiple therapeutic options exist for the treatment of moderate to severe psoriasis; however, none of the currently approved agents, including several highly effective biologic agents, can provide complete clearance of disease in all patients. Several studies suggest that complete clearance is associated with quantifiable improvements in quality of life,[21,18,16] and is increasingly sought by patients and physicians in this era of highly effective therapies for plaque psoriasis. A recent publication reported that patients who were considered to be responders, but lacked complete clearance, may still experience negative impact on their health-related quality of life as compared to those patients who achieved complete clearance. The patients who were considered cleared had a substantial improvement in their quality of life.[17] While available clinical studies have demonstrated that secukinumab treatment leads to rapid, clinically significant improvement in subjects with psoriasis,[20,6] it is anticipated that guselkumab treatment will result in higher proportions of patients achieving a nearly clear (PASI 90) or clear (PASI 100) response compared with treatment with secukinumab over 1 year of treatment.

A placebo arm was not included in this study for two main reasons. First, the primary endpoint is at Week 48 and it is not feasible to keep patients with moderate to severe psoriasis on placebo for that period of time. Second, given the historically low placebo rates observed in large Phase 3 moderate to severe psoriasis studies, and the proven efficacy of these two highly effective drugs, the value of the placebo arm for the purpose of demonstrating assay sensitivity is minimal. The efficacy of secukinumab was established (in individual studies vs placebo) using primary endpoints at Week 12.[6] However, it is known that neither agent reaches their maximal effect until after Week 12. In addition, psoriasis is a chronic disease that often requires chronic treatment, such that longer-term outcomes are clinically important. Therefore, endpoints at Weeks 12, 16, and 48 (with the primary endpoint of PASI 90 at Week 48) were selected to provide the most clinically meaningful evaluations of the relative performance of the 2 treatments. Ultimately, this study is designed to show superiority of efficacy of guselkumab after 1 year of treatment.

Biomarker and DNA Collection

Biomarker samples will be collected to evaluate the cellular and molecular mechanism of action of guselkumab and secukinumab, and to assess inter-individual variability in clinical outcomes to identify population subgroups that may respond differently to either drug. The goal of the biomarker analyses is to evaluate the PD effects of guselkumab and secukinumab, to further define the mechanism of action of blocking IL-23 compared to blocking IL-17A in psoriasis, and to aid in evaluating the drug's clinical response relationship. Serum biomarkers will be collected in all subjects to assess PD markers associated with the response to guselkumab and secukinumab.

Additionally, 3 optional substudies are planned: skin biopsy, [redacted] and genetic analysis. Skin biopsies will be collected in a subset of subjects at selected sites who consent to participate in the optional skin biopsy substudy to determine gene expression profiles and cellular content associated with response to guselkumab or secukinumab. Epigenetic evaluation may be conducted on skin samples obtained in the biopsy substudy. These exploratory analyses of psoriatic skin lesions may help to further define the cellular and molecular mechanism of action associated with blockade of IL-23 compared to blockade of IL-17A in psoriasis. [redacted]

It is recognized that genetic variation can be an important contributory factor to inter-individual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Genetic (DNA) analysis may help to explain inter-individual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the genetic (DNA) analysis is to collect a single DNA sample (from whole blood) to allow the identification of genetic factors, including single nucleotide

polymorphisms, that may influence the PD effects, efficacy, or tolerability of guselkumab and secukinumab, and to identify genetic factors associated with psoriasis. Epigenetic evaluation may be conducted on skin samples obtained in the biopsy substudy to assess potential epigenetic modifications associated with different immune cell infiltrates in psoriatic skin lesions. Only subjects who sign the consent form to participate in the genetic assessment will have whole blood DNA or skin samples collected.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within approximately 4 weeks before administration of the study drug.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

Subject population-related inclusion criteria

1. Be a man or a woman at least 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place).
2. Have a diagnosis of plaque-type psoriasis (with or without PsA) for at least 6 months before the first administration of study drug.
3. Have a PASI ≥12 at screening and at baseline.
4. Have an IGA ≥3 at screening and at baseline.
5. Have an involved BSA ≥10% at screening and at baseline.
6. Be a candidate for phototherapy or systemic treatment for psoriasis (either naïve or history of previous treatment).
7. Be considered, in the opinion of the investigator, suitable candidates for secukinumab (Cosentyx) therapy according to their country's approved secukinumab product labeling.

Reproduction-related inclusion criteria

8. Before the first administration of study drug, a woman must be either:

   - Not of childbearing potential: premenarchal; postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle-stimulating hormone level >40 IU/L); permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy.
   - Of childbearing potential and practicing a highly effective method of birth control, consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system; barrier methods: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal foam/gel/film/cream/suppository (if available in their locale); male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject).

   Note: If a female subject's childbearing potential changes after start of the study (eg, a woman who is not heterosexually active becomes active, a premenarchal woman experiences menarche), she must begin practicing a highly effective method of birth control, as described above.

9. A woman of childbearing potential must have a negative urine pregnancy test at screening and at Week 0 and agree to urine pregnancy testing before receiving injections.

10. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 16 weeks after receiving the last administration of secukinumab or at least 12 weeks after receiving the last administration of guselkumab.

11. A man who is sexually active with a woman of childbearing potential and who has not had a vasectomy must agree to use a barrier method of birth control (eg, either a condom [with spermicidal foam/gel/film/cream/suppository if available in their locale] or a partner with an occlusive cap [diaphragm or cervical/vault caps] plus spermicidal foam/gel/film/cream/suppository if available in their locale), during the study and for at least 16 weeks after receiving the last administration of secukinumab or at least 12 weeks after receiving the last administration of guselkumab. All men must also agree to not donate sperm during the study and for at least 16 weeks after receiving the last administration of secukinumab or at least 12 weeks after receiving the last administration of guselkumab.

Infectious disease-related inclusion criteria

12. Are considered eligible according to the following TB screening criteria:

- Have no history of latent or active TB before screening.
  - An exception is made for subjects who have a history of latent TB and
    - are currently receiving treatment for latent TB,
    - will initiate treatment for latent TB before the first administration of study drug,
    - or have documentation of having completed appropriate treatment for latent TB within 5 years before the first administration of study drug.
  - It is the *responsibility of the investigator* to verify the adequacy of previous anti-TB treatment and provide appropriate documentation.
- Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
- Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB before the first administration of study drug.
- Within 2 months before the first administration of study drug, have a negative QuantiFERON®-TB Gold test result, or have a newly identified positive QuantiFERON-TB Gold test result (Attachment 3) in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated before the first administration of study drug. Within 2 months before the first administration of study drug, a negative tuberculin skin test, or a newly identified positive tuberculin skin test in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated before the first administration of study drug, is additionally required if the QuantiFERON-TB Gold test is not approved/registered in that country or the tuberculin skin test is mandated by local health authorities.

  NOTE: The QuantiFERON-TB Gold test and the tuberculin skin test are not required at screening for subjects with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment as described above; subjects with documentation of having completed adequate treatment as described above are not required to initiate additional treatment for latent TB.
- Have a chest radiograph (posterior-anterior and lateral views, or per country regulations where applicable), taken within 3 months before the first administration of study drug and read by a qualified radiologist, with no evidence of current, active TB or old, inactive TB.

13. Agree not to receive a live virus or live bacterial vaccination during the study, or within 3 months after the last administration of study drug. For information on Bacille Calmette-Guérin (BCG) vaccination, see Inclusion Criterion 14.

14. Agree not to receive a BCG vaccination during the study, or within 12 months after the last administration of study drug.

Clinical laboratory-related inclusion criteria

15. Have screening laboratory test results within the following parameters, if one or more of the laboratory parameters is out of range, a single retest of laboratory values is permitted:

- Hemoglobin ≥10 g/dL (SI: ≥100 g/L)
- White blood cells ≥3.5 x 10^3/μL (SI: ≥3.5 GI/L)
- Neutrophils ≥1.5 x 10^3/μL (SI: ≥1.5 GI/L)
- Platelets ≥100 x 10^3/μL (SI: ≥100 GI/L)
- Serum creatinine ≤1.5 mg/dL (SI: ≤137 μmol/L)
- Aspartate aminotransferase ≤2 × upper limit of normal (ULN)
- Alanine aminotransferase ≤2 × ULN
- Alkaline phosphatase ≤2 × ULN

Other inclusion criteria

16. Agree to avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet light sources during study.

17. Be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

18. Must sign an informed consent form (ICF) [(or their legally acceptable representative must sign)] indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

19. Must sign a separate ICF if he or she agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample does not exclude a subject from participation in the study.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

Medical history-related exclusion criteria

1. Has a history or current signs or symptoms of severe, progressive, or uncontrolled renal, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances.

2. Has unstable cardiovascular disease, defined as a recent clinical deterioration (eg, unstable angina, rapid atrial fibrillation) in the last 3 months or a cardiac hospitalization within the last 3 months.

3. Has unstable suicidal ideation or suicidal behavior, that may be defined as an electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) rating at screening of: Suicidal ideation with intention to act ("4"), Suicidal ideation with specific plan and intent ("5"), or a suicide attempt (interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) in the last 6 months and is confirmed to be at risk by the investigator based on an evaluation by a mental health professional. The final decision on excluding a subject will be made at the judgment of the investigator.

4. Has a transplanted organ (with exception of a corneal transplant >3 months before the first administration of study drug).

5. Has a history of an infected joint prosthesis, or has received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.

6. Is pregnant, nursing, or planning a pregnancy (both men and women) while enrolled in this study and within 12 weeks following the last administration of study drug.

7. Has a nonplaque form of psoriasis (eg, erythrodermic, guttate, or pustular).

8. Has current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium).

9. Has had major surgery (eg, requiring general anesthesia and hospitalization) within 8 weeks before screening, or will not have fully recovered from such surgery, or has such surgery planned during the time the subject is expected to participate in the study (56 weeks).

   Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate.

10. Is known to have had a substance abuse (drug or alcohol) problem within the previous 12 months.

11. Had a known allergy or sensitivity to products containing latex.

Concomitant or previous medical therapies-related exclusion criteria

12. Has previously received guselkumab or secukinumab.

13. Has any contraindications to the use of secukinumab per local prescribing information.

14. Is not a suitable candidate for secukinumab therapy due to a history of inflammatory bowel disease.

15. Has received any anti-tumor necrosis factor α biologic therapy within 3 months before the first administration of study drug.

16. Has received any therapeutic agent directly targeted to IL-12, IL-17A, IL-17R, or IL-23 within 6 months of the first administration of study drug (including but not limited to ustekinumab, tildrakizumab [MK3222], risankizumab [BI-655066], ixekizumab [LY2439821], or brodalumab [AMG 827]) with the exception of secukinumab (which is completely excluded).

17. Has received natalizumab, belimumab, or agents that modulate B cells or T cells (eg, rituximab, alemtuzumab, abatacept, or visilizumab) within 12 months of the first administration of study drug.

18. Has received any systemic immunosuppressants (eg, methotrexate [MTX], azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, tacrolimus) or anakinra within 4 weeks of the first administration of study drug.

19. Has received phototherapy or any systemic medications/treatments that could affect psoriasis or IGA evaluations (including, but not limited to, oral or injectable corticosteroids, retinoids, 1,25-dihydroxy vitamin D3 and analogues, psoralens, sulfasalazine, hydroxyurea, apremilast, fumaric acid derivatives, herbal treatments, or traditional Taiwanese, Korean, or Chinese medicines) within 4 weeks of the first administration of study drug.

20. Has used topical medications/treatments that could affect psoriasis or IGA evaluations (including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, pimecrolimus, tacrolimus, or topical traditional Taiwanese, Korean, or Chinese medicines) within 2 weeks of the first administration of study drug.

21. Is currently receiving lithium, antimalarials, or intramuscular (IM) gold, or have received lithium, antimalarials, or IM gold within 4 weeks of the first administration of study drug.

22. Has received an experimental antibody or biologic therapy within the previous 6 months, or received any other experimental therapy or new investigational agent within 30 days or 5 half-lives (whichever is longer) of any study drug administration or is currently enrolled in another study using an investigational agent or procedure.

23. Has received, or is expected to receive, any live virus or bacterial vaccination within 3 months before the first administration of study drug. For BCG vaccine, see Exclusion Criterion 24.

24. Has had a BCG vaccination within 12 months of screening.

25. Has known intolerance or hypersensitivity to any biologic medication, or known allergies or clinically significant reactions to murine, chimeric, or human proteins, mAbs, or antibody fragments.

26. Subject has known allergies, hypersensitivity, or intolerance to guselkumab or its excipients (refer to Investigator's Brochure) or secukinumab or its excipients.

Infections or predisposition to infections

27. Has a history of chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection (eg, bronchiectasis), recurrent urinary tract infection (recurrent pyelonephritis or chronic nonremitting cystitis), fungal infection (mucocutaneous candidiasis), or open, draining, or infected skin wounds or ulcers.

28. Has a history of active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening. Refer to Inclusion Criterion 12 for information regarding eligibility with a history of latent TB.

29. Has a chest radiograph within 3 months before the first administration of study drug that shows an abnormality suggestive of a malignancy or current active infection, including TB.

30. Has had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystosis, aspergillosis). Subjects with a history of esophageal candidiasis or thrush would also be exceptions to this criterion.

31. Has persistently indeterminate (indeterminate on repeat sampling) QuantiFERON-TB Gold test results. Indeterminate results should be handled as described in Section 9.1.2.

32. Is infected with human immunodeficiency virus (HIV, positive serology for HIV antibody).

33. Tests positive for hepatitis B virus (HBV) infection (Attachment 5) or who are seropositive for antibodies to hepatitis C virus (HCV), unless they have 2 negative HCV RNA test results 6 months apart after completing antiviral treatment and prior to screening, and have a third negative HCV RNA test result at screening

34. Has or has had a serious infection (eg, sepsis, pneumonia or pyelonephritis), or has been hospitalized or received intravenous antibiotics for an infection during the 2 months before screening.

35. Has or has had herpes zoster within the 2 months before screening.

Malignancy or increased potential for malignancy

36. Currently has a known malignancy or has a history of malignancy within 5 years before screening (with the exception of a nonmelanoma skin cancer that has been adequately treated with no evidence of recurrence for at least 3 months before the first study drug administration or cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 3 months before the first study drug administration).

37. Has a history of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance; or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly.

Other exclusion criteria

38. Is unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.

39. Lives in an institution on court or authority order.

40. Has any condition that, in the opinion of the investigator, would make participation not be in the best interest (eg, compromise the well-being) of the subject or that could prevent, limit, or confound the protocol-specified assessments.

41. Is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If the subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 9.1.3, Screen Failure/Rescreening, describes options for retesting. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. A woman of childbearing potential who is heterosexually active must remain on a highly effective method of birth control (Inclusion Criterion 8) during the study and for at least 16 weeks after the last administration of secukinumab or at least 12 weeks after receiving the last administration of guselkumab.

2. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 16 weeks after the last administration of secukinumab or at least 12 weeks after receiving the last administration of guselkumab.

3. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control (ie, male condom, female diaphragm or cervical cap, or condom, Inclusion Criterion 11) during the study and for at least 16 weeks after the last administration of secukinumab or at least 12 weeks after receiving the last administration of guselkumab.

4. All men must agree to not donate sperm during the study and for at least 16 weeks after the last administration of secukinumab or at least 12 weeks after receiving the last administration of guselkumab.

5. Subjects must not receive a live virus or bacterial vaccination during the study and for 3 months after the last administration of any study drug. See Prohibition 6 for information regarding BCG vaccination.

6. Subjects must not receive a BCG vaccination during the study and for 12 months after the last administration of study drug.

7. Subjects must comply with restrictions on concomitant medications and therapies during the study (Section 8).

8. Subjects must avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet light sources during the study.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by study site. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (eg, treatment allocation, study drug preparation/accountability data [including unblinded personnel], and administration of study drug (see details in Section 6) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of DBL and unblinding.

Under normal circumstances, the blind should not be broken for subjects, investigators, or site monitors until the Week 56 database is locked and finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented by the IWRS, in the appropriate section of the electronic case report form (eCRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded should continue to return for scheduled evaluations. The decision to continue or discontinue study treatment for these subjects will be based upon consultation of the investigator with the medical monitor.

6. DOSAGE AND ADMINISTRATION

A 100 mg/mL solution of guselkumab in a single-use prefilled syringe (PFS) assembled with the UltraSafe PLUS™ Passive Needle Guard (PFS-U) device will be used. Subjects who are randomized to the guselkumab treatment arm will receive 2 injections: 1 injection of active guselkumab and 1 injection of placebo when guselkumab is scheduled to be administered (Weeks 0, 4, 12, 20, 28, 36, 44) or 2 injections of placebo when no guselkumab is scheduled to be administered (Weeks 1, 2, 3, 8, 16, 24, 32, and 40). The purpose of administering 2 injections is to mimic the 2 injections required for each secukinumab dose, and to thus maintain the blind. Commercially available secukinumab (Cosentyx) will be supplied as a single-use PFS and administered according to the manufacturer’s directions. Each 300 mg dose is given as 2 SC injections of 150 mg each. An appropriately qualified, unblinded member of the study staff will administer the drug and will have no other role in the conduct of the study.

All study drug injections will be administered at the investigational site. With the exception of the unblinded site personnel who dispense and/or administer the investigational product, all other site personnel and subjects will remain blinded to the treatment assignments until the last subject completes Week 56 evaluations and the database has been locked. Sites must ensure that they have the ability to physically blind and/or separate the blinded subject from the unblinded administrator. A physical barrier must be used such that the study drug can be administered by the unblinded site personnel, and the subject and other site personnel remain blinded.

7. TREATMENT COMPLIANCE

Because study drug will be administered at the investigational site for all randomized subjects, treatment compliance will be controlled by site personnel.

From Weeks 0 to 4 it is expected that all subjects will attend visits within a range of ± 3 days. After Week 4 and through Week 44, it is expected that all visits will occur within a range of ± 7 days. Any visits outside of these ranges should be discussed with the sponsor. If a study visit occurs outside the specified visit window, the subject should then resume his or her normal dose schedule relative to the baseline visit (Week 0) as soon as possible. All other follow-up study visits should occur within ± 14 days of the scheduled study visit. Any out-of-range visit should be documented in the subject's source notes.

Study-site personnel will maintain a log of all study drug administered. Drug supplies for each subject will be inventoried and accounted for. Information regarding study drug administrations that are administered outside of the scheduled windows or missed will be recorded. Subject charts and worksheets may be reviewed and compared with the data entries on the eCRFs to ensure accuracy. Although it is understood that treatment may be interrupted for many reasons, compliance with the treatment schedule is strongly encouraged.

8. CONCOMITANT THERAPY

Concomitant therapies must be recorded throughout the study from screening and continuing until 12 weeks after the last dose of study drug for randomized subjects. Concomitant therapies should also be recorded beyond Week 56 only in conjunction with SAEs that meet the criteria outlined in Section 12.3.2. Serious Adverse Events.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements) different from the study drug, as well as all shampoos used to treat psoriasis, moisturizers, or emollients, must be recorded in the eCRF. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

If a prohibited therapy is administered during the blinded active treatment phase (ie, Week 0 to Week 44 - unless agreed to by the medical monitor), the subject should be discontinued from study treatment. If a prohibited therapy is initiated during the safety follow-up period (Week 48 to Week 56), the subject should still complete his or her final study visit at Week 56, and the medication should be recorded as a concomitant medication.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

8.1.1. Concomitant Medications for Treatment of Psoriasis

8.1.1.1. Topical Therapy

Topical therapies that could affect psoriasis or the IGA evaluation (eg, corticosteroids, tar, anthralin, calcipotriene, tazarotene, methoxsalen, pimecrolimus, tacrolimus, and traditional

Taiwanese, Korean, or Chinese medicines) are not permitted at any time during the study. The only allowable concomitant treatments for psoriasis throughout the study are shampoos (containing tar or salicylic acid only) and topical moisturizers. Subjects should not use these topical agents (shampoos, moisturizers) on the day of a study visit. Nonmedicated shampoos may be used on the day of the study visit.

8.1.1.2. Phototherapy or Systemic Therapy for Psoriasis

The use of phototherapy or systemic antipsoriatic medications is not permitted at any time during the study. These medications include those targeted for reducing tumor necrosis factor α (including but not limited to infliximab, adalimumab, or etanercept), drugs targeted for reducing IL-12, IL-17A, IL-17R, or IL-23 (including but not limited to ustekinumab, tildrakizumab [MK3222], risankizumab [BI-655066], ixekizumab [LY2439821], or brodalumab [AMG827]), alpha-4 integrin antagonists (including but not limited to natalizumab), apremilast, steroids, any conventional systemic therapy that could affect psoriasis or the IGA evaluation (including but not limited to MTX, cyclosporine, acitretin), herbal treatments, or traditional Taiwanese, Korean, or Chinese medicines, and any other biological agent or other systemic medication that could affect psoriasis or the IGA evaluation.

8.1.2. Concomitant Medications for Conditions Other than Psoriasis

Every effort should be made to keep subjects on stable concomitant medications. If the medication is temporarily discontinued because of abnormal laboratory values, side effects, concurrent illness, or the performance of a procedure, the change and reason for it should be clearly documented in the subject's medical record.

The use of stable doses of nonsteroidal anti-inflammatory drugs is allowed. However, disease-modifying agents such as MTX, sulfasalazine, or IM gold are prohibited during the study. Lithium and antimalarial agents may not be used.

The use of corticosteroids for indications other than psoriasis should be limited to situations for which, in the opinion of the treating physician, there are no adequate alternatives. They should be used on a short-term basis, preferably for ≤2 weeks. Longer term use of corticosteroids should be discussed with the medical monitor or designee and may require discontinuation of study drug. Inhaled, otic, ocular, nasal or other routes of mucosal delivery of corticosteroids are allowed throughout the study.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, biomarker, and safety measurements applicable to this study.

Investigator-reported efficacy assessments (ie, IGA and PASI) should be completed before any study drug administrations, will be performed by an assessor trained by the sponsor, and captured electronically on a tablet device at the appropriate visits, as outlined in the Time and Events Schedule.

A urine pregnancy test will be performed to confirm the absence of pregnancy at every study drug administration visit. Additional urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

The total blood volume to be collected from each subject will be approximately 189.5 mL. In addition, repeat or unscheduled samples may be collected for safety reasons or for technical issues with the samples.

9.1.2. Screening Phase

All subjects will have a screening visit that will occur approximately 4 weeks before their Week 0 visit. The screening phase is designed to assess inclusion/exclusion criteria and establish baseline characteristics for a subject's psoriasis.

The recording of AEs and concomitant medications will start after the signing of the informed consent and will continue until the last study-related procedure has been completed. The eC-SSRS ('Baseline/Screening' version) should be completed after the subject signs consent but as the first assessment by the subject before any tests, procedures, or other consultations to prevent influencing subject perceptions.

Each subject will be asked to sign the consent form at the screening visit before any study-related procedures are conducted.

The recording of AEs and concomitant medications will start after the signing of the informed consent and will continue until the last study-related procedure has been completed.

As outlined in the eligibility criteria, all subjects must be questioned about a history of TB or other personal exposure to individuals with active TB. Potential subjects should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing. With the exception of subjects with a history of appropriately treated latent TB within 5 years before the first administration of study drug (Inclusion Criterion 12), subjects must undergo testing for TB (see Attachment 3 or Attachment 4) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The subject should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing. Investigators have the option to use both the QuantiFERON-TB Gold test and the tuberculin skin test to screen for latent TB if they believe, based on their judgment, that the use of both tests is clinically indicated in order to evaluate a subject who has high risk of having latent TB. If either the QuantiFERON-TB Gold test or the tuberculin skin test is positive, the subject is considered to have latent TB infection for the purposes of eligibility for this study.

Subjects with a negative QuantiFERON-TB Gold test result (and a negative tuberculin skin test result in countries in which the QuantiFERON-TB Gold test is not approved/registered or the tuberculin skin test is mandated by local health authorities) are eligible to continue with prerandomization procedures. Subjects with a newly identified positive QuantiFERON-TB Gold or tuberculin skin test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed, or the subject will be excluded from the study.

A subject whose first QuantiFERON-TB Gold test result is indeterminate should have the test repeated. In the event that the second QuantiFERON-TB Gold test result is also indeterminate, the subject should be excluded from the study.

Subjects will undergo screening for HBV (see Attachment 5) and antibodies to HCV and HIV.

9.1.3. Screen Failure/Rescreening

If, during the screening phase, the subject has not met all inclusion criteria or met any exclusion criteria, or is unable or unwilling to adhere to the prohibitions and restrictions of the study, the subject is considered to be a screen failure and is not eligible to be randomized at that time.

In general, if the subject is a screen failure, but at some timepoint in the future meets all the subject eligibility criteria, the subject may be rescreened after a new informed consent has been obtained. Subjects who are rescreened will be assigned a new subject number and will restart a new screening phase. Rescreening will be permitted once.

9.1.4. Double-Blind Treatment Phase

Week 0/Randomization

At Week 0, subjects who meet all inclusion criteria and do not demonstrate any exclusion criteria will be randomized.

Randomization visit procedures will be performed as specified on the Time and Events Schedule. The ‘Since Last Visit’ version of the eC-SSRS questionnaire should be completed by the subject first before any tests, procedures, or other consultations to prevent influencing subject perceptions (Section 9.6.1) and to confirm eligibility. After completion of required study procedures, subjects will be administered study drug according to their randomization assignment (guselkumab and placebo or secukinumab).

At Week 0, if a mental health evaluation is required based on the Week 0 eC-SSRS score, either this evaluation must be conducted prior to randomization or, if not feasible, the subject should be screen-failed and then re-screened after a completed mental health evaluation, if appropriate (see Section 9.6.1).

Week 1 through Week 44

All visit procedures will be performed as specified in the Time and Events Schedule. The 'Since Last Visit' version of the eC-SSRS should be completed by the subject first before any tests, procedures, or other consultations at postbaseline study visits to prevent influencing subject perceptions (Section 9.6.1) and to assess for potential discontinuation requirements. All other study procedures and evaluations should be completed before the subject is administered study drug.

9.1.5. Posttreatment Phase (Follow-Up)

Subjects will be followed for efficacy, safety, and biomarker information through Week 56 as shown in the Time and Events Schedule. The 'Since Last Visit' version of the eC-SSRS should be completed by the subject first before any tests, procedures, or other consultations at the follow-up visit to prevent influencing subject perceptions (Section 9.6.1). Subjects will be instructed that study drug will not be made available to them after they have completed/discontinued study drug and that they should return to their primary physician to determine subsequent treatment of their psoriasis.

9.2. Efficacy Evaluations

9.2.1. Evaluations

Efficacy evaluations chosen for this study are consistent with those utilized to evaluate other therapies for psoriasis. Efficacy evaluations include:

- IGA
- PASI

Efficacy assessments (IGA, PASI) will be performed at the site by an efficacy assessor trained by the sponsor and captured electronically in a tablet device at the appropriate visits as outlined by the Time and Events Schedule. The sponsor will provide IGA and PASI training. Documentation of this training will be maintained in the site's training files and by the sponsor.

9.2.1.1. Investigator's Global Assessment

The IGA documents the investigator's assessment of the subject's psoriasis at a given timepoint (Attachment 1). Overall lesions are graded for induration, erythema, and scaling. The patient's psoriasis is assessed as cleared (0), minimal (1), mild (2), moderate (3), or severe (4). A higher score indicates more severe disease.

9.2.1.2. Psoriasis Area and Severity Index

The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy (Attachment 2).[5] In the PASI system, the body is divided into 4 regions: the head, trunk, upper extremities, and lower extremities. Each of these areas is assessed separately for the percentage of the area involved, which translates to a numeric score that ranges from 0 (indicates no involvement) to 6 (90%-100% involvement), and for erythema, induration, and

scaling, which are each rated on a scale of 0 to 4. The PASI produces a numeric score that could range from 0 (no psoriasis) to 72. A higher score indicates more severe disease.

9.3. Pharmacokinetics and Immunogenicity

Serum samples will be analyzed to determine guselkumab concentrations and antibodies to guselkumab according to the Time and Events Schedule. Additionally, serum samples should be collected at the final visit from subjects who are withdrawn from the study.

Serum samples that test positive for antibodies to guselkumab will be further characterized to determine if antibodies to guselkumab could neutralize the biological effects of guselkumab in vitro (ie, neutralizing antibodies to guselkumab).

All sample analyses will be conducted by the sponsor or sponsor's designee.

9.4. Biomarkers

Biomarker sample collections will be conducted at the timepoints presented in the Time and Events Schedule to measure serum markers, gene expression and cellular profiles in skin biopsies, [redacted] and genetic associations with psoriasis or response to treatment (each explained in detail below). Data collected from these samples will be used for exploratory research that will include the following objectives:

1. To understand the molecular effects of guselkumab and secukinumab.
2. To understand psoriasis pathogenesis.
3. To understand why individuals differ in their responses to guselkumab or secukinumab.
4. [redacted]

Instructions for the collection and shipment of these samples can be found in the appropriate Laboratory Manual.

Serum Biomarkers

Serum samples will be collected from all subjects according to the Time and Events Schedule. These samples will be analyzed for the presence of serum biomarkers related to psoriasis, inflammation, and/or any observable PD relationship with either guselkumab or secukinumab response to treatment. Measurements will include but are not limited to serum IL-17A, IL-17F and IL-22 levels.

Skin Biopsy (RNA and Histology)

Skin biopsy samples will be collected according to the Time and Events Schedule from a subset of subjects who consent to participate in the biopsy substudy (target n = 45 per group, at predefined study sites capable of performing the skin biopsy procedure). Enrollment will be optional at selected predefined sites. Consenting subjects will undergo collection of skin biopsies which will be used for assessment of RNA expression, T cell receptor repertoire assessment, histology, epigenetic evaluation, and immunohistochemistry. Psoriasis pathogenesis involves the

dysregulation of IL-23- and IL-17A-mediated immune responses, and antagonism of either IL-23 or IL-17A has demonstrated clinical benefit in psoriasis.[1] The goal of the exploratory skin biopsy substudy is to further define the cellular and molecular mechanism of action of blocking IL-23 compared to blocking IL-17A in psoriasis. Skin samples will be processed to assess histologic changes pre-and post-treatment, including potential evaluation of specific immune cell subsets such as Th17 and regulatory T (Treg) cells. Skin samples will also be processed for RNA transcriptional profiling to determine gene expression profile changes associated with response to guselkumab or secukinumab. Evaluation may also be conducted on skin samples to assess epigenetic modifications associated with different immune cell infiltrates in psoriatic skin lesions.

9.5. Genetic (DNA) Analysis

Genetic (DNA) research may consist of the analysis of one or more candidate genes, single nucleotide polymorphisms, or analysis of the entire genome (as appropriate) in relation to guselkumab, secukinumab or psoriasis clinical endpoints. Whole blood samples of approximately 12 mL will be collected for genetic analyses at a single timepoint as specified in the Time and Events Schedule. Epigenetic evaluation may be conducted on skin samples obtained in the biopsy substudy to assess potential epigenetic modifications associated with different immune cell infiltrates in psoriatic skin lesions. Only subjects who sign the consent form to participate in the genetic (DNA) assessment will have whole blood DNA or skin samples collected.

9.6. Safety Evaluations

The safety and tolerability of study drugs (guselkumab, secukinumab, or placebo, where appropriate) will be monitored by collecting information on AEs, including injection site and allergic reactions, clinical laboratory tests, physical examinations, vital signs, eC-SSRS questionnaires, electrocardiograms (ECGs), concomitant medication review, and early detection of TB, as specified in the Time and Events Schedule. Serum and/or plasma samples collected for biomarker analyses may also be used to evaluate safety concerns that may arise during or after the study period.

Safety will be monitored through Week 56 or for 12 weeks after the last study drug administration for subjects who discontinue early. Any clinically relevant changes occurring during the study must be recorded on the AE section of the eCRF.

Clinically important abnormalities persisting at the end of the study/early withdrawal may be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the timepoints provided in the Time and Events Schedule:

Adverse Events

Adverse events will be reported by the subject for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at scheduled visits (refer to Time and Events Schedule) or by telephone contact approximately every 8 to 12 weeks. The following series of questions is suggested for use during the evaluation:

- "Have you had a new cough of >14 days' duration or a change in a chronic cough?"
- "Have you had any of the following symptoms:
  - Persistent fever?
  - Unintentional weight loss?
  - Night sweats?"
- "Have you had close contact with an individual with active TB?" (If there is uncertainty as to whether a contact should be considered "close," a physician specializing in TB should be consulted.)

If the evaluation raises suspicion that a subject may have TB reactivation or new TB infection, an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.

Investigators should be aware that TB reactivation in immunocompromised subjects may present as disseminated disease or with extrapulmonary features. Subjects with evidence of active TB should be referred for appropriate treatment.

Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON-TB Gold test, a repeat tuberculin skin test in countries in which the QuantiFERON-TB Gold test is not approved/registered or the tuberculin skin test is mandated by local health authorities, and, if possible, referral to a physician specializing in TB to determine the subject's risk of developing active TB and whether treatment for latent TB is warranted.

Study drug administration should be interrupted during the investigation. A positive QuantiFERON-TB Gold test or tuberculin skin test result should be considered detection of latent TB. If the QuantiFERON-TB Gold test result is indeterminate, the test should be repeated. Subjects who discontinue treatment for latent TB prematurely or who are noncompliant with therapy must immediately discontinue further administration of study drug and be encouraged to return for all subsequent scheduled study visits according to the Time and Events Schedule.

Allergic Reactions

The sponsor will proactively monitor reported AEs and query the site, if necessary, to capture anaphylactic reaction/serum sickness events in eCRFs.

Injection Site Reactions

An injection site reaction is any unfavorable or unintended sign that occurs at the study drug injection site. After administration of study drug at Week 0, all subjects will be carefully observed at the study site for at least 30 minutes after the SC injection of study drug for symptoms of an injection site reaction. If an injection site reaction is observed, the subject should be treated at the investigator's discretion. Any adverse reaction (eg, pain, erythema, and/or induration) should be noted on the AE page of the eCRF.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

All abnormal laboratory values will be evaluated for clinical significance by the investigator. If clinically significant abnormal laboratory values (in the opinion of the investigator) are detected, then the test(s) should be repeated until they return to normal or are otherwise explained by the Investigator.

Instructions for the collection, handling, and shipping of blood samples are provided in the Laboratory Manual.

The following tests will be performed by the central laboratory:

- Hematology Panel

  -hemoglobin
  -hematocrit
  -red blood cell count
  -white blood cell count
  -lymphocytes
  -monocytes
  -neutrophils
  -bands
  -eosinophils
  -basophils
  -platelets

- Serum Chemistry Panel

-sodium	-calcium
-potassium	-albumin
-chloride	-total protein
-alkaline phosphatase	-alanine aminotransferase
-urea	-total carbon dioxide
-creatinine	-total bilirubin
-glucose	- high-sensitivity C-reactive protein
-aspartate aminotransferase	-follicle-stimulating hormone[a]

[a]Testing required for selected subjects as defined in Inclusion Criterion 8.

- Lipid Panel[a]

-total cholesterol	-total cholesterol to high density lipoprotein cholesterol ratio
-low density lipoprotein cholesterol	-triglycerides
-high density lipoprotein cholesterol	

[a](Week 0 only; subjects must fast (ie, no food or beverages [except water]) for at least 8 hours before blood is drawn for lipid panel)

- Serology: HBV, including HBV serology and HBV DNA (when indicated, see Attachment 5), and antibodies to HCV and HIV.

Pregnancy Testing

Urine pregnancy testing is required for all women of childbearing potential at all study visits with study agent administration and at other visits as specified in the Time and Events Schedule. Pregnancy tests must be completed and negative at the study visit prior to administration of study drug. All pregnancy test results must be recorded in study source documents.

Physical Examination

Physical examinations will be performed by the investigator or designated physician, nurse practitioner or physician assistant as specified in the Time and Events Schedules. Any new, clinically significant finding (in the opinion of the investigator) must be captured as an AE. In addition, resolution of any abnormal findings during the study will be noted in the source document and in the eCRF.

Height and Weight

Height and weight will be measured as specified in the Time and Events Schedule. Subjects will be instructed to remove shoes and outdoor apparel and gear prior to these measurements.

Vital Signs

Blood pressure and heart rate measurements will be assessed at the timepoints specified in the Time and Events Schedule. If any clinically significant changes in vital signs are noted, they must be reported as AEs and followed to resolution, or until reaching a clinically stable endpoint.

Electrocardiogram

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same timepoint as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

9.6.1. Electronic Columbia-Suicide Severity Rating Scale

In light of the recent reports concerning suicidal ideation and behavior in patients with plaque psoriasis treated with an IL-17R antagonist (brodalumab),[3] the eC-SSRS will be used as a screening tool to prospectively evaluate the potential of guselkumab to induce suicidal ideation and behavior. The eC-SSRS defines 5 subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent, and is a fully-structured, subject self-report C-SSRS questionnaire, including standardized questions, follow-up prompts, error handling routines, and scoring conventions.[10,15] Two versions of the eC-SSRS will be used in this study, the 'Baseline/Screening' version and the 'Since Last Visit' version. The 'Baseline/Screening' version of the eC-SSRS will be conducted during the screening visit followed by the 'Since Last Visit' version of the eC-SSRS at Week 0, and all visits starting at Week 4 through Week 56.

Subjects will complete the eC-SSRS questionnaire using the sponsor-provided electronic tablets. Study site personnel will train the subjects on how to use the electronic device. The eC-SSRS will be provided in the local languages in accordance with local guidelines.

The eC-SSRS will be performed during each evaluation visit according to the assessment schedule. During a visit, subjects will be directed to a private, quiet place with the electronic device to complete the assessment. Subjects who do not have suicidal behavior or ideation will answer a limited number of questions and will usually complete the assessment in about 3 minutes. Subjects with significant suicidal ideation and behavior may require up to 10 minutes to answer all relevant questions. The eC-SSRS will be performed first at the screening visit (after signing informed consent) and before study agent administration. At all postbaseline visits, the eC-SSRS will be the first assessment/questionnaire that the subject must complete.

At the conclusion of each assessment, the site will receive an eC-SSRS Findings Report. At screening and Week 0, subjects with an eC-SSRS score greater than 0 or a response to the question of "Self-injurious behavior without suicidal intent" other than 'NO' must be determined to be not at risk by the investigator based on an evaluation by a mental health professional in order to be randomized. Subjects with a score on the eC-SSRS that is greater than 0 or a response to the question of "Self-injurious behavior without suicidal intent" other than 'NO' at any post-baseline visit will also be referred to an appropriate mental health professional for evaluation. If the subject's psychiatric disorder can be adequately treated with psychotherapy and/or pharmacotherapy then the subject, at the discretion of the investigator, should be continued with treatment. Ultimately, the determination of suicidality and risk is up to the investigator's clinical judgment following evaluation by a mental health professional (eg, psychiatrist, psychologist, or appropriately trained social worker or nurse).

Positive reports are generated from the eC-SSRS vendor for ANY of the following findings:

- Suicidal ideation with intention to act ("4")
- Suicidal ideation with specific plan and intent ("5")
- Made suicide attempt
- Interrupted suicide attempt
- Aborted suicide attempt
- Preparatory behaviors for making a suicide attempt.

Negative suicidality indication reports are generated from the eC-SSRS vendor when there are NO indications of the above.

The subject should not be released from the site until the eC-SSRS Findings Report (both for negative and positive reports) is reviewed by the investigator and the subject's risk has been assessed and follow-up determined, as appropriate.

For each score, the following actions and associated alerts will be generated, if applicable:

- Score of 0: No further action is needed.
- Score > 0: Subject risk assessed and referral to a mental health professional.
  - Score of 1, 2, or 3: Negative findings report will be generated.
  - Score of 4 or higher: Positive findings report will be generated. When the system reports that the subject has a positive suicidal indication (including for an incomplete assessment), the site will be immediately notified by fax/email and a telephone call from the eC-SSRS vendor.
- Self-injurious behavior without suicidal intent = YES or 'Question Mark (ambiguous response)': Subject risk assessed and referral to a mental health professional. Negative findings report will be generated.

Interruption or the discontinuation of study treatment should be considered for any subject who reports suicidal ideation with intention to act ("4"), suicidal ideation with specific plan and intent ("5"), or a suicide attempt (interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) on a post-baseline eC-SSRS assessment and who is deemed to be at risk by the investigator based upon evaluation by a mental health professional. Discussion of such subjects with the medical monitor or designee is required (See Section 10.2). The final decision on suitability for continuing in the study will be made by the investigator.

Any eC-SSRS finding, which in the opinion of the investigator is new or considered to be a worsening and clinically significant, should be reported on the AE eCRF (see Section 12).

9.7. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she has completed assessments at Week 56 of the double-blind phase. Subjects who prematurely discontinue study treatment for any reason before completion of the double-blind phase will not be considered to have completed the study.

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

Discontinuation of Study Treatment

A subject will not be automatically withdrawn from the study if he or she has to discontinue treatment before the end of the treatment regimen.

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- The subject is diagnosed with a malignancy, with the exception of no more than 2 localized basal cell skin cancers that are treated with no evidence of recurrence or residual disease.
- The subject is deemed ineligible according to the following TB screening criteria:
  - A diagnosis of active TB is made.
  - A subject has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination, or has had recent close contact with a person with active TB, and cannot or will not continue to undergo additional evaluation.

  - A subject undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON-TB Gold test result and/or an indeterminate QuantiFERON-TB Gold test result on repeat testing (refer to Section 9.6) (and/or a positive tuberculin skin test result in countries in which the QuantiFERON-TB Gold test is not approved/registered or the tuberculin skin test is mandated by local health authorities). Indeterminate QuantiFERON-TB Gold test results should be handled as described in Section 9.6.
  - A subject receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.

- The subject initiates a protocol-prohibited medication, eg, for a worsening of his or her psoriasis (unless agreed to by the medical monitor).
- The subject withdraws consent for administration of study drug.
- The subject is unable to adhere to the study visit schedule or comply with protocol requirements.
- The subject develops an allergic reaction such as bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension that occurs following a study drug administration.
- The subject has a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an injection of study drug. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.
- Discontinuation of study treatment should be considered for subjects who report suicidal ideation with intention to act ("4"), suicidal ideation with specific plan and intent ("5"), or a suicide attempt (interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) on a postbaseline eC SSRS assessment. Discussion of such subjects with the medical monitor or designee is required.
- Discontinuation of study treatment should be considered for subjects who develop a serious or opportunistic infection. Discussion of such subjects with the medical monitor or designee should also be considered.

Subjects who decide to discontinue study drug administration must be interviewed by the investigator to determine if a specific reason for discontinuing study drug can be identified. Subjects should be explicitly asked about the possible contribution of AEs to their decision to discontinue study drug; investigators should confirm that any AE information elicited has been documented. If the subject elects to discontinue study drug due to an AE, the event should be recorded as the reason for study drug discontinuation, even if the investigator's assessment is that the AE would not require study drug discontinuation. The reason for study drug discontinuation must be documented in the eCRF and in source documents. Study drug assigned to a subject who discontinues may not be assigned to another subject.

If the subject discontinues study treatment before his or her last scheduled injection, he or she should return for the remaining regularly scheduled study visits for at least 12 weeks after receiving the last administration of study drug. For subjects who complete their final study visit prior to Week 48, every effort should be made to conduct the Week 48 assessments as indicated in the Time and Events Schedule. For subjects who discontinue from the study prior to Week 48, serum is not to be collected for measurement of biomarkers.

Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

To ensure access for subject follow-up, study sites should try to obtain both primary and secondary telephone contact numbers from subjects (eg, home, work, and mobile phones), as well as other contact information such as email addresses, and emphasize the importance of follow-up information to the subject, before randomization. For subjects who withdraw from study participation, every effort should be made to conduct the Week 48 assessments, as indicated in the Time and Events Schedule.

If the subject fails to return for study visits (and thus is considered lost to follow-up), study site personnel must make all reasonable efforts to contact the subject to determine the subject's reason for discontinuation/withdrawal before considering the subject to be lost to follow-up. Such efforts should include repeated telephone calls, certified letters, email requests, etc. Measures taken to obtain follow-up information must be documented.

Withdrawal of consent should be a very unusual occurrence in a clinical trial; the investigator should make every effort to maintain good subject relationships to avoid withdrawals of consent. For subjects who truly request withdrawal of consent, it is recommended that the subject withdraw consent in writing; if the subject or the subject's representative refuses to do so or is physically unavailable, the study site should document the reason for the subject's failure to withdraw consent in writing, sign the documentation, and maintain it with the subject's source records. When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

10.3. Withdrawal From the Use of Research Samples

A subject who withdraws from the study will have the following options regarding the optional research samples:

- The collected samples will be retained and used in accordance with the subject's original separate informed consent for optional research samples.

- The subject may withdraw consent for optional research samples, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The subject may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

Descriptive statistics will include counts and proportions for categorical data, and median, mean, interquartile range, and range for continuous data. Graphical data displays may also be used to summarize the data.

In order to compare the proportion of subjects responding to the two treatments, the Cochran-Mantel-Haenszel chi-square test stratified by investigator site will be used. To test the non-inferiority of guselkumab to secukinumab, a 1-sided (α=0.025) Z-test with Mantel-Haenszel weights adjusted by investigator site will be used. A longitudinal modeling approach will also be used as a sensitivity analysis to compare the proportion of subjects responding to treatment. All statistical testing will be performed 2-sided at a significance level of 0.05 for superiority and 1-sided at a significance level of 0.025 for non-inferiority.

Subjects who discontinue study agent due to lack of efficacy or an AE of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could improve psoriasis are considered treatment failures. The baseline values will be assigned regardless of the observed data for continuous endpoints, zero will be assigned to improvement and percent improvement, and nonresponder status will be assigned to binary response variables. After applying the treatment failure rules, the remaining missing data will be assigned nonresponder status for binary variables. For the longitudinal analyses, treatment failure rules or missing data handling rules will not be applied.

11.1. Subject Information

Subjects will be included in the efficacy analyses according to their assigned treatment group regardless of whether or not they received the assignment treatment. For the primary efficacy analysis, data from all randomized and treated subjects will be analyzed. The treated population, which includes all randomized subjects who received at least 1 dose (complete or partial) of study medication, will also be used for PK, immunogenicity, and safety analyses by the actual treatment received.

Descriptive statistics by the randomized treatment group based on all randomized and treated subjects will be provided for subject dispositions, demographics, baseline disease characteristics, and prior and concomitant medications. Details will be provided in the SAP.

11.2. Sample Size Determination

This study is designed to evaluate the efficacy of guselkumab 100 mg vs secukinumab 300 mg. The assumptions for the sample size and power calculations were based on the data from the guselkumab CNTO1959PSO3001 and CNTO1959PSO3002 and the secukinumab Phase 3 studies (ERASURE and FIXTURE). The assumptions used are as follows:

- The proportion of subjects who achieve a PASI 90 response at Week 48 is 70% to 80% in subjects receiving guselkumab and 60% to 70% for subjects receiving secukimumab.
- The proportion of subjects who achieve a PASI 100 response at Week 48 is 44% to 51% in subjects receiving guselkumab and 35% to 40% for subjects receiving secukimumab.

Approximately 1,040 subjects are planned to be randomized in a 1:1 ratio to either guselkumab 100 mg (n=520) (administered at Weeks 0, 4, 12 and q8w thereafter until Week 44) or secukinumab 300 mg (n=520) (administered at Weeks 0, 1, 2, 3, and 4 and q4w thereafter until Week 44).

Based on the above assumptions, the planned sample size, and a noninferiority margin of 10%, the power to demonstrate the non-inferiority for the primary endpoint of PASI 90 at Week 48 and the major secondary endpoint of PASI 100 at Week 48 will be > 99%.

Table 1 provides the power for detecting a treatment difference (superiority of guselkumab over secukinumab) under varying assumptions at a significance level of 0.05 for the primary endpoint PASI 90 at Week 48 and the select major secondary endpoint of PASI 100 at Week 48 specified in Section 2.1.2.

Table 1: Power to Detect a Treatment Effect Based on Different Proportions of Subjects Achieving the Primary Endpoint PASI 90 at Week 48 and the Major Secondary Endpoint PASI 100 at Week 48

Secukinumab 300 mg (n=520)	Guselkumab 100 mg (n=520)	
	Primary Endpoint PASI 90 at Week 48	
60%	70%	92%
	75%	>99%
65%	75%	94%
	80%	>99%
70%	80%	96%
	Selected Major Secondary Endpoint PASI 100 at Week 48	
35%	44%	84%
	45%	91%
	46%	95%
40%	49%	83%
	50%	90%
	51%	95%

PASI = Psoriasis Area and Severity Index.

11.3. Efficacy Analyses

11.3.1. Analysis Data Set

For the primary analysis and major secondary analyses, all randomized and treated subjects will be included. For all the efficacy analyses, subjects will be analyzed according to the treatment group to which they are randomized, regardless of the treatment they actually receive.

11.3.2. Primary Analysis

The primary endpoint in this study is the proportion of subjects who achieve a PASI 90 response at Week 48. In the primary efficacy analysis, data from all randomized and treated subjects will be analyzed according to their assigned group.

To address the primary efficacy objective, the proportion of subjects achieving a PASI 90 response at Week 48 will be evaluated with a non-inferiority test followed by a superiority test. The following stepwise comparisons will be made to compare the efficacy of guselkumab to that of secukinumab at Week 48:

a. A non-inferiority margin of 10% was chosen based on a minimally clinically meaningful difference. This margin was also used as the non-inferiority margin for the ustekinumab psoriasis study C0743T12 and the guselkumab psoriasis CNTO1959PSO3001 and CNTO1959PSO3002 studies. To claim the non-inferiority of guselkumab over secukinumab, the lower bound of the 2-sided 95% confidence interval of P1 – P2 must be $\geq -10\%$, where P1 and P2 are the proportions of subjects achieving a PASI 90 response at Week 48 in the guselkumab and the secukinumab groups, respectively. If non-inferiority is not established, no further test will be conducted and Step b will be skipped.

b. If non-inferiority is established in Step a, the superiority test of guselkumab to secukinumab will be performed at 2-sided (α=0.05).

If both the non-inferiority test and the superiority test are positive, the major secondary hypotheses comparing the guselkumab group and the secukinumab group will be tested sequentially. Otherwise, all remaining p-values will be considered nominal.

11.3.3. Major Secondary Analyses

For the major secondary analysis, all non-inferiority tests will be performed 1-sided (α=0.025) with a non-inferiority margin of 10%. The major secondary analyses are:

- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving a PASI 75 response at both Week 12 and Week 48 will be performed. If non-inferiority is established, the superiority test on this endpoint will be performed.
- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving a PASI 90 response at Week 12 will be performed.
- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving a PASI 75 response at Week 12 will be performed.
- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving a PASI 100 response at Week 48 will be performed. If non-inferiority is established, the superiority test on this endpoint will be performed.
- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving an IGA score of cleared (0) at Week 48 will be performed. If non-inferiority is established, the superiority test on this endpoint will be performed.

11.3.3.1. Multiplicity Control

In order to control the overall Type 1 error rate, the primary analysis and major secondary analyses will be tested in a fixed sequence as ordered above. That is, the first major secondary analysis will be performed only if the primary endpoint is positive for both non-inferiority and superiority, and the subsequent analysis will be performed only if the preceding analysis in the sequence is positive.

11.3.4. Other Efficacy Analyses

In addition to the primary and major secondary analyses, the analyses for other efficacy endpoints will be performed.

- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving a PASI 90 response at both Week 16 and Week 48 will be performed. If non-inferiority is established, the superiority test on this endpoint will be performed.
- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving a PASI 75 response at Week 16 will be performed.
- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving a PASI 90 response at Week 16 will be performed.

- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving a PASI 90 response at all 7 visits from Week 24 through Week 48 will be performed. If non-inferiority is established, the superiority test on this endpoint will be performed.
- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving an IGA score of cleared (0) or minimal (1) at Week 16 will be performed.
- The non-inferiority test comparing guselkumab with secukinumab for the proportion of subjects achieving an IGA score of cleared (0) or minimal (1) at Week 12 will be performed.
- The proportions of subjects who achieve a PASI 75 response at Week 48 among PASI 75 responders at Week 12 will be summarized by treatment group.
- The proportions of subjects who achieve a PASI 90 response at Week 48 among PASI 90 responders at Week 16 will be summarized by treatment group.
- The proportions of subjects who achieve a PASI 50/75/90/100 response over time through Week 48 will be summarized by treatment group.
- The proportions of subjects who achieve an IGA score of cleared (0) response, IGA score of cleared (0) or minimal (1) response, and IGA of cleared (0), minimal (1), or mild (2) response over time through Week 48 will be summarized by treatment group.
- The percentages of improvement in PASI over time through Week 48 will be summarized by treatment group.

Furthermore, subgroup analyses will be performed to evaluate consistency of the primary endpoint and select major secondary endpoints over demographics (including baseline weight), baseline disease characteristics and prior medications. Additional efficacy analyses may be performed and will be documented in the SAP.

11.4. Criteria for Endpoints

PASI 50 Responders: Subjects with ≥50% improvement in PASI from baseline.

PASI 75 Responders: Subjects with ≥75% improvement in PASI from baseline.

PASI 90 Responders: Subjects with ≥90% improvement in PASI from baseline.

PASI 100 Responders: Subjects with 100% improvement in PASI from baseline.

11.5. Pharmacokinetic Analyses

Serum guselkumab concentrations over time will be summarized for the guselkumab group. Descriptive statistics, including arithmetic mean, SD, median, interquartile range, minimum, and maximum will be calculated at each sampling timepoint. All concentrations below the lowest quantifiable sample concentration of the assay (BQL) or missing data will be labeled as such in the concentration data listing or statistical analysis system (SAS) dataset. The BQL concentrations will be treated as zero in the summary statistics.

11.6. Immunogenicity Analyses

The incidence and titers of antibodies to guselkumab will be summarized for all subjects who receive at least 1 dose of guselkumab and have appropriate samples for detection of antibodies to guselkumab (ie, subjects with at least 1 sample obtained after their first dose of guselkumab). A listing of subjects who are positive for antibodies to guselkumab will be provided in the clinical study report.

The incidence of neutralizing antibodies (NAbs) to guselkumab will be summarized for subjects who are positive for antibodies to guselkumab and have samples evaluable for NAbs.

11.7. Biomarker Analyses

Biomarker samples outlined in Section 9.4 will be used to assess serum markers, skin gene expression and cellular profiles, [redacted] and genetic (DNA) data for biomarker analyses. Biomarker analyses will address the following objectives:

1. To understand the molecular effects of guselkumab and secukinumab.
2. To understand psoriasis.
3. To understand why people may respond differently to guselkumab and secukinumab.
4. [redacted]

These analyses are considered exploratory and will be summarized in a separate technical report.

Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information.

Changes in serum/RNA or other biomarkers over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in select biomarkers and clinical response will be explored. RNA analyses will be summarized in separate technical reports.

Results will be presented in a separate report.

11.8. Safety Analyses

Safety data, including but not limited to, AEs, SAEs, infections, serious infections, changes in laboratory assessments, changes in vital signs, changes in electrocardiograms (ECGs), and suicidal ideation and behavior based on eC-SSRS will be summarized. Treatment-emergent AEs will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms.

Safety Definitions

Injection Site Reactions

An injection site reaction is any unfavorable or unintended sign that occurs at an injection site and will be recorded as an AE. Detailed instructions for the evaluation of injection site reactions are in the Trial Center File.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using MedDRA. All reported AEs with onset during the treatment phase (ie, treatment-emergent AEs, and AEs that have worsened since baseline) will be included in the analysis.

Summaries, listings, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe AE or an SAE.

The following analyses will be used to assess the safety of subjects in the study:

- The incidence and type of AEs.
- The incidence and type of SAEs.
- The incidence and type of infections.
- The incidence and type of reasonably related AEs.
- The incidence and type of injection site reactions.
- The laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry).

In addition, National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grades will be used in the summary of laboratory data. A listing of subjects with post-baseline abnormal laboratory results based on NCI-CTCAE grades will also be provided.

Vital Signs

Descriptive statistics of heart rate and blood pressure (systolic and diastolic) values and changes from baseline will be summarized by treatment group.

Electrocardiogram

Electrocardiogram data will be collected at baseline and Weeks 16 and 48. Electrocardiogram data at each visit and change from baseline will be summarized by ECG parameters and by treatment group.

Electronic Columbia-Suicide Severity Rating Scale

Suicide-related thoughts and behaviors based on the eC-SSRS will be summarized descriptively by treatment group.

Anticipated Events

An anticipated event is an AE (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen. For the purposes of this study the event of psoriasis will be considered an anticipated event. Serious adverse events relating to lack of efficacy (eg, events attributed to "psoriasis") or progression of the disease under study will not be individually unblinded for expedited reporting. These anticipated events will be recorded and reported as outlined in Attachment 6.

11.9. Interim Analysis

No formal interim analysis is planned for this study.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last AE recording).

Serious Adverse Event

An SAE, based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use, is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also 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 intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For guselkumab, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure. For secukinumab the expectedness of an AE will be determined by whether or not it is listed in the package insert/summary of product characteristics.

Adverse Event Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An AE that is not related to the use of the drug.

Doubtful

An AE for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An AE that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 12 weeks after the last dose of study drug, must be reported using the SAE Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 6.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual SAEs the sponsor will make a determination of relatedness in addition to and independent of the investigator’s assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the investigational institute where required). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

Serious adverse events relating to lack of efficacy (eg, events attributed to “psoriasis”) or progression of the disease under study will not be individually unblinded for expedited reporting. These anticipated events will be recorded and reported as described in Attachment 6. All SAEs and nonserious AEs that represent any of the following diagnoses or any symptoms associated with the following diagnoses (eg, chest pain, dizziness) must be reported to the sponsor and will require efforts to obtain additional medical records:

- Myocardial infarction.
- Stroke.
- Cardiovascular death.
- Unstable angina.
- Coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery).
- Transient ischemic attack.
- Venous and peripheral arterial vascular thrombotic events (ie, deep vein thrombosis and pulmonary embolism).
- Congestive heart failure.
- Cardiac arrhythmia.
- Syncope of a cardiovascular origin.
- Severe/accelerated hypertension leading to hospitalization.

If the event is an SAE, the procedures outlined in Section 12.3.2, Serious Adverse Events, should be followed. If the event is a nonserious AE, procedures outlined in the Trial Center File for nonserious AEs (as described above) should be followed.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the SAE Form, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the subject's source documentation). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience, the investigator may choose to hospitalize the subject for the duration of the treatment period.

The cause of death of a subject in a study within 12 weeks, whether or not the event is expected or associated with the study drug, is considered an SAE.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the SAE Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.3.4. Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first administration of study agent(s) in subjects participating in this clinical study must be reported by the investigator according to the procedures in Section 9.6. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

14.1.1. Guselkumab

The guselkumab supplied for this study is a sterile liquid for SC injection in a single-use PFS assembled with the PFS-U. Each single-use PFS-U contains 100 mg (1 mL fill of liquid)

guselkumab in a 1 mL glass syringe with a 27 gauge, ½-inch fixed needle and a latex-free rigid needle shield. No preservatives are present. The guselkumab solution should be essentially free of visible particulate matter. Guselkumab will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

Placebo is supplied as a sterile liquid for SC injection at a fill volume of 1.0 mL in a single-use PFS assembled with the PFS-U. Each PFS-U contains 10 mM L-histidine, 8.5% (w/v) sucrose, and 0.055% (w/v) polysorbate 80 at pH 5.8.

14.1.2. Cosentyx (Secukinumab)

Commercial secukinumab (Cosentyx) will be supplied as an active comparator to the study sites. Details on secukinumab are available in the secukinumab (Cosentyx) package insert, and details regarding the secukinumab drug product for individual countries are available in the Site Investigational Product Procedures Manual.

14.2. Packaging

The investigational supplies will be uniquely packaged to assure that they are appropriately managed throughout the supply chain process.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

14.4.1. Guselkumab

Guselkumab and placebo for guselkumab will be supplied to the study sites. All guselkumab and placebo for guselkumab must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C) and protected from exposure to light. The sterile product does not contain preservatives and is designed for single use only. Protection from light is not required during dose preparation or administration of guselkumab.

Further details regarding the preparation and storage of guselkumab and placebo will be provided in the Site Investigational Product Procedures Manual.

14.4.2. Cosentyx (Secukinumab)

Cosentyx will be supplied to the sites. All Cosentyx must be stored in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF). Keep the product in the original carton to protect from light until the time of use. Do not freeze. To avoid foaming do not shake. The sterile product does not contain preservatives and is designed for single use only. Before injection, remove Cosentyx prefilled syringe from the refrigerator and allow Cosentyx to reach room temperature (15 to 30 minutes) without removing the needle cap.

The removable cap of the Cosentyx PFS contains natural rubber latex and should not be handled by latex-sensitive individuals.

Visually inspect Cosentyx for particulate matter and discoloration prior to administration. Cosentyx injection is a clear to slightly opalescent, colorless to slightly yellow solution. Do not use if the liquid contains visible particles, is discolored or cloudy. Cosentyx does not contain preservatives; therefore, administer the PFS within 1 hour after removal from the refrigerator. Discard any unused product remaining in the PFS.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the subject must be documented on the drug accountability form. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure for guselkumab.
- Package Insert/Summary of Product Characteristics for secukinumab.
- Site Investigational Product Procedures Manual.
- Laboratory Manual.
- IWRS Manual.
- Electronic Data Capture (eDC) Manual.
- Electronic Device and User Manual.
- Electronic Columbia-Suicide Severity Rating Scale.

- Sample ICF.
- Sample genetic research for ICF, as applicable.
- ECG Manual.
- Recruitment materials, as needed.
- Biopsy Manual (for biopsy substudy sites only).

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross (1 pint/473 mL of blood for donation).

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials

- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed. The physician may also recontact the subject for the purpose of obtaining consent to collect information about his or her survival status.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

Subjects will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the subject will be asked to sign and personally date a separate ICF indicating agreement to participate in the

optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the subject.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA and biomarker research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand guselkumab and co-medications in the protocol, if applicable, to understand plaque-type psoriasis, to understand differential drug responders, and to develop tests/assays related to guselkumab and co-medications in the protocol, if applicable and plaque-type psoriasis. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal From the Use of Samples in Future Research).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations. Only countries where secukinumab is approved for use in psoriasis will be involved in this study.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific

protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.

- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or equivalent document).

Investigator-completed efficacy evaluations (IGA, PASI) and the subject-completed eC-SSRS will be recorded directly into an electronic tablet device during the visit at the study site. These data will be considered electronic source documentation.

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory and direct transmission of efficacy and eC-SSRS data into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an

agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). At these visits, the monitor will compare data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last scheduled study assessment shown in the Time and Events Schedule for the last subject participating in the study. The final data from the study

site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding guselkumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including genetic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of guselkumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report (CSR) generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of genetic or exploratory biomarker analyses performed after the CSR has been issued will be reported in a separate report and will not require a revision of the CSR. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: Investigator's Global Assessment

Induration (I) (averaged over all lesions; use the National Psoriasis Foundation Reference card for measurement)
0 = no evidence of plaque elevation
1 = minimal plaque elevation, = 0.25 mm
2 = mild plaque elevation, = 0.5 mm
3 = moderate plaque elevation, = 0.75 mm
4 = severe plaque elevation, > 1 mm

Erythema (E) (averaged over all lesions)
0 = no evidence of erythema, hyperpigmentation may be present
1 = faint erythema
2 = light red coloration
3 = moderate red coloration
4 = bright red coloration

Scaling (S) (averaged over all lesions)
0 = no evidence of scaling
1 = minimal; occasional fine scale over less than 5% of the lesion
2 = mild; fine scale dominates
3 = moderate; coarse scale predominates
4 = severe; thick, scale predominates

Total Average = (I + E + S) / 3

Investigator's Global Assessment based upon above Total Average
0 = Cleared, except for residual discoloration
1 = Minimal - majority of lesions have individual scores for I + E + S / 3 that averages 1
2 = Mild - majority of lesions have individual scores for I + E + S / 3 that averages 2
3 = Moderate - majority of lesions have individual scores for I + E + S / 3 that averages 3
4 = Severe - majority of lesions have individual scores for I + E + S / 3 that averages 4
Note: Scores should be rounded to the nearest whole number. If total ≤ 1.49, score = 1; if total ≥ 1.50, score = 2.

Attachment 2: Psoriasis Area and Severity Index

The Psoriasis Area and Severity Index (PASI) is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score that can range from 0 to 72. The severity of the disease is calculated as follows.

In the PASI system, the body is divided into 4 regions: the head, trunk, upper extremities, and lower extremities, which account for 10%, 30%, 20%, and 40% of the total BSA, respectively. Each of these areas is assessed separately for erythema, induration and scaling, which are each rated on a scale of 0 to 4.

The scoring system for the signs of the disease (erythema, induration, and scaling) are: 0 = none, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.

The scale for estimating the area of involvement for psoriatic lesions is outlined below.

0 = no involvement
1 = 1% to 9% involvement
2 = 10% to 29% involvement
3 = 30% to 49% involvement
4 = 50% to 69% involvement
5 = 70% to 89% involvement
6 = 90% to 100% involvement

To help with the area assessments, the following conventions should be noted:

a. The neck is considered part of the head
b. The axillae and groin are part of the trunk
c. The buttocks are part of the lower extremities

The PASI formula is:

$$PASI = 0.1 (Eh + Ih + Sh) Ah + 0.3 (Et + It + St) At + 0.2 (Eu + Iu + Su) Au + 0.4 (El + Il + Sl) Al$$

Where E = erythema, I = induration, S = scaling, A = area,

h = head, t = trunk, u = upper extremities, and l = lower extremities

Attachment 3: QuantiFERON®-TB Gold Testing

The QuantiFERON®-TB Gold test is one of the interferon-γ (IFN-γ) based blood assays for TB screening (Cellestis, 2009). It utilizes the recently identified *M. tuberculosis*-specific antigens ESAT-6 and CFP-10 in the standard format, as well as TB7.7 (p4) in the In-Tube format, to detect in vitro cell-mediated immune responses in infected individuals. The QuantiFERON®-TB Gold assay measures the amount of IFN-γ produced by sensitized T-cells when stimulated with the synthetic *M. tuberculosis*-specific antigens. In *M. tuberculosis*-infected persons, sensitized T lymphocytes will secrete IFN-γ in response to stimulation with the *M. tuberculosis*-specific antigens and, thus, the QuantiFERON®-TB Gold test should be positive. Because the antigens used in the test are specific to *M. tuberculosis* and not found in BCG, the test is not confounded by BCG vaccination, unlike the tuberculin skin test. However, there is some cross-reactivity with the 3 Mycobacterium species, *M. kansasii*, *M. marinum*, and *M. szulgai*. Thus, a positive test could be the result of infection with one of these 3 species of Mycobacterium, in the absence of *M. tuberculosis* infection.

In a study of the QuantiFERON®-TB Gold test (standard format) in subjects with active TB, sensitivity has been shown to be approximately 89% (Mori et al, 2004). Specificity of the test in healthy BCG-vaccinated individuals has been demonstrated to be more than 98%. In contrast, the sensitivity and specificity of the tuberculin skin test was noted to be only about 66% and 35% in a study of Japanese patients with active TB and healthy BCG-vaccinated young adults, respectively. However, sensitivity and specificity of the tuberculin skin test depend on the population being studied, and the tuberculin skin test performs best in healthy young adults who have not been BCG-vaccinated.

Data from a limited number of published studies examining the performance of the QuantiFERON®-TB Gold assay in immunosuppressed populations suggest that the sensitivity of the QuantiFERON®-TB Gold test is better than the tuberculin skin test even in immunosuppressed patients (Ferrara et al, 2005; Kobashi et al, 2007; Matulis et al, 2008). The ability of IFN-γ-based tests to detect latent infection has been more difficult to study due to the lack of a gold standard diagnostic test; however, several TB outbreak studies have demonstrated that the tests correlated better than the tuberculin skin test with the degree of exposure that contacts had to the index TB case (Brock et al, 2004; Ewer et al, 2003). In addition, TB contact tracing studies have shown that patients who had a positive QuantiFERON®-TB Gold test result and were not treated for latent TB infection were much more likely to develop active TB during longitudinal follow-up than those who had a positive tuberculin skin test and a negative QuantiFERON®-TB Gold test result (Higuchi et al, 2007; Diel et al, 2008).

Although the performance of the new IFN-γ-based blood tests for active or latent *M. tuberculosis* infection have not been well validated in the immunosuppressed population, experts believe these new tests will be at least as, if not more, sensitive, and definitely more specific, than the tuberculin skin test (Barnes, 2004; personal communication, April, 2008 TB Advisory Board).

Performing the QuantiFERON®-TB Gold Test

The QuantiFERON®-TB Gold test In-Tube format will be provided for this study. The In-Tube format contains 1 additional *M. tuberculosis*-specific antigen, TB7.7 (p4), which is thought to increase the specificity of the test.

To perform the test using the In-Tube format, blood is drawn through standard venipuncture into supplied tubes that already contain the *M. tuberculosis*-specific antigens. Approximately 3 tubes will be needed per subject, each requiring 1 mL of blood. One tube contains the *M. tuberculosis*-specific antigens, while the remaining tubes contain positive and negative control reagents. Thorough mixing of the blood with the antigens is necessary prior to incubation. The blood is then incubated for 16 to 24 hours at 37°C, after which tubes are centrifuged for approximately 15 minutes at 2000 to 3000 g. Following centrifugation, plasma is harvested from each tube, frozen, and shipped on dry ice to the laboratory. The laboratory will perform an ELISA to quantify the amount of IFN-γ present in the plasma using spectrophotometry and computer software analysis.

The laboratory will analyze and report results for each subject, and sites will be informed of the results. Subjects who have an indeterminate result should have the test repeated.

Adherence to Local Guidelines

Local country guidelines **for immunocompromised patients** should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

In countries in which the QuantiFERON®-TB Gold test is not considered approved/registered, a tuberculin skin test is additionally required.

References

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Attachment 4: Tuberculin Skin Testing

Administering the Mantoux Tuberculin Skin Test

The Mantoux tuberculin skin test (CDC, 2000) is the standard method of identifying persons infected with *Mycobacterium tuberculosis*. Multiple puncture tests (Tine and Heaf) should not be used to determine whether a person is infected because the amount of tuberculin injected intradermally cannot be precisely controlled. Tuberculin skin testing is both safe and reliable throughout the course of pregnancy. The Mantoux tuberculin test is performed by placing an intradermal injection of 0.1 mL of tuberculin into the inner surface of the forearm. The test must be performed with tuberculin that has at least the same strength as either 5 tuberculin units (TU) of standard purified protein derivative (PPD)-S or 2 TU of PPD-RT 23, Statens Seruminstitut, as recommended by the World Health Organization. PPD strengths of 1 TU or 250 TU are not acceptable (Menzies, 2000). Using a disposable tuberculin syringe with the needle bevel facing upward, the injection should be made just beneath the surface of the skin. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable needles and syringes should be placed in puncture-resistant containers for disposal. Institutional guidelines regarding universal precautions for infection control (eg, the use of gloves) should be followed. A trained health care worker, preferably the investigator, should read the reaction to the Mantoux test 48 to 72 hours after the injection. Subjects should never be allowed to read their own tuberculin skin test results. If a subject fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a subject who fails to return within 72 hours has a negative test, tuberculin testing should be repeated. The area of induration (palpable raised hardened area) around the site of injection is the reaction to tuberculin. For standardization, the diameter of the induration should be measured transversely (perpendicular) to the long axis of the forearm. Erythema (redness) should not be measured. All reactions should be recorded in millimeters, even those classified as negative.

Interpreting the Tuberculin Skin Test Results

In the US and many other countries, the most conservative definition of positivity for the tuberculin skin test is reserved for immunocompromised patients, and this definition is to be applied in this study to maximize the likelihood of detecting latent TB, even though the subjects may not be immunocompromised at baseline.

In the US and Canada, an induration of 5 mm or greater in response to the intradermal tuberculin skin test is considered to be a positive result and evidence for either latent or active TB.

In countries outside the US and Canada, country-specific guidelines **for immunocompromised patients** should be consulted for the interpretation of tuberculin skin test results. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

Treatment of Latent Tuberculosis

Local country guidelines **for immunocompromised patients** should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

References

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Attachment 5: Hepatitis B Virus (HBV) Screening With HBV DNA Testing

Subjects must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

- Subjects who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this study.
- Subjects who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this study.
- Subjects who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this study.
- Subjects who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this study, regardless of the results of other hepatitis B tests.
- Subjects who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of hepatitis B virus deoxyribonucleic acid (HBV DNA test). If the HBV DNA test is **positive**, the subject ***is NOT eligible*** for this study. If the HBV DNA test is **negative**, the subject ***is eligible*** for this study. In the event the HBV DNA test cannot be performed, the subject ***is NOT eligible*** for this study.

For subjects who **are not eligible for this study due to HBV test results**, consultation with a physician with expertise in the treatment of hepatitis B virus infection is recommended.

Eligibility based on hepatitis B virus test results			
	Hepatitis B test result		
Action	**Hepatitis B surface antigen (HBsAg)**	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**
Include	—	—	—
	—	+	—
	—	+	+
Exclude	+	— *or* +	— *or* +
Require testing for presence HBV DNA*	—	—	+
* If HBV DNA is detectable, exclude from the clinical study. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, exclude from the clinical study.			

Attachment 6: Anticipated Events

Anticipated Event

An anticipated event is an AE (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the event of psoriasis will be considered anticipated event.

Reporting of Anticipated Events

All AEs will be recorded in the eCRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any anticipated event that meets SAE criteria will be reported to the sponsor as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

INVESTIGATOR AGREEMENT

CNTO 1959 (guselkumab) Clinical Protocol CNTO1959PSO3009 Amendment 1

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Philippe Szapary, MD, MSCE

Institution: Janssen Research & Development

Signature: [redacted] Date: 05-OCT-2017

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Approved, Date: 5 October 2017