Janssen Research & Development *

Statistical Analysis Plan

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

Protocol CNTO1959PSO3009; Phase 3
AMENDMENT 1

CNTO 1959 (Guselkumab)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

AMENDMENT HISTORY

Summary of the Amendment 1

This statistical analysis plan (SAP) was amended to implement the following modifications to the original SAP:

1. To remove the database lock (DBL) at Week 48 and the associated analyses specifically related to Week 48 DBL since the protocol was amended to remove the Week 48 DBL.

2. To clarify the per-protocol analysis set in terms of the definition of subjects who violated the specified exposure to study agent
3. To modify the sensitivity analysis based on multiple imputation (MI) by first imputing intermittent missing data and then using regression method to impute the remaining missing data. In addition, to spell out details about the MI including number of imputations and seeds.

4. To add sensitivity analyses for all the major secondary endpoints.

5. To add the detailed investigator site pooling strategy given the enrollment has completed.

Additionally, minor grammatical, formatting, or spelling changes were made.

ABBREVIATIONS

AE	adverse event
CI	confidence interval
CRF	case report form
CSR	Clinical Study Report
DBL	Database lock
DC	Discontinuation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic case report form
eC-SSRS	Electronic Columbia-Suicide Severity Rating Scale
FDA	Food and Drug Administration
IgG1λ	immunoglobulin G1 lambda
IGA	Investigator's Global Assessment
IWRS	interactive web response system
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NAbs	neutralizing antibodies
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PASI	Psoriasis Area and Severity Index
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the analysis of efficacy, safety and pharmacokinetics for the guselkumab (CNTO 1959) clinical study CNTO1959PSO3009. Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that inhibits the biological activity of IL-23 and therefore has the potential for the treatment of psoriasis.

1.1. Trial Objectives

Primary Objectives

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 evaluate:

- 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.

1.2. Trial 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.

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.

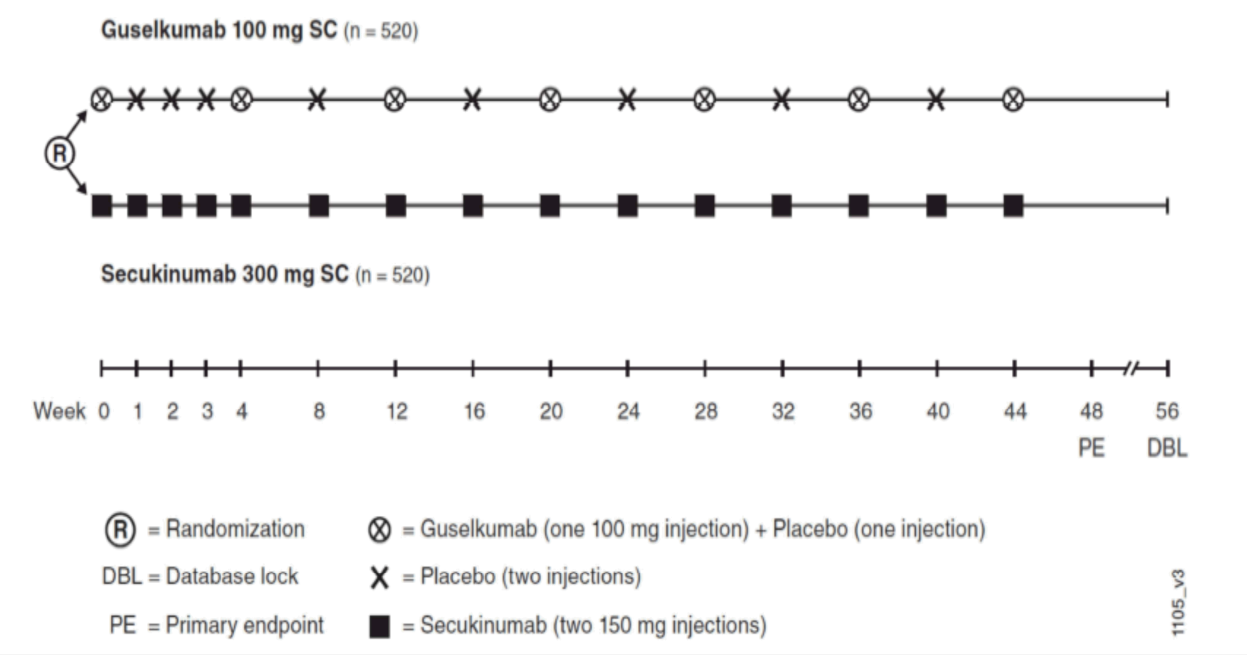
After Week 44 through Week 56 (Follow-up Period)

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

There is one database locks (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 diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



1.3. Statistical Hypotheses for Trial Objectives

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.

Primary Hypothesis:

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 noninferiority 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.

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 noninferiority 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.
- Non-inferiority test to secukinumab at Week 48 as assessed by the proportion of subjects who achieve an IGA score of cleared (0) or minimal (1) 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) or minimal (1) at Week 48.

1.4. Sample Size Justification

This study is designed to evaluate the efficacy of guselkumab 100 mg vs secukinumab 300 mg. The power and sample size were evaluated for the primary endpoint of PASI 90 at Week 48. In addition, since the response rate for guselkumab for PASI 100 at Week 48 is around 50% where the variability is the highest, the power and sample size were also evaluated for this major secondary endpoint. 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).[1] 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 secukinumab.
- 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 secukinumab.

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 major secondary endpoint of PASI 100 at Week 48.

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

	Primary Endpoint PASI 90 at Week 48	
Secukinumab 300 mg (n=520)	Guselkumab 100 mg (n=520)	
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.

1.5. Randomization and Blinding

1.5.1. Procedures for Randomization and Stratification

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 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.

1.5.2. 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 of the protocol) 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.

2. GENERAL ANALYSIS DEFINITIONS

This analysis plan provides the general analysis definitions and describes the planned subject information, efficacy, safety, pharmacokinetics, and antibody analyses for the two planned DBLs.

2.1. Imputation Rules for Partial or Missing AE Dates

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the study agent start

  - The day of study agent start, if the month/year of the onset of AE is the same as month/year of the study agent start date and month/year of the AE resolution date is different
  - The day of study agent start or day of AE resolution date, whichever is the earliest, if month/year of the onset of AE and month/year of the study agent start date and month/year of the AE resolution date are same

- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the study agent start date
  - Month and day of the study agent start date, if this date is in the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the study agent start date,
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the date of death, if the death occurred in that month.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.

Completely missing resolution dates will not be imputed.

2.2. Visit Windows

Nominal visits will be used for all by-visit analyses in the study unless otherwise specified, regardless of the scheduled visit window. The study visits scheduled should occur at the times delineated in the Time and Events Schedule of the protocol. 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.

2.3. Pooling Algorithm for Analysis Centers

For efficacy analyses, investigator sites may be pooled as a stratification factor if there are sites with less than 10 subjects randomized. Sites with small number of subjects randomized will be pooled with the sites with larger number of randomized subjects by similar region/location when appropriate, so the number of subjects within the aggregated sites is at least 10. Note that site size and geography were considered when aggregating site sizes. Specific pooling strategy can be found in Attachment 1.

2.4. Analysis Sets

2.4.1. Efficacy Analysis Set

2.4.1.1. Full Analysis Set

For the efficacy analyses in this study, the full analysis set (FAS) will be used according to subjects' assigned treatment to which they were randomized, regardless of the treatment they actually received. The FAS includes all randomized subjects. The full analysis set will be used for all primary and secondary efficacy analyses. In addition, for endpoints that include a non-inferiority test, analyses will also be performed using the per protocol analysis set as defined below.

2.4.1.2. Per Protocol Analysis Set

The per protocol population includes subjects in full analysis set except those

- who did not meet the inclusion criteria 3, 4 or 5 in the protocol as listed below:
  - Have a PASI ≥12 at screening and at baseline.
  - Have an IGA ≥3 at screening and at baseline.
  - Have an involved BSA ≥10% at screening and at baseline.
- who violated the exclusion diagnosis criteria 7 or 8:
  - Has a nonplaque form of psoriasis (eg, erythrodermic, guttate, or pustular).
  - Has current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium).
- who violated the concomitant or previous psoriasis medications or therapies-related exclusion criteria (12, 13, and 15 through 22) as listed below:
  - Has previously received guselkumab or secukinumab.
  - Has any contraindications to the use of secukinumab per local prescribing information.
  - Has received any anti-tumor necrosis factor α biologic therapy within 3 months before the first administration of study drug.

- 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).
- 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.
- 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.
- 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, fumaric acid derivatives, herbal treatments, or traditional Taiwanese, Korean, or Chinese medicines) within 4 weeks of the first administration of study drug.
- 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.
- 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.
- 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.

- who did not complete the specified exposure to study agent as outline below
  - subjects randomized to guselkumab at Week 0 but did not receive all scheduled guselkumab administrations, received one or more extra guselkumab administrations, or received one or more secukinumab administrations prior to the specified time period for the endpoints (eg, Week 12 or Week 48).
  - subjects randomized to secukinumab at Week 0 but did not receive all scheduled secukinumab administrations, received one or more extra secukinumab administrations, or received one or more guselkumab administrations prior to the specified time period for the endpoints.

However, for those who did not complete the specified exposure to study agent as outline above, subjects who discontinued the study agent due to unsatisfactory therapeutic effect or an adverse event (AE) of worsening of psoriasis, or subjects who started prohibited medications and continued receiving study agents prior to the specified timepoint for the endpoints will be

included in the per protocol analysis and the treatment failure rules specified in Section 5.1.3.2 will apply.

Subjects who were excluded from the per protocol analyses will also be summarized.

2.4.2. Safety Analysis Set

In contrast to the efficacy analysis set, safety analyses will be performed on the safety analysis set, which is defined as all randomized and treated subjects who received at least 1 injection of study agent (partial or complete) according to the actual treatment received during the study, irrespective of the treatment assigned at randomization.

2.4.3. Pharmacokinetics Analysis Set

The PK analysis set is defined as subjects who received at least one injection of guselkumab and have at least one valid blood sample drawn for PK analysis.

2.4.4. Immunogenicity Analysis Set

The immunogenicity analysis set is defined as all subjects who received at least one injection of guselkumab and have at least one appropriate sample collected post guselkumab administration for the detection of antibodies to guselkumab.

In both PK and immunogenicity analyses, subjects will be analyzed according to the treatment they actually receive, regardless of the treatment they are randomized to.

2.5. Definition of Subgroups

To evaluate the consistency of efficacy based on demographic characteristics, baseline disease characteristics, and psoriasis medication history, subgroup analyses will be performed for the primary endpoint, PASI 90, and the major secondary endpoints of PASI 100 and IGA score of cleared (0), all assessed at Week 48. The subgroups for subgroup analyses include the following:

Baseline demographics:

- Sex (male, female)
- Race
- Baseline Age (<45 years, 45 to <65 years, ≥65 years)
- Baseline weight (≤90 kg, >90 kg)
- BMI (Normal [<25], Overweight [25 -<30], Obese [≥30])

Baseline disease characteristics:

- Age at diagnosis (years) (<25, ≥25)
- Psoriasis disease duration (years) (<15, ≥15)
- Baseline PASI (<20, ≥20)
- Baseline IGA (<4, =4)

- Baseline BSA (<20%, ≥20%)
- Psoriatic arthritis (Yes, No)

Psoriasis medication history:

- Phototherapy (ultraviolet B light [UVB] or psoralen and ultraviolet A light therapy [PUVA])
  - Never used
  - Ever used
- Non-biologic systemics (PUVA, MTX, cyclosporine, acitretin, apremilast, or tofacitinib)
  - Never used
  - Ever Used
- Biologics (etanercept, infliximab, alefacept, efalizumab, ustekinumab, briakinumab, ixekizumab, brodalumab, adalimumab, tildrakizumab, or risankizumab)
  - Never used
  - Ever Used
- Non-biologic systemics or biologics (as defined above)
  - Never used
  - Ever used
- Anti-TNFα agent (etanercept, infliximab, adalimumab)
  - Never used
  - Ever used
- IL-12/23 inhibitors (ustekinumab, briakinumab, tildrakizumab, or risankizumab)
  - Never used
  - Ever used
- IL-17 inhibitors (ixekizumab, or brodalumab)
  - Never used
  - Ever used
- Subjects who had an inadequate response to, were intolerant to, or had a contraindication to any of the following four biologic therapies: etanercept, infliximab, adalimumab or ustekinumab

2.6. Statistical Methods

2.6.1. Study Day

Study Day 1 refers to the first study agent administration date. The study day for an event is defined as:

- Event date - (date of Study Day 1) +1, if event date is ≥ date of Day 1
- Event date - date of Day 1, if event date < date of Day 1

2.6.2. Baseline

In general, the baseline measurement is defined as the closest measurement taken prior to or at the time of the first study agent administration date unless otherwise specified.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

No formal interim analysis is planned for this study. There is no Data Monitoring Committee for this study.

4. SUBJECT INFORMATION

Either the full analysis set or the safety analysis set will be used for the subject information analyses as specified below unless otherwise noted. The number of subjects in each analysis set will be summarized by treatment group and overall. In addition, the distribution of subjects by country, and site will be presented.

Simple descriptive statistics, such as mean, median, standard deviation, interquartile range, maximum, and minimum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data and no formal statistical analyses for treatment comparisons will be performed. In addition, subject listings will also be used to present the data.

4.1. Demographics and Baseline Characteristics

4.1.1. Demographics

Table 2 presents a list of the demographic variables that will be summarized by treatment group, and overall for the full analysis set.

Table 2: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Weight (kg) (<= 90 kg, > 90 kg)	
Height (cm)	
Categorical Variables:	
Age (<45 years, 45 to <65 years, and ≥65 years)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other, Multiple, Unknown, Not reported)	
Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)	
BMI (Normal [<25], Overweight [25 -<30], Obese [≥30])	

[a] If multiple race categories are indicated, then Race is recorded as "Multiple."

4.1.2. Baseline Characteristics

Psoriasis baseline disease characteristics (ie, psoriasis disease duration [years], age at diagnosis [years], BSA [%], psoriatic arthritis, baseline IGA score, and baseline PASI score [0-72]) will be summarized by treatment group for the full analysis set.

4.2. Disposition Information

Screened subjects will be summarized overall.

The number of subjects in the following disposition categories will be summarized by treatment group and overall:

- Subjects randomized
- Subjects who received study agent
- Subjects who completed the study
- Subjects who discontinued study agent
- Reasons for discontinuation of study agent
- Subjects who terminated study prematurely
- Reasons for termination of study

The above categories will include summaries over the period of Week 44 (the last study agent administration) and Week 56 if appropriate.

Listings of subjects will be provided for the following categories:

- Subjects who discontinued study agent
- Subjects who terminated study prematurely
- Subjects who were unblinded during the study period
- Subjects who were randomized yet did not receive study agent

4.3. Treatment Compliance

Study agent compliance will be summarized descriptively through Week 44 for the full analysis set. Number of subjects by randomized treatment versus actual treatment will be presented in a summary table.

4.4. Extent of Exposure

The exposure data will be summarized through Week 44. The number and percentage of subjects who receive study agent will be summarized by treatment group for the safety analysis set. Descriptive statistics will be presented for the following parameters:

- Number of administrations
- Cumulative total dose

In addition, the study agent lots received by treatment, including matching placebo for active treatment will be summarized.

4.5. Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical trial. Subjects with major protocol deviations will be identified prior to database lock and will be summarized by category by treatment group through Week 56 for the full analysis set.

- Entered but did not satisfy criteria
- Developed withdrawal criteria but not withdrawn
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other: to be defined in the major protocol deviation criteria document

A listing of subjects with major protocol deviations will also be provided by randomized treatment group.

4.6. Prior and Concomitant Medications

Subjects' prior psoriasis medication history with topical agents, phototherapy, non-biologic systemic therapies, and biologic medications will be summarized by treatment group for the full analysis set. See Section 2.5 for list of medications in each category. In addition, reasons for which subjects discontinued previous systemic therapies including PUVA, methotrexate, cyclosporine, etanercept, infliximab, adalimumab and ustekinumab (contraindication, inadequate response, intolerance [ie, AEs], or other) will be summarized by randomized treatment group for the full analysis set.

The number of subjects who received concomitant treatment with a moisturizer for psoriasis will be summarized by randomized treatment group for the full analysis set.

Listings of subjects who received concomitant corticosteroids for indications other than psoriasis and/or psoriatic arthritis and of subjects who received concomitant prophylactic treatment for latent TB infection will be provided.

5. EFFICACY

In general, efficacy data summaries will be provided by treatment group for the full analysis set.

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 noninferiority of guselkumab to secukinumab, a 1-sided (α=0.025) Z-test[2] with Mantel-Haenszel weights adjusted by investigator site after pooling will be used. All statistical testing will be performed 2-sided for superiority and 1-sided for non-inferiority.

Descriptive statistics, such as mean, median, standard deviation, minimum and maximum, interquartile range for continuous variables, and counts and percentages for categorical variables will be used to summarize the data. Graphical data displays and subject listings may also be used to summarize the data.

5.1. Analysis Specifications

5.1.1. Level of Significance

All statistical procedures to test superiority hypotheses will be performed at a 2-sided significance level of 0.05 and 1-sided at a significance level of 0.025 for non-inferiority. This study is designed to maintain an overall Type I error of 0.05 or less for the primary analysis and major secondary analyses. Nominal p-values will be reported for other secondary analyses.

5.1.1.1. Multiplicity Adjustment for Testing Procedures

The primary endpoint in this study is the proportion of subjects who achieve a PASI 90 response at Week 48. The primary analyses will be evaluated by a non-inferiority test with a non-inferiority margin of 10% followed by a superiority test between the guselkumab 100 mg treatment group and the secukinumab 300 mg group.

In addition, there are 6 major secondary endpoints in this study to be compared between the guselkumab 100 mg group and the secukinumab 300 mg group:

- 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.
- 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 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 each subsequent analysis will be performed only if the preceding analysis in the sequence is positive.

5.1.2. Definition of the Efficacy Endpoints and Calculation of the Efficacy Instruments

5.1.2.1. Investigator's Global Assessment

The Investigator's Global Assessment (IGA) documents the investigator's assessment of the subject's psoriasis at a given time point. 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).

Efficacy endpoints related to the IGA score are defined below:

IGA cleared responder

Subjects who achieve an IGA score of cleared (0) will be considered IGA cleared responders.

IGA cleared or minimal responder

Subjects who achieve an IGA score of cleared (0) or minimal (1) will be considered IGA cleared or minimal responders.

IGA mild or better responder

Subjects who achieve an IGA score of cleared (0), minimal (1), or mild (2) will be considered IGA mild or better responders.

5.1.2.2. 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. 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 can range from 0 (no psoriasis) to 72. A higher score indicates more severe disease.

Efficacy endpoints related to the PASI score are defined below:

PASI 50 Responder

Subjects with ≥50% improvement in PASI from baseline will be considered PASI 50 responders.

PASI 75 Responder

Subjects with ≥75% improvement in PASI from baseline will be considered PASI 75 responders.

PASI 90 Responder

Subjects with ≥90% improvement in PASI from baseline will be considered PASI 90 responders.

PASI 100 Responder

Subjects with 100% improvement in PASI from baseline (ie, a PASI score of 0) will be considered PASI 100 responders.

5.1.3. Data Handling Rules

The following treatment failure rules and data handling rules will be applied to the PASI and IGA related efficacy analyses in this study.

5.1.3.1. Treatment Failure Criteria

Subjects who discontinue study agent due to lack of efficacy, an adverse event (AE) of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could affect their psoriasis are considered as treatment failures.

The protocol-prohibited medications/therapies include:

Topical Therapies:

- Any topical therapies used for psoriasis (with the exception of topical moisturizers and shampoos containing tar or salicylic acid only)

Phototherapy or Systemic Therapies:

- Any systemic corticosteroid used for psoriatic arthritis or psoriasis with the exception of intra-articular corticosteroids.
- Any other anti-psoriatic systemic therapy or biologic therapy.
- Phototherapy of UVB or PUVA.
- Any other phototherapy for psoriasis.

5.1.3.2. Treatment Failure Rules

A subject who meets one or more of the treatment failure criteria specified in Section 5.1.3.1 will be considered a treatment failure from that point onward. The baseline values will be used for all directly measured endpoints regardless of the actual measurements. Zero will be assigned to improvement and percent improvement, and non-responder status will be assigned to binary response variables.

Treatment failure is assumed to have occurred at the earlier of the following dates:

- Date of discontinuation (DC) of study treatment due to lack of efficacy or an AE of worsening of psoriasis or
- Date of initiation of a protocol-prohibited medication/therapy during the study that could improve psoriasis

5.1.3.3. Missing Data Imputation

After the treatment failure rules are applied, the remaining missing data will be handled as follows for all of the efficacy analyses including the analyses at key visits (eg, Week 12 and Week 48) and over time:

- Non-responder imputation will be applied for binary endpoints.
- No imputation will be performed for continuous endpoints and the values will remain as missing.

5.2. Primary Efficacy Endpoint(s)

5.2.1. Definition

The primary endpoint in this study is the proportion of subjects who achieve a PASI 90 response at Week 48. Refer to Section 5.1.2.2 for the definition of a PASI 90 responder.

5.2.2. Estimand

Population: subjects with moderate-to-severe plaque psoriasis who are randomized and treated with guselkumab 100 mg or secukinumab 300 mg.

Endpoint: the proportion of subjects who achieve a PASI 90 response at Week 48

Measure of Intervention: the effect of the initially randomized treatment regardless of what treatments are actually received. Non-responder status will be assigned if treatment failure criteria are met or data are missing.

5.2.3. Analysis Methods

The primary endpoint will be compared between the guselkumab 100 mg group and the secukinumab 300 mg group. In the primary efficacy analysis, data from all randomized will be analyzed according to their assigned treatment group (ie, full analysis set). The number and proportion of subjects who achieve a PASI 90 response at Week 48 will be summarized for each treatment group respectively.

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. First a non-inferiority test with a non-inferiority margin of 10% will be conducted. 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. In addition, in studies with biologic agents, placebo response rates for PASI 90 are consistently low (eg, <5% Cosentyx® SmPC, <5% STELARA SmPC, <5% guselkumab). Further, there is no placebo data at Week 48 for any clinical study of biologics. Therefore, the preservation of benefit for the Week 48 endpoints is based on the historic response rates of the active comparator, ie, secukinumab. Based on the 2 placebo-controlled Phase 3 secukinumab studies (FIXTURE and ERASURE), a PASI 90 response was estimated to occur in 64.6% (95% confidence interval [CI]: 60.7%, 68.6%) of subjects receiving secukinumab 300 mg at Week 48, whereby a 10% non-inferiority margin would preserve at least 80% of the secukinumab benefit.

   To claim the non-inferiority of guselkumab to secukinumab, a 1-sided (α=0.025) Z-test with Mantel-Haenszel (MH) weights adjusting for investigator site[2] will be used. That is, the lower bound of the 2-sided 95% confidence interval (CI) 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 100 mg and the secukinumab 300 mg groups, respectively. The 2-sided 95% CI on the difference between guselkumab 100 mg and the secukinumab 300 mg groups will be calculated adjusting for investigator site after pooling using Mantel-Haenszel weights.[2] 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 using the CMH chi-square test stratified by investigator site after pooling will be performed at a significance level of 0.05. The proportion difference between guselkumab 100 mg and the secukinumab 300 mg groups and its 2-sided 95% CI will be provided based on normal approximation with Mantel-Haenszel weights adjusting for investigator site.

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.

5.2.4. Data Handling

Subjects who meet treatment failure criteria specified in Section 5.1.3.1 prior to Week 48 will be considered PASI 90 nonresponders at Week 48. In addition, subjects with a missing PASI score at Week 48 or who do not return for evaluation at Week 48 will be considered PASI 90 nonresponders at Week 48.

5.2.5. Sensitivity Analysis

To assess the robustness of the primary endpoint analysis results, the following three sensitivity analyses will be conducted.

Sensitivity Analysis 1

For subjects who have a missing PASI score at Week 48, the score will not be imputed. That is, the analysis will be performed using observed data, after applying treatment failure rules (as defined in Section 5.1.3.2).

Sensitivity Analysis 2

The second sensitivity analysis will be performed by using multiple imputations (MI), after applying treatment failure rules (as defined in Section 5.1.3.2). The intermittent missing PASI scores which include PASI scores at Week 0, Week 4 through Week 48 will be imputed using the Markov Chain Monte Carlo (MCMC) algorithm with 200 imputed data sets and seed = 123 to make the missing data pattern monotone. The PASI 90 responses will then be derived based on the imputed score at or before Week 48. The remaining missing data for the PASI 90 response will be imputed with monotone logistic regression with treatment group, baseline PASI, investigator site and PASI 90 response status starting from Week 4 in the model with one imputed dataset and seed = 789 to fill in the remaining missing items in each of the 200 copies of datasets. If the model fails to converge, investigator site will not be included as an explanatory variable. The proportion difference of PASI 90 response at Week 48 adjusted for investigator site (pooling) using Mantel-Haenszel weight between the guselkumab 100 mg and the secukinumab 300 mg groups and its 95% CI combining multiple datasets will also be provided. In addition, the superiority test of guselkumab to secukinumab combining all the multiple imputation datasets using the CMH chi-square test stratified by investigator site will be performed at a significance level of 0.05.

Sensitivity Analysis 3

A generalized linear model with logit link for binary repeated measurement data will also be performed as a sensitivity analysis to compare the proportion of subjects responding to treatments at Week 48, after applying treatment failure rules (as defined in Section 5.1.3.2). The model will include baseline PASI score, treatment group, investigator site, visit starting from Week 4, the interaction of treatment group and visit, and the interaction of baseline PASI score

and visit as explanatory variables. If the model fails to converge, investigator site will not be included as an explanatory variable. The derived odds ratio on PASI 90 at Week 48 and its 95% CI will be provided. In addition, the proportion difference of PASI 90 response at Week 48 between the guselkumab 100 mg and the secukinumab 300 mg groups and its 95% CI will also be provided. For subjects who do not return for evaluation at any visit, the missing PASI score will not be imputed.

5.2.6. Subgroup Analysis

For each of the subgroups defined in Section 2.5, the proportion of subjects achieving a PASI 90 response at Week 48 by treatment group will be summarized, respectively. Under the assumption of normal distributions, the 95% confidence interval without adjusting for investigator site of the difference between the guselkumab 100 mg and the secukinumab 300 mg groups for the primary endpoint will also be provided. In addition, the proportion of PASI 90 responders at Week 48 by investigator site will be summarized.

5.2.7. Per Protocol Analyses

The primary analysis will also be performed on the per protocol analysis set defined in Section 2.4.1.2.

5.3. Major Secondary Endpoints

The analyses for the major secondary endpoints will be performed in the order listed in Section 5.1.1.1.

The sections below outline the analysis methods and the data imputation rules for the major secondary analyses to be performed.

5.3.1. Definition

There are 6 major secondary endpoints in this study to be compared between the guselkumab 100 mg group and the secukinumab 300 mg group:

- 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.
- An IGA score of cleared (0) or minimal (1) at Week 48.

5.3.2. Analysis Methods

The major secondary efficacy analyses described in this section will be performed using the full analysis set. For the major secondary analyses, all non-inferiority tests will be performed 1-sided (α=0.025) with a non-inferiority margin of 10%. The margin of 10% was similarly determined as for the primary endpoint. All superiority statistical testing will be performed at a two-sided

significance level of 0.05. In addition, all the major secondary analyses will also be performed on the per protocol analysis set defined in Section 2.4.1.2. The same statistical methods used for the primary endpoint will also be used to analyze the major secondary endpoints. In addition, similar Sensitivity Analyses 1 and 2 as performed for the primary endpoint will be performed for the major secondary endpoints. For the Sensitivity Analysis 2 for the endpoints of PASI 75 response and PASI 90 response at Week 12 where non-inferiority test only is specified for these 2 endpoints, 1-side Wald test with Mantel-Haenszel weights adjusted by investigator site will be performed. The sensitivity analyses using MI will be performed similarly as that done for the primary endpoint including using the same seeds and same number of imputations.

In addition, subgroup analyses for the IGA score of cleared (0) at Week 48 and PASI 100 at Week 48 will be performed similarly as for the primary endpoint.

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.
- 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 48 will be performed. If non-inferiority is established, the superiority test on this endpoint will be performed.

5.3.3. Data Handling

Unless otherwise specified, data handling rules specified in Section 5.1.3 will be applied to the major secondary analyses.

5.4. Other Efficacy Variable(s)

Other secondary efficacy endpoints include the endpoints related to

- PASI
- IGA

5.4.1. Definition

Refer to Section 5.1.2 for the definitions of the other efficacy endpoints described in the following section.

5.4.2. Analysis Methods

Most of the other secondary efficacy analyses described in this section will be performed using the full analysis set. For the other secondary analyses, all non-inferiority tests will be performed 1-sided (α=0.025) with a non-inferiority margin of 10%. The margin of 10% was similarly determined as for the primary endpoint. All the non-inferiority analyses will also be repeated for the per protocol population (Section 2.4.1.2). All superiority statistical testing will be performed 2-sided (α=0.05). Nominal p-values will be presented. The same statistical methods used for the primary endpoint will also be used to analyze the secondary endpoints.

5.4.2.1. Analyses Related to IGA

- 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 an IGA score of cleared (0) response, IGA score of cleared (0) or minimal (1) response, and IGA score of mild or better (≤2) response over time through Week 56 will be summarized by treatment group. Line plots will be provided displaying the proportions and 95% CIs of subjects achieve an IGA score of cleared (0); and an IGA score of cleared (0) or minimal (1) through Week 48. The 95% CI will be calculated based on normal approximation.
- The proportions of subjects achieving an IGA score of cleared (0) response, IGA score of cleared (0) or minimal (1) response, and IGA score of mild or better (≤2) response will also be summarized over time through Week through Week 56 by treatment group using observed data after applying treatment failure rules.

5.4.2.2. Analyses Related to PASI

- 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 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 PASI 100 responders, PASI 90 responders, PASI 75 responders, and PASI 50 responders will be summarized over time through Week 56 by treatment group. Line plots will be provided displaying proportions and 95% CIs of PASI 100 responders and PASI 90 responders through Week 48. The 95% CI will be calculated based on normal approximation.
- The proportions of PASI 100 responders, PASI 90 responders, PASI 75 responders, and PASI 50 responders, will be summarized over time through Week 56 by treatment group using observed data after applying treatment failure rules.
- The percent improvement from baseline in PASI will be summarized over time through Week 56 by treatment group.
- The proportion of subjects who achieve 100% improvement, ≥90%, ≥75%, or ≥50% improvement from baseline in PASI component (induration, erythema, and scaling) and region component (head, trunk, upper extremities, and lower extremities) will be summarized at Week 48 by treatment group.

5.4.3. Data Handling

Data handling rules specified in Section 5.1.3 will be applied to all IGA related and PASI related analyses.

6. SAFETY

Safety will be assessed by summarizing the incidence and type of AEs and examining changes in laboratory parameters (hematology and chemistry), vital signs and electrocardiogram (ECG) parameters, and suicidal ideation and behavior as measured by the eC-SSRS (electronic Columbia-Suicide Severity Rating Scale).

In all the safety analysis, subjects who were randomized and received at least 1 (partial or complete) dose of study agent will be included and analyzed according to the treatment they actually received, regardless of the treatment they are randomized to. No formal hypothesis testing is planned.

Depending on the safety data categories, the cumulative safety data will be analyzed through Week 56. Unless otherwise specified, tabular summaries of safety events for the study periods are presented as follows:

- Guselkumab 100 mg
- Secukinumab 300 mg

This allows between-group comparisons of safety between the guselkumab 100 mg group and the secukinumab 300 mg group based on the same follow-up period in each group.

6.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE starting at or after the initial administration of study agent through the end of the trial is considered to be treatment emergent. If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study agent based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, event rate per 100 subject-years of follow-up for serious infections will be provided.

Summary tables will be provided for:

- AEs
- Serious AEs (SAEs)
- AEs leading to discontinuation of study agent administration
- AEs by severity
- AEs by relationship to study agent
- Infections
- Serious infections
- Infections treated with oral or parenteral antimicrobial treatment parenteral antibiotics
- Injection-site reactions
- AEs of psoriasis

In addition to the summary tables, listings will be provided for subjects who:

- Had SAEs
- Had AEs leading to discontinuation of study agent administration
- Had AEs of severe intensity
- Had serum sickness-like reactions or anaphylactic reactions

Any unfavorable or unintended sign that occurs at the injection site is an injection site reaction and will be recorded as an injection site reaction by the investigator on the eCRF. An infection is defined as any AE that was recorded as an infection by the investigator on the eCRF.

The treatment-emergent adverse events of psoriasis include any event of erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, and worsening or exacerbation of psoriasis. Incidence of these events will be summarized.

Since safety should be assessed relative to exposure and follow-up, most AE summary tables will include average weeks of follow-up and average number of study agent administrations for each treatment group.

6.2. Clinical Laboratory Tests

All clinical laboratory reports will be displayed for the subjects included in the safety analysis set. The clinical laboratory parameters to be evaluated by the central laboratory include but are not limited to:

- **Hematology**: hemoglobin, hematocrit, lymphocytes, neutrophils, platelets, red blood cell (RBC) count and white blood cell (WBC) count.
- **Chemistry**: albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total carbon dioxide (CO2), total bilirubin, blood urea nitrogen/urea, calcium, chloride, creatinine, glucose, potassium, total protein, sodium.

Box plots of laboratory measurements and change from baseline will be provided for the selected laboratory measurement.

Applicable laboratory results will be graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE version 4.03). The worst NCI-CTCAE will be summarized by treatment group.

For non-fasting glucose, the screening measurement will be used as the baseline measurement. A listing of subjects with 1 or more NCI-CTCAE toxicity grade ≥2 in hematology and clinical chemistry laboratory measurements will be provided.

6.3. Vital Signs and Physical Examination Findings

Vital signs variables including heart rate, blood pressure (systolic and diastolic) will be measured at visits as per the schedule of events in the protocol. Descriptive statistics of the observed value and change from baseline of the vital signs will be summarized by treatment group.

Physical exam findings will not be analyzed except that they are captured as AEs and are included in the analyses of AEs.

6.4. Electrocardiogram

A supine 12-lead ECG will be performed at Weeks 0, 16, and 48, as specified in the Time and Events Schedule. Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and change from baseline at each scheduled time point.

In addition, summary of post-baseline ECG abnormalities different from Week 0 and a listing of subjects with any post-baseline ECG abnormalities different from Week 0 measurement will be provided.

6.5. Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)

The electronic Columbia-Suicide Severity Rating Scale (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 five subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent, and is a fully-structured subject self-report questionnaire, including standardized questions, follow-up prompts, error handling routines, and scoring conventions. The Screening version of the eC-SSRS will be conducted at Screening followed by the Since Last Visit version of the eC-SSRS at all other visits through Week 56 except at Week 1, 2, and 3.

The eC-SSRS will be performed during each evaluation visit according to the assessment schedule. The eC-SSRS will be performed at screening after signing informed consent, and before study agent administration, and as the first assessment for all post-baseline visits. The baseline is defined as the most severe/maximum eC-SSRS score at either screening or Week 0.

In addition, potential suicide related adverse events including suicidal ideation, suicidal behavior excluding completed suicide, and completed suicide will be identified by the investigators and collected in the eCRF.

The following are eC-SSRS categories and have binary responses (yes/no). A “yes” response to any eC-SSRS category will be assigned a score as below:

Suicidal Ideation (1-5)

1 = Wish to be Dead

2 = Non-specific Active Suicidal Thoughts

3 = Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act

4 = Active Suicidal Ideation with Some Intent to Act, without Specific Plan

5 = Active Suicidal Ideation with Specific Plan and Intent

Suicidal Behavior (6-10)

6 = Preparatory Acts or Behavior

7 = Aborted Attempt

8 = Interrupted Attempt

9 = Actual Attempt (non-fatal)

10 = Completed Suicide

If no events qualify for a score of 1 to 10, a score of 0 will be assigned (0 = “Negative result [no suicidal ideation or behavior]”). Higher scores indicate greater severity.

The summary for suicidal ideation and behavior will be based on the safety analysis set. Suicidal ideation and behavior will be summarized based on the most severe/maximum post baseline eC-SSRS outcome or AE of suicidal ideation, suicidal behavior excluding completed suicide, or completed suicide through Week 56.

The maximum score assigned for each subject will also be summarized into one of three broad categories: No suicidal ideation or behavior, suicidal ideation, suicidal behavior. A shift table for change in eC-SSRS categories of no suicidal ideation or behavior, suicidal ideation, and suicidal behavior from baseline through Week 56 will be presented, where the baseline category is based on eC-SSRS score and the post baseline is based on eC-SSRS or AE data.

7. PHARMACOKINETICS/IMMUNOGENICITY

7.1. Pharmacokinetics

Blood samples for measuring serum guselkumab concentrations (pre-injection if it is injection visit) will be collected from all subjects at scheduled visits as indicated in the Time and Events Schedule in the protocol.

The PK analysis will be based on subjects who received at least 1 administration of guselkumab and had at least one evaluable serum sample. No imputation of missing concentration data will be performed, that is, data summaries will be based on the observed data.

All concentrations below the lowest quantifiable concentration in a sample or missing data will be labeled as such in the concentration data listings or Statistical Analysis Software™ dataset. Concentrations below the lowest quantifiable concentration in a sample will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented.

For analysis of serum guselkumab concentrations, descriptive statistics, including arithmetic mean, SD, median, interquartile range, minimum, and maximum will be calculated at each scheduled sampling time point for the guselkumab group. The PK concentration data may be displayed graphically.

All summaries for serum guselkumab concentration will exclude data collected after subjects (1) did not receive a scheduled guselkumab administration within ± 14 days of the protocol scheduled dosing date, or those subjects who discontinued study agent, (2) received a partial, incorrect, or an additional guselkumab administration, (3) or have invalid sample data if the sample is taken after study agent administration or a concentration value falls outside the predefined range (±10*SD). Of note, serum guselkumab concentrations prior to the first of such events will be included in the summaries.

If needed, a population PK analysis using a nonlinear mixed-effects modeling approach will be used to characterize the disposition characteristics of guselkumab in the current study. Data may be combined with those from pivotal Phase 3 studies (CNTO1959PSO3001 and CNTO1959PSO3002) to support a relevant structural model. Details will be given in a

population PK analysis plan and results of the population PK analysis will be presented in a separate technical report.

The effect of serum guselkumab concentrations on efficacy of guselkumab will be explored.

7.2. Immunogenicity (Antibodies to Guselkumab)

Blood samples will be collected for the detection of antibodies to guselkumab at the specified visits as shown in the Time and Events schedule in the protocol.

The antibodies to guselkumab analysis will be based on subjects who receive at least 1 dose of guselkumab and have at least one samples collected post guselkumab administration for the detection of antibodies to guselkumab. No imputation of missing data will be performed, that is, data summaries will be based on the observed data.

The following analyses will be performed for guselkumab group as appropriate:

- Summary of antibodies to guselkumab status (incidence of positive antibodies to guselkumab and antibody titers)
- List of subjects positive for antibodies to guselkumab

In addition, 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.

The effect of antibodies to guselkumab on PK, efficacy, and safety will be explored.

REFERENCES

1. Langley RG, Elewski BE, Lebwohl M, et al; ERASURE Study Group; FIXTURE Study Group. Secukinumab in plaque psoriasis - results of two phase 3 trials. N Engl J Med. 2014;371(4):326-338.
2. Miettinen O, Nurminen M. Comparative analysis of two rates. Statistics in Medicine. 1985; 4:213-226.

ATTACHMENT

Attachment 1 Summary of Pooling Centers for Analysis

Site #	City	State/ Province	Country/ US Region	Number of Subjects Randomized	Sites to be combined	Number of Subjects per Pooled Site	Site Group
[redacted]	[redacted]		Australia	5	[redacted]	15	[redacted]
			Australia	2			
			Australia	3			
			Australia	5			
			Australia	7		14	
			Australia	7			
			Australia	3		11	
			Australia	8			
			Australia	1		18	
			Australia	17			
			Australia	13			
		[redacted]	Canada	7		15	
			Canada	8			
			Canada	10			
			Canada	10			
			Canada	10			
			Canada	15			
			Canada	9		19	
			Canada	5			
			Canada	5			
			Canada	10			
			Canada	24			
			Canada	25			
			Canada	10			
			Canada	10			

Site #	City	State/ Province	Country/ US Region	Number of Subjects Randomized	Sites to be combined	Number of Subjects per Pooled Site	Site Group
[redacted]			Czech Republic	4	[redacted]	11	[redacted]
			Czech Republic	7			
			Czech Republic	5		16	
			Czech Republic	7			
			Czech Republic	4			
			Czech Republic	10		17	
			Czech Republic	7			
			Czech Republic	11			
			Spain	4		13	
			Spain	6			
			Spain	3			
			Spain	8		17	
			Spain	4			
			Spain	4			
			Spain	1			
			Spain	3		12	
			Spain	6			
			Spain	3			
			Spain	12			
			Spain	8		14	
			Spain	3			
			Spain	3			
			France	11			
			France	16			
			France	8		13	

Site #	City	State/ Province	Country/ US Region	Number of Subjects Randomized	Sites to be combined	Number of Subjects per Pooled Site	Site Group
[redacted]	[redacted]		France	2	[redacted]		
			France	3			
			France	18			[redacted]
			Germany	7		19	
			Germany	12			
			Germany	5		15	
			Germany	4			
			Germany	6			
			Germany	9		22	
			Germany	5			
			Germany	8			
			Germany	4		15	
			Germany	8			
			Germany	3			
			Germany	7		13	
			Germany	6			
			Germany	15			
			Germany	10			
			Germany	5		13	
			Germany	8			
			Hungary	3		13	
			Hungary	9			
			Hungary	1			
			Hungary	6		16	
			Hungary	4			
			Hungary	6			
			Hungary	6		16	
			Hungary	7			

Site #	City	State/ Province	Country/ US Region	Number of Subjects Randomized	Sites to be combined	Number of Subjects per Pooled Site	Site Group
[redacted]			Hungary	3	[redacted]		[redacted]
			Poland	20			
			Poland	20			
			Poland	10			
			Poland	10			
			Poland	10	[redacted]	13	
			Poland	3			
			Poland	30			
			Poland	11			
			Poland	10			
			Poland	18			
			Poland	15			
			Poland	20			
			Poland	29			
			Poland	4	[redacted]	13	
			Poland	9			
			Poland	19			
		[redacted]	United States	2	[redacted]	10	
			United States	8			
			United States	1		10	
			United States	4			
			United States	5			
			United States	9		10	
			United States	1			
			United States	5		11	

Site #	City	State/ Province	Country/ US Region	Number of Subjects Randomized	Sites to be combined	Number of Subjects per Pooled Site	Site Group
[redacted]		[redacted]	United States	6	[redacted]		
			United States	9		23	[redacted]
			United States	2			
			United States	4			
			United States	8			
			United States	4		25	[redacted]
			United States	21			
			United States	3		14	[redacted]
			United States	11			
			United States	4		14	[redacted]
			United States	5			
			United States	2			
			United States	3			
			United States	4		16	[redacted]
			United States	8			
			United States	4			
			United States	5		15	[redacted]
			United States	7			
			United States	3			
			United States	1		19	[redacted]

Site #	City	State/ Province	Country/ US Region	Number of Subjects Randomized	Sites to be combined	Number of Subjects per Pooled Site	Site Group
[redacted]	[redacted]	[redacted]	United States	3	[redacted]		
			United States	4			
			United States	5			
			United States	1			
			United States	5			
			United States	3		13	[redacted]
			United States	10			
			United States	19			[redacted]
			United States	5		20	[redacted]
			United States	3			
			United States	10			
			United States	2			
			United States	9		14	[redacted]
			United States	4			
			United States	1			