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Statistical Analysis Plan

**A Phase 3, Multicenter, Randomized, Double-blind, Placebo controlled Study
Evaluating the Efficacy and Safety of Guselkumab for the Treatment of Subjects with
Palmoplantar Pustulosis**

Protocol CNTO1959PPP3001; Phase 3

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).

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AMENDMENT HISTORY**ABBREVIATIONS**

AE	Adverse Event
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database Lock
DLQI	Dermatology Life Quality Index
DPS	Data Presentation Specifications
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EQ-5D	EuroQOL Five Dimensions Questionnaire
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
LLOQ	Lower Limit Of Quantitation
LOCF	Last Observation Carried Forward
MMRM	Mixed-model for Repeated Measures
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
IGA	Investigator's Global Assessment
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
PAO	Pustulotic Arthro-Osteitis
PASI	Psoriasis Area and Severity Index
PGA	Physician's Global Assessment
PI	Principal Investigator
PK	Pharmacokinetics
PPP	Palmoplantar Pustulosis
PPPASI	Palmo-Plantar Area and Siverity Index
PPSI	Palmo-Planter Severity Index
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SF-36	36- Item Short Form Health Assessment Questionnaire
SSR	Sample Size Re-estimation
TEAEs	Treatment-Emergent AEs

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 CNTO1959PPP3001 study, where 4 DBLs will occur at Week 16, Week 24, Week 52 and Week 84, respectively. This document provides analysis plan for all of these 4 DBLs.

Guselkumab is a fully human immunoglobulin G1 lambda (IgG1 λ) monoclonal antibody (mAb) that inhibits the biological activity of IL-23 and therefore has the potential for the treatment of palmoplantar pustulosis.

1.1. Trial Objectives

Primary Objectives

- To evaluate the efficacy of CNTO 1959 for the treatment of subjects with palmoplantar pustulosis.

Secondary Objectives

- To assess the safety and tolerability of CNTO 1959 in subjects with palmoplantar pustulosis.
- To evaluate the effect of treatment with CNTO 1959 on patient-reported signs and symptoms of palmoplantar pustulosis.
- To evaluate the durability of clinical response to different dose levels and dose regimens of CNTO 1959 in palmoplantar pustulosis.
- To evaluate the PK and immunogenicity following subcutaneous (SC) administration of CNTO 1959.
- To evaluate the effect of treatment with CNTO 1959 on health-related quality of life.

Exploratory Objectives

- To explore the efficacy of CNTO 1959 on pustulotic arthro-osteitis (PAO) in the subset of subjects with PAO at screening.
- To explore the effect of treatment with CNTO 1959 on patient-reported signs and symptoms of PAO.
- To explore biomarkers in subjects with palmoplantar pustulosis.

1.2. Trial Design

This is a Phase 3, randomized, double-blind, multicenter placebo-controlled study in subjects with palmoplantar pustulosis. The target population is adult men and women, with a diagnosis of palmoplantar pustulosis (with or without PAO) for at least 24 weeks before screening. Subjects must have a PPPASI total score ≥ 12 and a PPPASI severity score of pustules/vesicle on the palms or soles ≥ 2 at screening and baseline. Subjects must have inadequate response to conventional therapies (topical treatment, and/or phototherapy, and/or systemic treatment).

Subjects with drug-induced palmoplantar pustulosis (eg, a new onset of palmoplantar pustulosis or an exacerbation of palmoplantar pustulosis from beta blockers, calcium channel blockers, or

lithium, or biologic therapy etc.) are excluded. Subjects who have ever received CNTO 1959 are also excluded.

This study will be conducted using an adaptive statistical design permitting one interim analysis and the potential to stop the study for futility and increase sample size for the final analysis with a maximum allowable sample size of 225 patients.

Week 0 through Week 60 (Blinded Treatment Period)

As depicted in Figure 1, approximately 150-225 subjects who satisfy all inclusion and exclusion criteria will be randomized in a 1:1:1 ratio to one of three arms:

- **Group I** (n = 50, max75): CNTO 1959 200 mg at Weeks 0, 4, 12 and q8w thereafter through Week 60.
- **Group II** (n = 50, max75): CNTO 1959 100 mg at Weeks 0, 4, 12 and q8w thereafter through Week 60.
- **Group III** (n = 50, max75): Placebo at Weeks 0, 4, and 12. Beginning at Week 16, subjects will be randomized in a 1:1 ratio to CNTO1959 200 mg arm (Group IIIa) or 100 mg arm (Group IIIb), and will receive the assigned dose of CNTO 1959 at Weeks 16, 20 and q8w thereafter through Week 60.

Subject will be assigned to 1 of 3 treatment groups using a stratified block randomization method in a 1:1:1 ratio at Week 0 and Group III subjects will be allocated in a 1:1 ratio to 1 of 2 treatment groups at Week 16. Stratification factors will be PPPASI total score range (≤ 20 score, 21-30 score, ≥ 31 score) and smoking status (smoking or non-smoking).

After Week 60 until Week 84 (Observational Period)

The observational period will begin from Week 60 and extend until Week 84. All subjects will no longer receive the study drug during the observational period. Efficacy and safety will be evaluated at Week 72, and also the durability of clinical response at Week 84.

The investigators and subjects will be unblinded after the last subject has completed the Week 60 visit. The end of the study is defined as the time when the last subject completes the Week 84 visit. Database locks will occur at Weeks 16, 24, 52 and 84. Additional DBLs may also occur after Week 52 DBL during the study.

A serum sample for biomarkers will be collected from all subjects.

A diagram of the study design is provided below in Figure 1. When approximately 40% of the 150 randomized subjects have completed Week 16 visit or have ended study participation before Week 16 visit, an interim analysis is planned to be conducted to re-estimate the sample size and determine whether to stop the study early for futility. An Independent Data Monitoring Committee (IDMC) will be constituted for safety monitoring and interim analysis review of this study.

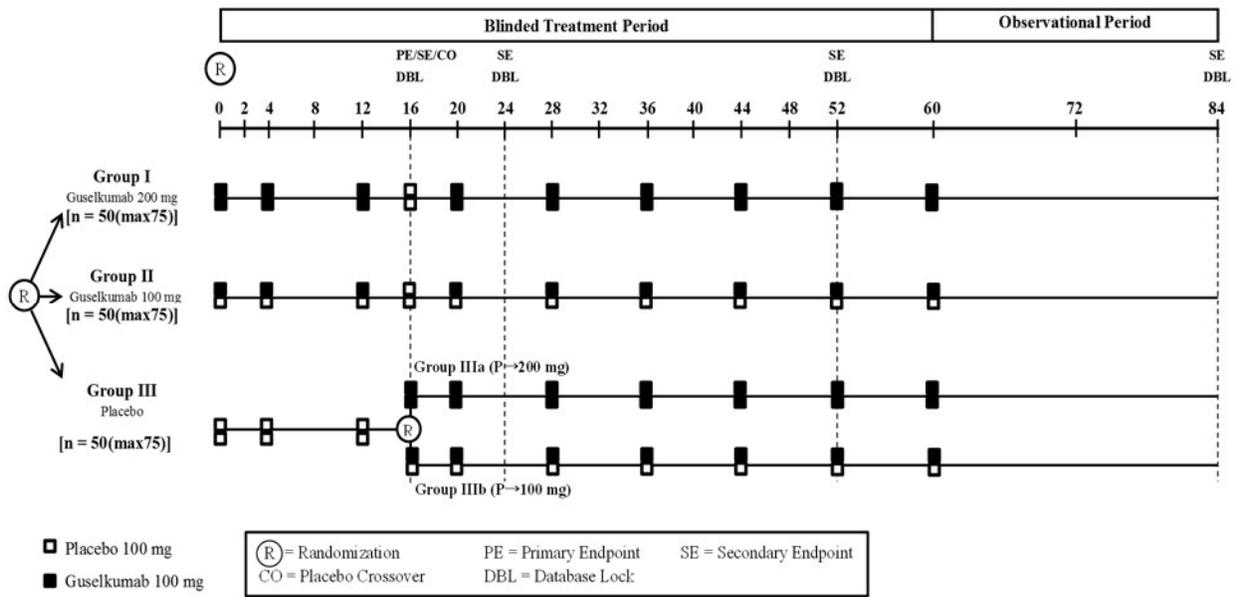


Figure 1 Study Schema

1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis is that CNTO 1959 treatment is superior to placebo as assessed by the change from the baseline of Palmoplantar Pustulosis Area and Severity Index (PPPASI) total score at Week 16.

1.4. Sample Size Justification

This study is designed to evaluate the efficacy of CNTO 1959 versus placebo in subjects with palmoplantar pustulosis at Week 16. Palmoplantar Pustulosis Area and Severity Index (PPPASI) total score will be used in this study as the primary variable. A fixed-sequence testing procedure, starting with the high dose group (CNTO 1959 200 mg), will be used to control the overall Type I error rate at the 0.05 level (2-sided) for comparisons of the 2 CNTO 1959 treatment groups with the placebo group.

The sample size was chosen to achieve at least 90% power to detect treatment difference between CNTO 1959 groups and placebo for the primary endpoint at a significance level of 0.05 (2-sided).

The assumptions for the sample size and power calculations came from the results of a phase 2 study in subjects with PPP (CNTO1959PPP2001):

Table 1: Change from baseline in PPPASI score at Week 16 in CNTO1959PPP2001 study		
	Placebo	CNTO1959 200 mg
n	24	25
Mean ± SD	-6.40 ± 7.545	-10.24 ± 8.072
LS mean ^a	-5.47	-11.12
LS mean difference (SE) (versus Placebo) ^a		-5.65 (2.061)
95% CI for difference in LS mean (versus Placebo) ^a		(-9.80, -1.50)

p-value (versus Placebo) ^a	0.009
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a) Based on ANCOVA with treatment as a factor and baseline PPPASI total score as a covariate.

Since the baseline PPPASI total score in CNTO1959PPP2001 study is deemed unbalanced across the comparison groups due to its exclusion from stratification factors, LS-means should be able to provide fairer comparisons than would comparisons of the raw means and as a result, the assumed treatment effect size is based upon the LS mean difference. Assuming a 5.5 treatment effect for both CNTO 1959 groups and a common standard deviation (SD) of 8.1 in change from baseline in PPPASI score at Week 16, 47 subjects per group will provide statistical power of 90% for comparisons of CNTO 1959 200 mg versus placebo at a significance level of 0.05 (2-sided).

Difference	SD	Power
4.5	7.5	82%
	8.1	75%
	8.5	71%
5.0	7.5	89%
	8.1	84%
	8.5	80%
5.5	7.5	94%
	8.1	90%
	8.5	87%

Based on the two sample t-test with equal variances of Query Advisor. Release 7.0.

To account for a larger common standard deviation, assuming a fixed 5.5 difference between groups and a common SD of 10, the required number of patients per group for a 90% power is 75. Meanwhile, an evaluable long-term safety population for CNTO 1959 is considered to have at least 50 patients per group. Therefore, the study design is pre-planned as 50 patients per group but with the option of an adaptive sample size re-estimation with a maximum allowable sample size of 75 patients per group (225 in total).

1.5. Randomization and Blinding

1.5.1. Procedures for Randomization

Central randomization will be implemented in this study.

At week 0, subjects will be randomly assigned to 1 of 3 treatment groups in a 1:1:1 ratio 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 block and will be stratified by PPPASI total score range at baseline (≤ 20 score, 21-30 score, ≥ 31 score) and smoking status (smoking or non-smoking). 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.

At week 16, Group III subjects will be allocated in a 1:1 ratio to 1 of 2 active treatment groups. Stratification factors will be PPPASI total score range at baseline (≤ 20 score, 21-30 score, ≥ 31 score) and smoking status (smoking or non-smoking).

1.5.2. Blinding

The study site personnel, investigators, and the randomized subjects will be blinded to the subject's allocation.

The investigators and subjects will be unblinded after the last subject has completed the Week 60 visit. The end of the study is defined as the time when the last subject completes the Week 84 visit. Database locks will occur at Weeks 16, 24, 52 and 84. Additional DBLs may also occur at other times during the study. At the Week 16 DBL, the data will be unblinded to limited sponsor personnel for preparation of submission. However, medical monitors will remain blinded to the subject-level data until the last subject has completed the Week 60 visit. See Appendix 2 – Unblinding plan for details.

In general, randomization codes will be disclosed fully only after the last subject has completed the Week 60 visit. However, in order to conduct the safety monitoring and interim analysis, the randomization codes and the translation of randomization codes into treatment and control groups will be disclosed to IDMC and Statistical Support Group (SSG) who support IDMC and only for those subjects included in the safety/interim analysis.

Emergency Unblinding

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 (ie, study drug serum concentrations, antibodies to study drug, study drug preparation/accountability data, treatment allocation, biomarker and specific laboratory data) 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 database lock and unblinding.

Under normal circumstances, the blind should not be broken until the last subject has completed the Week 60 visit. 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, time, 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. Additionally, a given subject's treatment assignment may be unblinded to the sponsor, Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and site personnel to fulfill regulatory reporting requirements for serious unexpected associated adverse reactions (SUAs). A separate code break procedure will be available for use by Sponsor's Global Medical Safety (GMS) group to allow for unblinding of individual subjects to company with specific requests from regulatory or health authorities.

2. GENERAL ANALYSIS DEFINITIONS

The full analyses including subject information, efficacy, safety, pharmacokinetics, and antibody analyses will be performed for 3 planned DBLs: 24/52/84 DBLs. Subject information, primary efficacy endpoint and selected secondary efficacy and safety endpoints will be analyzed for Week 16 DBL as well. Data from these 4 planned DBLs will be analyzed in a similar manner as described in the subsequent sections.

2.1. Visit Windows

Nominal visits will be used for all by-visit analyses in the study. The study visits scheduled post enrollment should occur at the times delineated in the Time and Events Schedule of the protocol.

If a study visit occurs outside this window, the subject should then resume his or her normal dose schedule relative to the baseline visit (Week 0). The sponsor must be contacted for any significant deviation in the scheduling of a visit outside the appropriate window.

2.2. Baseline Measurements and partial/missing date rules

For each parameter, the baseline measurement is defined as the last measurement taken prior to or at the date of the first study agent administration at Week 0.

In the listings, partial/missing dates should be listed as they are entered into the database.

The purpose of imputing a partial/missing start date is to define whether the AE/Medication started whilst taking study drug or to determine the analysis period the AE/Medication/Protocol deviation should be included or to determine the treatment failure start date.

Partial/Missing Start Date:

Missing status	Imputation rules
Missing day	Impute the 1 st of the month unless month is same as month of first administration then impute first administration date.
Missing day and month	Impute 1 st January unless year is the same as first administration date

	then impute first administration date.
Completely missing	Impute first administration date unless the end date suggests it could have started prior to this in which case impute the 1 st January of the same year as the end date.

Partial/Missing End Date:

Missing status	Imputation rules
Missing day	Impute the last day of the month.
Missing day and month	Impute 31 st December.
Completely missing	For adverse event, if the start date is complete then do not impute the end date. For concomitant medications/therapies, if the start date is complete and end date is suggested to be after the first administration date, then do not impute the end date. Otherwise: if start date is prior to first administration date then impute first administration date - 1; if start date is on or after first administration date then impute last visit date.

The remaining partial dates will be handled by applying the imputation rule of assuming first of the month and first of the year, if day and month are missing, respectively. Exclude completely missing date from the calculations of durations.

2.3. Analysis Sets

2.3.1. Randomized Analysis Set

Randomized analysis set is the population of all randomized subjects at Week 0, regardless of whether or not they received the study treatment and had any post-baseline efficacy assessment. Randomized analysis set will be the primary analysis population for efficacy analyses.

2.3.2. Per-Protocol Analysis Set (PPS)

The PPS is a subset of the randomized analysis set. The per-protocol analysis set will exclude those subjects with any of the major protocol deviations which are considered to interfere with the efficacy evaluation. The major protocol deviations will be determined prior to DBL and entered into the clinical database deviation dataset. The following list of protocol deviations may affect the interpretation of the efficacy endpoints and therefore, subjects in randomized analysis set with any of these protocol deviations will be excluded from PPS:

- Subjects who did not satisfy inclusion criteria 3, 4 in the protocol
 - Has a ≥ 12 PPPASI total score at screening and at baseline.
 - Has a moderate or more severe pustules/vesicle on the palms or soles (≥ 2 PPPASI severity score) at screening and baseline.
- Subjects who did not satisfy exclusion criteria 21-31 in the protocol:
 - Has previously received CNTO 1959.

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- Has received focal infection treatment (e.g., tonsillectomy and dental therapy) within 24 weeks of the first administration of any study agent.
 - Has received any anti-TNF α biologic therapy within 12 weeks or 5 half-lives of the first administration of study drug, whichever is longer.
 - Has received any therapeutic agent directly targeted to IL-12, IL-17, or IL-23 within 24 weeks of the first administration of study drug (including but not limited to tocilizumab, ustekinumab, tildrakizumab [MK3222], secukinumab [AIN457], ixekizumab [LY2439821], or brodalumab [AMG 827])
 - Has received natalizumab, belimumab, or agents that modulate B cells or T cells (eg, rituximab, alemtuzumab, abatacept, or visilizumab) within 52 weeks of the first administration of study drug.
 - Has received phototherapy or any systemic medications/treatments that could affect palmoplantar pustulosis or efficacy 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 palmoplantar pustulosis or efficacy evaluations (including, but not limited to, corticosteroids, vitamin D3 derivatives, tacrolimus, and antibiotics) within 2 weeks of the first administration of study drug.
 - Has received any systemic medications/treatments that could affect pustulotic arthro-osteitis or efficacy evaluation of pustulotic arthro-osteitis (eg, bisphosphonates, immunosuppressants [eg, methotrexate, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, tacrolimus]) or anakinra within 4 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 24 weeks, 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.
 - 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.
 - Subjects who did not complete specified exposure to study agent :
 - Received incorrect dose at any scheduled visits before Week 16 (baseline, Week 4 or Week 12), including subjects who were randomized to Placebo but received Guselkumab, or randomized to Guselkumab but received a dose more or less than the randomized dose (100 or 200 mg).
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- Subjects who did not discontinue from study before Week 16 but did not attend Week 16 visit within the visit window specified in the Time and Events Schedule of the protocol.

Primary analysis including sensitivity analysis and major secondary analyses will be also performed using PPS for the analysis period of Week 0 through Week 16 (See section 2.4 for analysis periods).

2.3.3. Safety Analysis Set

Safety analysis set will include subjects who received at least 1 injection of study drug.

Safety analysis set will be used for summarizing the safety data (including but not limited to, AEs, SAEs, infections, serious infections, mortality, changes in laboratory assessments, and changes in vital signs) by the treatment they actually received.

Similar to randomized analysis set, a few subsets of safety analysis set will be also defined for different analysis periods (See section 2.4).

2.3.4. Pharmacokinetic and Immunogenicity Analysis Set

PK analysis set will include all subjects who received at least 1 guselkumab injection and have at least 1 PK sample evaluated for serum guselkumab concentration.

Immunogenicity analysis set will include subjects who receive at least 1 guselkumab injection and have appropriate samples for detection of antibodies to guselkumab (ie, subjects with at least 1 sample obtained after their first dose of guselkumab). PK/PD(pharmacodynamics) analysis set will include all subjects who have evaluable data of both PK and PD at the same visit which includes Week0 and at least one of Week 16, 20, 48 and 52 visit.

2.4. Analysis Periods and Treatment Groups

This study is composed by 2 study phases: double-blind phase (Week 0 through Week 60) and open-label observational phase (after Week 60). All the subjects who passed the screening are randomized at Week 0 and subjects who are randomized to placebo at Week 0 will be re-randomized at Week 16 unless subjects withdraw the study participation before Week 16. 4 DBLs are planned for this study at Week 16, Week 24, Week 52 and Week 84, respectively. Based on the above study design features, the following analysis periods and treatment groups are defined to analyze the data according to the data collection type.

Visit-by-visit data

Hereinafter in this document, visit-by-visit data is referred as those data which are collected at specified visits in the Time and Events Schedule of the protocol, such as, efficacy assessments, vital signs, 12-lead ECG and laboratory assessments.

Through Week 16

- Analyses of efficacy endpoints for placebo comparison though Week 16 will be based on the randomized analysis set and PPS (for primary endpoints and selected secondary endpoints) and will be summarized by the following treatment groups:
 - **Placebo:** subjects randomized to placebo group at Week 0.
 - **Guselkumab 100 mg:** subjects randomized to guselkumab 100 mg at Week 0.
 - **Guselkumab 200 mg:** subjects randomized to guselkumab 200 mg at Week 0.
- Analyses of safety endpoints for placebo comparison though Week 16 will be based on the safety analysis set and will be summarized by the following treatment groups:
 - **Placebo:** subjects who received placebo at Week 0.
 - **Guselkumab 100 mg:** subjects who received guselkumab 100 mg at Week 0.
 - **Guselkumab 200 mg:** subjects who received guselkumab 200 mg at Week 0.

From Week 16 through Week 24/52/84

- Analyses of efficacy endpoints from Week 16 though Week 24/52/84 will be based on the following treatment groups:
 - **Placebo → Guselkumab 100 mg:** subjects randomized to placebo group at Week 0 and randomized to Guselkumab 100 mg at Week 16.
 - **Placebo → Guselkumab 200 mg:** subjects randomized to placebo group at Week 0 and randomized to Guselkumab 200 mg at Week 16.
 - **Guselkumab 100 mg:** subjects randomized to guselkumab 100 mg at Week 0.
 - **Guselkumab 200 mg:** subjects randomized to guselkumab 200 mg at Week 0.
- Analyses of safety endpoints from Week 16 though Week 24/52/84 will be based on the following treatment groups:
 - **Placebo → Guselkumab 100 mg:** subjects received placebo at Week 0 and received Guselkumab 100 mg at Week 16.
 - **Placebo → Guselkumab 200 mg:** subjects received placebo at Week 0 and received Guselkumab 200 mg at Week 16.
 - **Guselkumab 100 mg:** subjects who received guselkumab 100 mg at Week 0.
 - **Guselkumab 200 mg:** subjects who received guselkumab 200 mg at Week 0.

To summarize the visit-by-visit data, for Week 24 DBL, 2 analysis periods (from Week 0 through Week 16 and from Week 16 through Week 24) will be included, whilst for Week 16/52/84 DBL, only 1 analysis period (for Week 16 DBL: from Week 0 through Week 16; for Week 52 DBL: from Week 16 through Week 52; for Week 84 DBL: from Week 16 through Week 84) will be included.

Summary data

Hereinafter in this document, summary data is referred as those safety data which are collected at any time throughout the study, such as, adverse events and concomitant medications.

Through Week 16

- Analyses of safety summary data for placebo comparison through Week 16 will be based on the safety analysis set and will be summarized by the following treatment groups:
 - **Placebo:** subjects who received placebo at Week 0.
 - **Guselkumab 100 mg:** subjects who received guselkumab 100 mg at Week 0.
 - **Guselkumab 200 mg:** subjects who received guselkumab 200 mg at Week 0.

Through Week 24/52/84

- Analyses of safety summary data for placebo comparison through Week 24/52/84 will be based on the safety analysis set and will be summarized by the following treatment groups:
 - **Placebo:** subjects who received placebo at Week 0. Only the safety events that occurred while the subjects had been receiving placebo only will be included in this group.
 - **Placebo → Guselkumab 100 mg:** subjects who received placebo at Week 0 and later crossed over to receive guselkumab 100 mg at Week 16. Only the safety events from these subjects that occurred on and after their first administration of guselkumab will be included in this group.
 - **Placebo → Guselkumab 200 mg:** subjects who received placebo at Week 0 and later crossed over to receive guselkumab 200 mg at Week 16. Only the safety events from these subjects that occurred on and after their first administration of guselkumab will be included in this group.
 - **Guselkumab 100 mg:** subjects who received guselkumab 100 mg at Week 0. All the safety events from these subjects that occurred at and after Week 0 will be included in this group.
 - **Guselkumab 200 mg:** subjects who received guselkumab 200 mg at Week 0. All the safety events from these subjects that occurred at and after Week 0 will be included in this group.

To summarize the safety summary data, for Week 24 DBL, 2 analysis periods (from Week 0 through Week 16 and from Week 0 through Week 24) will be included, whilst for Week 16/52/84 DBL, only 1 analysis period (for Week 16 DBL: from Week 0 through Week 16; for Week 52 DBL: from Week 0 through Week 52; for Week 84 DBL: from Week 0 through Week 84) will be included.

PK, immunogenicity and PK/PD analysis

From Week 0 through Week 24/52/84

- **Placebo → Guselkumab 100 mg:** subjects who received placebo at Week 0 and later crossed over to receive guselkumab 100 mg at Week 16.
- **Placebo → Guselkumab 200 mg:** subjects who received placebo at Week 0 and later crossed over to receive guselkumab 200 mg at Week 16.
- **Guselkumab 100 mg:** subjects who received guselkumab 100 mg at Week 0.
- **Guselkumab 200 mg:** subjects who received guselkumab 200 mg at Week 0.

2.5. Data cut-off for Week 16, 24 and 52

The selections of data to be included in the analysis period though Week 16/24/52 will be done by determining a patient specific Week 16/24/52 cut-off date and including all data measured and observed up to the this cut-off date in the Week 16/24/52 analyses. The patient specific cut-off date is defined as:

- The Week 16/24/52 visit date in patients who had Week 16/24/52 visit.
- Patients who discontinued prior to Week 16/24/52 visit have no cut-off date and all their data should be included in the Week 16/24/52 analyses. A discontinuation with the discontinued study day $\leq 112/168/364$ will be considered as discontinuation prior to Week 16/24/52 visit.
- For patients who had no Week 16/24/52 visit and did not discontinue prior to Week 16/24/52 visit, the cut-off date for Week 16/24/52 will be the last visit date up to study day (day relative to the first day of treatment, which is day 1) of Week 18/26/56. An upper limit of study day 126/182/392 will be used for the selection of cut-off data to avoid the inclusion of data obtained at a late discontinuation visit. Week 18/26/56 has been defined as half way between scheduled Week 16/24/52 visit and scheduled Week 20/28/60 visit.
- For visit-by-visit data, the data accrued at the visits took place before or at the cut-off date (visit date \leq cut-off date) will be included.
- For summary data, all events which started up to the cut-off date (start date \leq cut-off date) will be included and end dates after the cut-off date will be left unchanged, if reported.

2.6. 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 co-primary endpoints and major secondary endpoints. The subgroups for subgroup analyses include, but are not limited to, the following:

Baseline demographics:

- Sex (male, female)
- Baseline Age (< 65 years/ ≥ 65 years)
- Baseline weight (≤ 70 kg/ > 70 kg, ≤ 90 kg/ > 90 kg)

- Baseline weight (by quartiles: $< Q1$, $\geq Q1$ and $< Q2$, $\geq Q2$ and $< Q3$, $\geq Q3$)
- BMI (Normal (<25)/Overweight (≥ 25))

Baseline disease characteristics:

- Age at diagnosis (years) ($<25/\geq25$)
- Palmoplantar pustulosis disease duration (years) ($<15/\geq15$)
- Baseline PPPASI (rounding value ≤ 20 , 21-30, ≥ 31)
- Baseline PPSI (≤ 3 , 4-9, >9)
- PGA score (<4 , ≥ 4)
- Baseline DLQI ($<10/\geq10$)
- Baseline smoking status (smoking/non-smoking)

Palmoplantar pustulosis medication history:

- Phototherapy (ultraviolet B light [UVB] or psoralen and ultraviolet A light therapy [PUVA]) (Never used, Ever used)
- Non-biologic systemics (PUVA, methotrexate, cyclosporine, acitretin, or apremilast, tofacitinib) (Never used, Ever used)
- Biologics (etanercept, infliximab, adalimumab, alefacept, efilizumab, ustekinumab, briakinumab, secukinumab, ixekizumab, or brodalumab) (Never used, Ever used)
- Non-biologic systemics or biologics (as defined above) (Never used, Ever used)
- Anti-TNF α agent (etanercept, infliximab, adalimumab) (Never used, Ever used)
- IL-12/23 inhibitors (ustekinumab, briakinumab) (Never used, Ever used)
- IL-17 inhibitors (secukinumab, ixekizumab, or brodalumab) (Never used, Ever used)
- Had an inadequate response to, or had a contraindication to any of the three non-biologic systemics therapies (PUVA, methotrexate, or cyclosporine) (Yes, No)
- Had an inadequate response to, or had a contraindication to any of the four biologic systemics therapies (etanercept, infliximab, adalimumab, or ustekinumab) (Yes, No)
- Had an inadequate response to, or had a contraindication to etanercept (Yes, No)

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

3.1. Interim Analysis

An interim analysis is planned when approximately 40% of the 150 randomized subjects have completed Week 16 visit or have ended study participation before Week 16 visit. Details of the plan for the interim analysis will be specified in the IDMC statistical analysis plan document.

3.2. Independent Data Monitoring Committee Review

An external IDMC has been established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study and to meet interim analysis objectives. The IDMC consists of 3 members (including 2 dermatologists and 1 statistician) who are independent of the sponsor. None of the members is participating as an investigator in the current study.

The major function of the IDMC is to monitor the safety of the study agent by reviewing the serious adverse events (SAEs) each month and by reviewing the study safety data approximately every 4 months. The content of the safety summaries for safety review and efficacy summaries for interim analysis are defined and documented in the IDMC statistical analysis plan developed by sponsor. An independent statistical supporting group, provided by EPS Corporation, supports the IDMC and is the liaison between sponsor and the DMC.

In addition, the IDMC roles and responsibilities, and the general procedures (including communications) are defined and documented in the IDMC Charter developed by sponsor detailing the safety data monitoring and interim efficacy review to be conducted by the IDMC.

4. SUBJECT INFORMATION

Unless specified otherwise, a ‘Guselkumab combined’ column that combines all guselkumab groups and a ‘Total’ column that combines guselkumab treatment groups and placebo will be presented as well. All subject information data will be listed in the patient listings.

Descriptive statistics (mean, median, standard deviation [SD], interquartile range, maximum, and minimum for continuous variables, and counts and percentages for discrete variables) will be used to summarize the data. In addition, subject listings will also be used to present the data.

4.1. Demographics and Baseline Characteristics

The following subjects’ demographic and disease characteristics variables will be summarized for Week 16 DBL for the randomized subjects at Week 0 by the treatment group to which they were randomized:

Demographics

- Age (mean and categories of $< 65/\geq 65$ years)
- Sex (male/female)
- Ethnicity (Hispanic or Latino/Not Hispanic or Latino/Not Reported/Unknown)
- Race (White/Black or African American/Asian, American Indian or Alaska Native/Native Hawaiian or other Pacific Islander/Other/Unknown/Not reported)
- Baseline weight (kg) (mean and categories of ≤ 70 kg/ > 70 kg, ≤ 90 kg/ > 90 kg)
- Height (mean)
- BMI (kg/m^2) (mean and categories of Normal (< 25)/Overweight (≥ 25)): = weight (kg) / (height (m) 2)

Baseline disease characteristics:

- Age at diagnosis (years) (mean and categories of $<25/\geq 25$): calculated from date of diagnosis of palmoplantar pustulosis and date of birth.
- Palmoplantar pustulosis disease duration (years) (mean and categories of $<15/\geq 15$): calculated from date of screening and date of diagnosis of palmoplantar pustulosis.
- PPPASI score (0-72) (mean and categories of rounding value ≤ 20 , 21-30, ≥ 31)
- PPSI score (0-12) (mean and categories of ≤ 3 , 4-9, >9)
- PGA score (Clear (0)/Minimal (1)/Mild (2)/Moderate (3)/Severe (4)/Very Severe (5) and <4 , ≥ 4)
- DLQI score (0-30) (mean and categories of $<10/\geq 10$)
- EQ-5D VAS score (0-100) (mean)

Baseline substance use:

- Alcohol (Current/Former/Never)
- Smoking status (smoking/non-smoking).

In addition, the numbers and percentages of patients with medical history of interest will be provided for Week 24 DBL.

4.2. Disposition Information

Completion status of study treatment will be summarized for 4 analysis periods:

- Through Week 16 (for Week 16 DBL)
- Through Week 24 (for Week 24 DBL)
- Through Week 52 (for Week 52 DBL)
- Through Week 84 (for Week 84 DBL)

Completion status of study treatment through Week 84 will be based on the eCRF page of “Treatment Disposition at Treatment Period”.

However, completion status of study treatment through Week 16/24/52 is not captured in eCRF and will be defined as follows:

- A patient will be considered a Week 16/24/52 completer if: a) has Week 16/24/52 visit, or b) has no Week 16/24/52 visit but has not discontinued from the treatment before or on Week 16/24/52 cut-off date (i.e. no discontinuation is reported or discontinuation is reported on the eCRF page of “Treatment Disposition at Treatment Period” but with a Treatment Disposition Date greater than Week 16/24/52 cut-off date).
- A patient was considered a Week 16/24/52 non-completer if has no Week 16/24/52 visit and discontinued from the treatment before Week 16/24/52 cut-off date (i.e. discontinuation is reported on the eCRF page of “Treatment Disposition at Treatment Period” with a Treatment Disposition Date before Week 16/24/52 cut-off date).

The number of subjects who completed and discontinued study agent as well as the reasons for discontinuation of study agent will be summarized. For through Week 84, the number of subjects who discontinued study participation, and the primary reason for discontinuation of study participation will be tabulated based on the eCRF page of “Trial Disposition”.

In addition, subjects who were randomized but never treated, subjects who were unblinded during the study, subjects who discontinued the treatment through Week 24/52/84, and subjects who discontinued the study participation through Week 84, will be presented in data listings.

Analysis periods and treatment groups for the above analyses will be:

- Through Week 16 (for Week 16 DBL) by randomized treatment group at Week 0
- Through Week 24/52/84 (for Week 24/52/84 DBL)
 - **Placebo:** subjects who were randomized to placebo at Week 0. Only the discontinuations that occurred while the subjects had been receiving placebo only will be included in this group.
 - **Placebo → Guselkumab 100 mg:** subjects who were randomized to placebo at Week 0 and later randomized to guselkumab 100 mg at Week 16. Only the discontinuations from these subjects that occurred on and after their first administration of guselkumab will be included in this group.
 - **Placebo → Guselkumab 200 mg:** subjects who were randomized to placebo at Week 0 and later randomized to guselkumab 200 mg at Week 16. Only the discontinuations from these subjects that occurred on and after their first administration of guselkumab will be included in this group.
 - **Guselkumab 100 mg:** subjects who were randomized to guselkumab 100 mg at Week 0. All the discontinuations from these subjects that occurred at and after Week 0 will be included in this group.
 - **Guselkumab 200 mg:** subjects who were randomized to guselkumab 200 mg at Week 0. All the discontinuations from these subjects that occurred at and after Week 0 will be included in this group.

4.3. Treatment Compliance

Treatment compliance will be summarized over certain analysis periods:

- Through Week 16 (for Week 24 DBL)
- From Week 16 through Week 24 (for Week 24 DBL)
- From Week 16 through Week 52 (for Week 52 DBL)
- From Week 16 through Week 84 (for Week 84 DBL)

Treatment compliance will be assessed by the number and percentage of subjects who actually received the treatment which they were assigned (i.e. randomized) to at each scheduled administration visit. Thus, treatment compliance through Week 16 will be summarized by the treatment group to which they were randomized at Week 0: Placebo, Guselkumab 100 mg and Guselkumab 200 mg. Treatment compliance from Week 16 through Week 24/52/84 will be based on the subjects in randomized analysis set who continued the study participation after

Week 16. Meanwhile, subjects randomized to placebo group at Week 0, will be summarized by the treatment group to which they were randomized at Week 16: Guselkumab 100 mg and Guselkumab 200 mg and subjects who were randomized to Guselkumab at Week 0 will continue being analyzed by the randomized group at Week 0: Guselkumab 100 mg and Guselkumab 200 mg.

In addition, treatment compliance will be assessed by protocol deviations related to study agent administration (ie, incorrect dose). Treatment groups for the this analysis will be similar to Section 4.2.

4.4. Extent of Exposure

The extent of exposure will be summarized for safety analysis set of Week 24/52/84 DBLs. Descriptive statistics will be presented for number of guselkumab administrations and cumulative total dose of guselkumab.

Analysis periods and treatment groups described for summary data in section 2.4 will be also applied to the exposure data.

In addition, the average exposure (number of guselkumab administrations) and average duration of follow-up (weeks) will be shown in all adverse event tables.

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 summarized by category:

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

In addition, all protocol deviations will be listed.

Analysis periods and treatment groups for the above analyses will be similar to Section 4.2.

4.6. Prior and Concomitant Medications

Subjects' previous psoriasis medication/ therapy including previous experience with topical agents, phototherapy (UVB or PUVA), non-biologic systemic therapies (PUVA, methotrexate, acitretin, cyclosporine, tofacitinib, apremilast), biologic medications (etanercept, infliximab, efalizumab, alefacept, brodalumab, ixekizumab, secukinumab, briakinumab, adalimumab, ustekinumab), Anti-TNF α agent (etanercept, infliximab, adalimumab), IL-12/23 inhibitors (briakinumab, ustekinumab), and IL-17 inhibitors (brodalumab, ixekizumab, secukinumab) will

be summarized. For those medications even taken by any patient, total cumulative duration of treatment will be summarized as a categorical variable (≤ 3 months, > 3 months, Unknown). In addition, reasons for which subjects discontinued these medications (contraindication, inadequate response, intolerance [ie, AEs], or other) will be summarized. When summarizing the total cumulative duration and reasons for discontinuing the medications, medications/therapies will be classified as 4 categories: topical agents, phototherapy (UVB or PUVA), non-biologic systemic medications (methotrexate, acitretin, cyclosporine, tofacitinib, apremilast) and biologic medications (etanercept, infliximab, efalizumab, alefacept, brodalumab, ixekizumab, secukinumab, briakinumab, adalimumab, ustekinumab).

General concomitant medications and concomitant phototherapy will be summarized by medication/phototherapy category (as per eCRF) and indication. Subjects who received concomitant corticosteroids for indications other than palmoplantar pustulosis and/or pustulotic arthro-osteitis will be listed.

The prior and concomitant medications will be summarized for Week 24/52/84 DBLs. Analysis periods and treatment groups described for summary data in section 2.4 will be applied to analyze the concomitant medications and concomitant phototherapy.

4.7. Smoking status

Smoking status is considered to be an important factor to influence the treatment effect. Smoking status will be summarized for the following analysis periods and visits:

- Through Week 24 (for Week 24 DBL): Screening~Week 0, Week 0~Week 12, Week 12~Week 24
- Through Week 52 (for Week 52 DBL): Screening~Week 0, Week 0~Week 12, Week 12~Week 24, Week 24~Week 36, Week 36~Week 48, Week 48~Week 52
- Through Week 84 (for Week 84 DBL): Screening~Week 0, Week 0~Week 12, Week 12~Week 24, Week 24~Week 36, Week 36~Week 48, Week 48~Week 60, Week 60~Week 72, Week 72~Week 84

The average daily cigarette consumption will be derived for each patient by visit and then summarized by treatment group. Non-smoker will be treated as 0 consumption per day.

A categorical variable reflecting the smoking status (Smoking, Non-smoking) at baseline will be derived for each subject based on the eCRF page of “Substance Use Tobacco”. If the first treatment date of a subject is included in any period with reported cigarette consumption more than 0, this subject will be considered “Smoking” at baseline; otherwise will be considered “Non-smoking” at baseline. Partial/missing smoking start dates or end dates will be imputed in the rules as described in Section 2.2. This derived smoking status at baseline will be used as the adjusted variable instead of the smoking status variable from IWRS in the efficacy analyses of next section.

5. EFFICACY

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. All efficacy data will be listed in the patient listings.

All the efficacy analyses described in this section will be performed for Week 24/52/84 DBLs, whilst for Week 16 DBL, the primary analysis (Section 5.2.2), the major secondary analyses (Section 5.3.2) as well as selected other secondary analyses will be performed. Note that the general definitions for analysis periods and treatment groups described in section 2.4 and general data cut-off rules for Week 16/24/52 weeks described in section 2.5 are applicable for efficacy analyses. A ‘Guselkumab combined’ column that combines guselkumab 100 mg and 200 mg groups will be presented.

5.1. General Data Handling Rules

General data handling rules used for multiple efficacy endpoints are provided in this section. Specific data handling rules for reporting purposes related with individual efficacy endpoint are provided along with the definition for that endpoint.

5.1.1. Treatment Failure

Treatment Failure Criteria

During the study period from Week 0 to Week 16, subjects who discontinue study agent due to lack of efficacy or an AE of worsening of palmoplantar pustulosis, or who started a protocol-prohibited medication/therapy that could improve palmoplantar pustulosis are considered treatment failures.

The particular protocol-prohibited medications/therapies include:

Topical Therapies:

- Any topical therapies used for palmoplantar pustulosis (with the exception of topical moisturizers only: a list of Standardized Medication Names for topical moisturizers will be selected based on medical review and documented in DPS).

Phototherapy or Systemic Therapies:

- Any systemic corticosteroid used for an indication of “Palmoplantar Pustulosis” or “Pustulotic Arthro-Osteitis” with the exception of intra-articular corticosteroids.
- Any other anti-psoriatic systemic therapy or biologic therapy.
- Phototherapy of UVB or PUVA or any other phototherapy for an indication of “Palmoplantar Pustulosis”.

Treatment Failure Rules

For subjects who meet a treatment failure criterion specified in section 5.1.1 during the analysis period from Week 0 through Week 16, with respect to the attending visits after TF until Week 16, the baseline values will be assigned regardless of the observed data for continuous endpoints,

zero will be assigned to improvement and percent improvement, and a nonresponder status will be assigned to binary response variables. Note that TF data handling rule will NOT be applied to the analysis periods other than from Week 0 through Week 16.

5.1.2. Missing Data imputation

From Week 0 through Week 60

After the treatment failures are applied to the period from Week 0 through Week 16, the remaining missing data will be handled with last scheduled observation (irrespective of baseline or post-baseline) carried forward (LOCF) for overtime summaries of the efficacy analyses.

From Week 60 until Week 84

No imputation will be performed for missing data (eg, lost to follow-up, missed study visit) and the values will remain as missing.

5.2. Primary Efficacy Endpoint

Primary endpoint of this study is change from baseline in PPPASI total score at Week 16.

5.2.1. Definition

PPPASI

The PPPASI assesses the severity of palmoplantar pustulosis lesions and their response to therapy. In the PPPASI system, the palms and soles are divided into 4 regions: the right palm, left palm, right sole, and left sole, which account for 20%, 20%, 30%, and 30%, respectively, of the total surface area of the palms and soles. Each of these areas is assessed separately for erythema, pustules/vesicle and desquamation/scale, which are each rated on a scale of 0 to 4. The PPPASI produces a numeric score that can range from 0 to 72. A higher score indicates more severe disease.

5.2.2. Analysis Methods

The change from baseline in PPPASI total score through Week 16 will be analyzed using an MMRM with treatment (CNTO 1959 high dose, CNTO 1959 low dose, or placebo), smoking status (smoking or non-smoking), week (2, 4, 8, 12, 16), and treatment-by-week interaction as fixed effects and baseline PPPASI score as a covariate. After the application of treatment failure rules (see section 5.1.1), the un-imputed PPPASI data (without LOCF (see section 5.1.2)) will be used for MMRM analyses and data is assumed to be missing at random (MAR). An unstructured covariance structure will be used to model the within-patient error. If the model with unstructured covariance structure doesn't converge, the compound symmetry structure will be used. Based on the MMRM model described above, treatment effects of CNTO 1959 groups versus placebo group at Week 16 will be estimated based on the differences of least-square (LS) means. The p-values for the LS mean differences along with the 2-sided 95% CIs will be presented.

The study will be considered positive if the guselkumab 200 mg group is significantly different from the placebo group in the primary endpoint. A fixed-sequence testing procedure will be used to control the overall Type I error rate at the 0.05 level for the primary endpoint. Specifically, the high dose group (i.e., CNTO 1959 200 mg) will first be compared with the placebo group at the 2-sided 0.05 level of significance. Only if this test is positive will the low dose group (i.e., CNTO 1959 100 mg) be compared with the placebo dose group at the 2-sided 0.05 level of significance.

Reference SAS codes for MMRM analysis are provided in Appendix 1.

5.2.3. Data Handling

Subjects who meet treatment failure criteria specified in Section 5.1.1 prior to Week 16 will have their baseline values assigned to the attending visits after TF until Week 16.

5.2.4. Sensitivity Analysis

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

Sensitivity Analysis 1

MMRM analysis described earlier for the primary analysis will be repeated using the data without applying treatment failure rules, i.e. the observed data.

Sensitivity Analysis 2

The primary endpoint (change from baseline in PPPASI total score at Week 16) will be analyzed using an ANCOVA model with treatment (CNTO 1959 high dose, CNTO 1959 low dose, or placebo) and smoking status (smoking or non-smoking) as factors and baseline PPPASI score as a covariate, based on the data after applying treatment failure rules (as defined in Section 5.1.1).

Sensitivity Analysis 3

ANCOVA analysis performed for Sensitivity Analysis 2 will be repeated using the data after applying treatment failure rules (as defined in Section 5.1.1) and LOCF (as defined in Section 5.1.2).

5.2.5. Subgroup Analysis

The subgroup analysis by each subgroup variable defined in Section 2.6 will be carried out using the primary efficacy model - MMRM model given earlier (Section 5.2.2), with the additional fixed effect of subgroup variable. For instance, to investigate the sex subgroup, the MMRM model will include treatment, smoking status, sex, week, treatment-by-week interaction, sex-by-week interaction, sex-by-treatment interaction and sex-by-treatment-by-week interaction as fixed effects and the covariate baseline. The results from subgroup analyses will be presented graphically by a forest plot, which shows the least-square (LS) means difference between the guselkumab treatment groups and placebo group and its 95% confidence interval (when the number of subjects permits).

5.2.6. Per-Protocol Analysis

The primary analysis (Section 5.2.2) will also be performed on per-protocol analysis set (Section 2.3.2).

5.3. Major Secondary Endpoints

5.3.1. Definition

PPSI

The PPSI assesses the severity of palmoplantar pustulosis lesions and their response to therapy with a score ranging from 0 to 12. In the PPSI system, the more severely affected location (palms or soles) will be identified as the evaluation sites at screening. The identified site will be assessed at all subsequent visits. Evaluation sites are assessed separately for erythema, pustules/vesicle and desquamation/scale, for the most severe skin lesion rated on a scale of 0 to 4.

PPPASI 50 Responder

Subjects with $\geq 50\%$ improvement in PPPASI from baseline will be considered PPPASI 50 responders.

5.3.2. Analysis Methods

The change from baseline in PPSI through Week 16 will be analyzed using the same MMRM model as described for the PPPASI, except for including the baseline PPSI score, instead of baseline PPPASI score, as the covariate. Treatment effects of CNTO 1959 groups versus placebo group will be estimated based on the differences of least-square (LS) means. The p-values for the LS mean differences along with the 2-sided 95% CIs will be presented. This MMRM analysis will be based on the PPSI data with the application of treatment failure rules.

The proportion of subjects who achieve a PPPASI-50 at Week 16 will be compared between the CNTO 1959 treatment groups and placebo group using a CMH chi-square test stratified by baseline PPPASI total score (≤ 20 , 21-30, ≥ 31) and smoking status (smoking or non-smoking). This analysis will be based on the PPPASI data with the application of treatment failure rules and LOCF.

Major secondary endpoints of this study are not prospectively powered and all p-values reported for secondary endpoints will not adjust for multiple comparisons.

5.3.3. Data Handling

Data handling rules specified in Section 5.1 will be applied to the major secondary analyses.

5.3.4. Subgroup Analysis

Subgroup analyses for PPSI will be conducted in a similar manner as for the primary endpoint described in Section 5.2.5.

For the proportion of subjects who achieve a PPPASI-50 at Week 16, the difference between the guselkumab treatment groups and placebo group and its 95% confidence interval (when the

number of subjects permits) will be presented for each of the subgroups defined in Section 2.6 in a forest plot.

5.3.5. Per-Protocol Analysis

The analyses for major secondary endpoints (Section 5.3.2) will also be performed on per-protocol analysis set (Section 2.3.2).

5.4. Other Secondary Endpoints

5.4.1. Definition

PPPASI-75, 90, 100 Responder

Subjects with $\geq 75/90/100\%$ improvement in PPPASI from baseline will be considered PPPASI 75/90/100 responders.

PPSI-50, 75, 90, 100 Responder

Subjects with $\geq 50/75/90/100\%$ improvement in PPSI from baseline will be considered PPSI 50/75/90/100 responders.

Physician's Global Assessment

The PGA documents the Physician's Global Assessment of the subject's palmoplantar overall skin lesions status. The patient's palmoplantar pustulosis is assessed as clear (0), almost clear (1), mild (2), moderate (3), severe (4), or very severe (5).

Efficacy endpoints related to the PGA score are defined below:

PGA clear or almost clear responder

Subjects who achieve a PGA score of clear (0) or almost clear (1) will be considered PGA clear or almost clear responders.

PGA clear or almost clear or 2-grade improvement responder

Subjects who achieve a PGA score of clear (0) or almost clear (1), or have at least a 2-grade improvement from baseline will be considered PGA clear or almost clear or 2-grade improvement responder responders.

Dermatology Life Quality Index (DLQI)

The DLQI is a dermatology-specific quality of life instrument designed to assess the impact of the disease on a subject's quality of life. It is a 10-item PRO questionnaire that, in addition to evaluating overall quality of life, can be used to assess 6 different aspects that may affect quality of life: symptoms and feelings (items 1 and 2), daily activities (items 3 and 4), leisure (items 5 and 6), work or school performance (items 7), personal relationships (items 8 and 9), and treatment (items 10). The DLQI is calculated by summing the score of each component resulting in a maximum of 30 and a minimum of 0. A higher score indicates more severe disease.

DLQI data will be handled as below:

- If two or more response options are ticked for one question, the response option with the highest score should be recorded.
- Regarding question 7, if it is answered 'yes', it will be scored 3. If it is answered 'no' or 'not relevant', but the following question is not answered or answered 'Not at all', it will be scored 0. If it is answered 'no' or 'not relevant' and either 'a lot' or 'a little' is ticked for the following question, it will be scored 2 (a lot) or 1 (a little).
- If one question's answer is not available, this question will be scored 0. The total score will then be calculated.
- If two or more questions' answers are unavailable, the questionnaire is not scored. Hence, the total score will be set to missing.
- If one question from one of the 6 component scores is missing, the affected component score will be set to be missing.

EQ-5D

The EQ-5D is designed for self-completion by subjects and consists of 2 pages - the EQ-5D descriptive system and the EQ visual analog scale (EQ VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and unable. The EQ VAS records the respondent's self-rated health on a vertical, visual analog scale where the endpoints are labeled 'Best imaginable health state' (score of 100) and 'Worst imaginable health state' (score of 0). EQ-5D descriptive system can be converted into a single summary EQ-5D Index¹. EQ-5D index scores in this analysis will be derived based on the Japanese population.

SF-36

The SF-36 consists of 8 subscales: limitations in physical functioning due to health problems, limitations in usual role activities due to physical health problems, bodily pain, general mental health (psychological distress and well-being), limitations in usual role activities due to personal or emotional problems, limitations in social functioning due to physical or mental health problems, vitality (energy and fatigue), and general health perception. These subscales are scored from 0 to 100 with higher scores indicating better health. Another algorithm yields 2 summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

Table 2 SF-36 subscales and items

Subscales	Items
Physical functioning	3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j
Role limitations due to physical health	4a, 4b, 4c, 4d

Role limitations due to emotional problems	5a, 5b, 5c
Energy/ fatigue	9a, 9e, 9g, 9i
Emotional well being	9b, 9c, 9d, 9f, 9h
Social functioning	6, 10
Pain	7, 8
General health	1, 11a, 11b, 11c, 11d

Calculations for 8 subscales and summary scores will be based on the recommended algorithms described in Chapter 7 (Scoring the SF-36) of the SF-36 user's manual (Japanese Edition version 2)² Subscales are calculated whenever $\geq 50\%$ of the items that comprise the individual subscale are available (nonmissing). Any missing items will be estimated using the average value across the nonmissing items for that subscale. If $< 50\%$ of the items that comprise the subscale is available, the subscale will not be calculated. If any of the individual subscales that comprise the physical component score or the mental component score are missing, then the physical or mental component summary scores cannot be calculated.

MRI

MRI will be performed only for those subjects who had a diagnosis of PAO at screening. MRI image of PAO will be centrally evaluated. The MRI score will be globally assessed as None, Mild, Moderate, Severe, or Not Applicable.

5.4.2. Analysis Methods

An over-time descriptive analysis will be undertaken for the following efficacy endpoints:

- Observed value, change and percent improvement ($=(\text{baseline} - \text{post-baseline}) / \text{baseline} * 100\%$) from baseline in PPPASI total score
- Observed value, change and percent improvement ($=(\text{baseline} - \text{post-baseline}) / \text{baseline} * 100\%$) from baseline in PPSI total score
- Proportion of PPPASI-50, 75, 90, 100 responder
- Proportion of PPSI-50, 75, 90, 100 responder
- Proportion of subjects achieving 0 (none) or 1 (slight) in PPSI sub scores (erythema, pustular/vesicle, desquamation/scale)
- Observed PGA score
- Proportion of PGA clear or almost clear responder
- Proportion of PGA clear or almost clear or 2-grade improvement responder
- Observed values and change from baseline in DLQI
- Observed values and change from baseline in EQ-5D index and VAS score

- Observed values and change from baseline in EQ-5D in PAO subjects
- Observed values and changes from baseline in SF-36 PCS and MCS score
- Observed MRI score in PAO subjects

Change from baseline in DLQI, EQ-5D and SF-36 PCS and MCS score through Week 16 will be analyzed using a MMRM model with treatment (CNTO 1959 high dose, CNTO 1959 low dose, or placebo), smoking status (smoking or non-smoking), week (2, 4, 8, 12, 16), and treatment-by-week interaction as fixed factors and baseline correspondent score as a covariate. The proportions of PPPASI-75/90/100, PPSI-50/75/90/100, PGA clear or almost clear, PGA clear or almost clear or 2-grade improvement responder at Week 2, 4, 8, 12, 16 will be analyzed using the same stratified CMH chi-square test for PPPASI-50 (Section 5.3.2).

Line plots of over-time Mean \pm SD will be produced for observed value, change from baseline in PPPASI and PPSI total score by treatment group. Proportions of subjects achieving PPPASI-50 response by treatment group at all scheduled visits will be shown using the line plots as well.

5.4.3. Data Handling

Data handling rules specified in Section 5.1 will be applied to the other secondary endpoints. Note that MMRM analyses will be based on the data after applying treatment failure rules (as defined in Section 5.1.1) only and other analyses will be based on the data after applying both treatment failure rules (as defined in Section 5.1.1) and LOCF (as defined in Section 5.1.2).

6. SAFETY

Safety will be assessed by summarizing the incidence and type of AEs, and examining changes in vital signs and laboratory parameters (hematology and chemistry) and electrocardiogram (ECG) parameters. Safety evaluation will be based on safety set. All safety data will be listed in the patient listings.

All the safety analyses described in this section will be performed for Week 24/52/84 DBLs, whilst for Week 16 DBL, only the tables for all TEAEs and SAE will be provided. Note that the general definitions for analysis periods and treatment groups described in section 2.4 and general data cut-off rules for Week 16/24/52 weeks described in section 2.5 are applicable for safety analyses. A ‘Guselkumab combined’ column that combines all guselkumab groups (100 mg or 200 mg or placebo \rightarrow 100 mg or placebo \rightarrow 200 mg) will be presented.

6.1. Adverse Events

Treatment-emergent AEs (TEAEs) will be summarized by system organ class and preferred term defined by the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs are those AEs that occurred after the start of initial study agent administration and those AEs that were present at baseline but worsened in severity after the start of initial study agent administration.

The following TEAEs summary tables will be provided:

- Any AEs

- Frequent AEs: defined as TEAEs with occurrence in 2 or above of patients in ‘Guselkumab combined’ group
- SAEs
- AEs that are reasonably related to study agent
- AEs that lead to permanent discontinuation of study agent administration
- AE by intensity
- Injection-site reactions
- Infections
- Serious infection
- Infections require oral or parenteral antimicrobial treatment

These summary tables will provide the count and percentage of subjects with 1 or more of the specified TEAEs by treatment group. Frequent TEAEs, defined as TEAEs with occurrence in more than 2 patients in ‘Guselkumab combined’ group, will be summarized in a separate table. For Week 52/84 DBL, the frequency and timing of TEAEs onset after the first study drug administration will be characterized by a TEAE table by onset period. If a TEAE has multiple occurrences on one subject, the earliest occurrence will be used for this analysis. In addition to the summary tables, listings of subjects with the following TEAEs will be provided: SAEs, AEs of severe intensity, AEs of psoriasis, AEs leading to permanent discontinuation of study injections, and possible serum sickness like reactions and anaphylactic reactions.

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

Since safety should be assessed relative to exposure and follow-up, all AE summary tables will summarize the average weeks of follow-up and the number of administration for each treatment group.

6.2. Clinical Laboratory Tests

Analysis on Laboratory data will be based on the following clinical hematology and chemistry parameters:

- Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC), platelet count, lymphocytes, neutrophils, eosinophils, monocytes, basophils
- Chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), total carbon dioxide (CO₂), total bilirubin, blood urea nitrogen/Urea, calcium (and calcium corrected), chloride, creatinine, glucose, potassium, total protein, sodium, hsCRP, HbA1c, total cholesterol, LDL, HDL, total cholesterol to HDL ratio, triglycerides

Summaries of observed values and changes from baseline will be presented by scheduled visit for each laboratory analytic. All values lower than LLOQ concentrations will be treated as the value of LLOQ in the summary statistics. For selected hematology analytics (hemoglobin,

hematocrit, RBC, WBC, platelet count) and all chemistry analytics, box plots will be provided for observed values and change from baseline by scheduled visit.

The number and percentage of subjects by maximum post-baseline Common Terminology Criteria for Adverse Events (CTCAE) Grade will be summarized for the laboratory variables with CTCAE toxicity grading criteria available in Table 3 below. To evaluate the maximum post-baseline CTCAE grade, all the post-baseline data, including the measurements from scheduled and unscheduled post-baseline visits, will be utilized. In addition, a listing of subjects with 1 or more CTCAE toxicity grade ≥ 2 in hematology and clinical chemistry laboratory measurements will be provided. Abnormalities in selected laboratory parameters (Alanine aminotransferase increased, Aspartate aminotransferase increased, Total bilirubin increased, Platelet count decreased, Neutrophils decreased) will be further investigated by shift tables from the baseline (categories: 0, ≥ 1) to the maximum post-baseline CTCAE grade (categories: 0, 1, 2, 3, 4) through Week 24/52/84. Treatment groups described in section 2.4 for summary data will be applied to this analysis.

Table 3 Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03)

Laboratory analytic	Unit	Grading Criteria			
		Grade 1	Grade 2	Grade 3	Grade 4
Hematology					
Hemoglobin decreased	g/L	< LLN - 100	<100 - 80	<80	-
WBC decreased	10e9 /L	<LLN - 3.0	<3.0 - 2.0	<2.0 - 1.0	<1.0
Platelet count decreased	10e9 /L	<LLN - 75.0	<75.0 - 50.0	<50.0 - 25.0	<25.0
Lymphocytes decreased	10e9 /L	<LLN - 0.8	<0.8 - 0.5	<0.5 - 0.2	<0.2
Neutrophils decreased	10e9 /L	<LLN - 1.5	<1.5 - 1.0	<1.0 - 0.5	<0.5
Chemistry					
Albumin decreased	g/L	<LLN - 30	<30 - 20	<20	-
Alkaline phosphatase increased	-	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alanine aminotransferase increased	-	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Aspartate aminotransferase increased	-	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Total bilirubin increased	-	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Calcium corrected increased	mmol/L	>ULN - 2.9	>2.9 - 3.1	>3.1 - 3.4	>3.4
Calcium corrected decreased	mmol/L	<LLN - 2.0	<2.0 - 1.75	<1.75 - 1.5	<1.5

Creatinine increased	-	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
Glucose increased	mmol/L	>ULN - 8.9	>8.9 - 13.9	>13.9 - 27.8	>27.8
Potassium increased	mmol/L	>ULN - 5.5	>5.5 - 6.0	>6.0 - 7.0	>7.0
Sodium increased	mmol/L	>ULN - 150	>150 - 155	>155 - 160	>160
Sodium decreased	mmol/L	<LLN - 130	-	<130 - 120	<120
Cholesterol increased	mmol/L	>ULN - 7.75	>7.75 - 10.34	>10.34 - 12.92	>12.92
Triglycerides increased	mmol/L	>ULN - 3.42	>3.42 - 5.7	>5.7 - 11.4	>11.4

LLN=Lower Limit; ULN=Upper Limit.

6.3. Vital Signs and weight

Vital signs and weight will be measured at scheduled visits as per the TIME AND EVENTS SCHEDULE in protocol. Descriptive statistics of heart rate, systolic blood pressure, diastolic blood pressure, temperature and weight values and changes from baseline will be summarized by scheduled visit.

6.4. Electrocardiogram

The ECG continuous variables including heart rate, RR interval, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: QT corrected according to Bazett's formula (QTcB) and QT corrected according to Fridericia's formula (QTcF) will be summarized for the observed values and changes from baseline by scheduled visit.

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

7. PHARMACOKINETICS/IMMUNOGENICITY AND OTHER EXPLORATORY EVALUATIONS

7.1. Pharmacokinetics

Blood samples for measuring serum guselkumab concentrations will be collected from all subjects at the specified visits as indicated in the TIME AND EVENTS SCHEDULE in protocol. Pharmacokinetics analyses will be based on the PK analysis set (section 2.3.4).

All PK data including actual sampling time will be listed. All serum guselkumab 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 dataset. All subjects and samples excluded from the analysis will be clearly documented.

Serum guselkumab concentrations over time from Week 0 through Week 24/52/72 will be summarized by the treatment group defined as section 2.4 (see definition of treatment group in pharmacokinetics analyses in section 2.4) for each scheduled visit with arithmetic mean, SD, coefficient of variation (%CV), median, minimum, maximum, 25% quartile and 75% quartile

Serum guselkumab concentrations over time from Week 0 to Week 24/52/72 will be also summarized by the following subgroup:

- Baseline weight category (≤ 70 kg/ > 70 kg, ≤ 90 kg/ > 90 kg)
- Baseline weight (by quartiles)
- Antibodies to guselkumab status by subject positive/negative through Week 24/52/72 or (If the incidence of subject positive is low, the former will be selected. If appropriate, summary by category of titer level for positive subject will be considered.)

Number of subjects with serum guselkumab concentrations below the lowest quantifiable concentration in a sample (less than $0.01\mu\text{g/mL}$) will be tabulated by scheduled visit and the treatment group. This table will be also generated by weight category (≤ 70 kg/ > 70 kg).

PK concentration data from Week 0 to Week 24/52/72 will be also displayed graphically by following figures.

- Median (IQR) of serum guselkumab concentration time profiles through Week 24/52/72 (in linear and semi-log scales) with nominal sampling time will be presented in figure by the treatment group.
- Median (IQR) figure by the treatment group will be also generated for following subgroup:
 - Baseline weight category (≤ 70 kg/ > 70 kg, ≤ 90 kg/ > 90 kg)
 - Antibodies to guselkumab status by subject positive/negative through Week 24/52/72 or at each schedule visit. (If the incidence of subject positive is low, the former will be selected.)

For descriptive statistics of serum concentration of guselkumab, the following data handling rules will be applied;

- All BQL concentrations (i.e. $<0.01\mu\text{g/mL}$) will be treated as “0” (zero) in the summary statistics.
- Serum concentrations of guselkumab data will be calculated based on the number of subjects with observed data, including BQL, at each sampling time.
- When more than half ($>50\%$) of the serum concentrations of guselkumab are BQL at each scheduled time point, mean, median, minimum and 25% quartile will be shown as ‘BQL’, and SD and %CV and 75% quartile will be shown as ‘NC’ (not calculated). Maximum observed value will be presented as maximum.

- When the number of serum concentrations data of guselkumab at each scheduled time point is less than or equal to 2, only N and mean will be calculated, and SD, %CV, median, minimum, maximum, 25% quartile and 75% quartile will be shown as ‘NC’ regardless of the number of BQL.
- If there is the data of samples without the visit time window as indicated in the TIME AND EVENTS SCHEDULE in protocol, this data will be excluded from descriptive statistics and indicated as such in the concentration data listing.
- If adequate doses are not administered (including missing dose, received a partial, incorrect, or an additional guselkumab administration), the observed data after the inadequate administration will be excluded from descriptive statistics. Of note, serum guselkumab concentrations prior to the first of such events will be included in the summaries.
- Data of samples with no information about the sampling date and time and/or the drug administration (time and dosage) will be excluded from descriptive statistics.
- Sampling time at Week 0 pre-dose will be substituted with “0” in the figure. The data point which mean of serum guselkumab concentration is BQL will be treated as LLOQ value (e.g. 0.01 µg/mL) in graph.
- The elapsed time from last dosing of PK sampling will be described in listing.

7.2. Immunogenicity Analyses

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 protocol. Immunogenicity analyses will be based on the immunogenicity analysis set (section 2.3.4).

The incidence of positive antibodies, neutralizing antibody (Nabs, as appropriate) and the maximum titers of antibodies to guselkumab from Week 0 to Week 16/52/72 will be summarized by the treatment group. A ‘Total’ column that combines all treatment groups will be also presented.

The summary of following endpoints at the following visit will be presented by the treatment group and antibodies to guselkumab status (subject positive/negative) evaluated at the same visit:

- Change from baseline in PPPASI at Week 16/52
- PPPASI-50 responder/no responder at Week 16/52
- PPPASI-75 responder/no responder at Week 16/52
- Injection-Site Reactions status through Week 16/52

If appropriate, these summary by category of titer level for positive subjects will also be considered.

As for placebo crossover groups (placebo->guselkumab 100mg , placebo->guselkumab 200 mg), the data at Week 16 will be treated as baseline. And it will be excluded from summarizing above endpoints.

A listing of individual immune response including antibody status (negative/positive), Nab status, serum maximum titers, serum guselkumab concentration, Injection-Site Reactions status , change from baseline in PPPASI total score, PPPASI-50, PPPASI-75 at all sampling time points for all subjects will be provided.

7.3. Pharmacokinetic/Pharmacodynamic Relationships

Pharmacokinetic/Pharmacodynamic analyses will be based on the PK/PD analysis set (section [2.3.4](#)).

The change from baseline score for PPPASI total score at Week 16, 20, 48 and 52 versus serum CNTO 1959 concentrations (same visit point) are plotted for each visit using the data from individual subjects (vertical axis: the change from baseline score, horizontal axis: serum guselkumab concentration).

If data permits, relationship between the proportions of PPPASI-50/75/90 responder at Week 16, 20, 48 and 52 and serum guselkumab concentration (same visit point) for subjects randomized to gusekumab at Week 0 (combined guselkumab 100 mg and 200 mg group) will be assessed by summarizing the proportions of responder by quartile of guselkumab concentration, for each schedule visit. Also, relationship between the proportions of PPPASI-50/75/90 responder at Week 20, 48 and 52 and guselkumab concentration (same visit point) for subjects randomized to placebo at Week 0 will be assessed by summarizing the proportions of responder by quartile of guselkumab concentration for each schedule visit after combined guselkumab 100 mg and 200 mg group . As for PPPASI-50/75/90 at Week 52, the relationship of these endpoints and median of trough guselkumab concentration (calculated using guselkumab concentration at Week 20, 28, 36, 44 and 52 for each subject) will be also assessed by summarizing the proportions of responder by quartile of median trough guselkumab concentration for subjects randomized to gusekumab at Week 0 (combined guselkumab 100 mg and 200 mg group).

This relationship will be also explored graphically by drawing a bar-chart whose height represents the proportion of responder for each guselkumab concentration quartile (\leq 1st quartile, $>$ 1st quartile and \leq 2nd quartile, $>$ 2nd quartile and \leq 3rd quartile, $>$ 3rd quartile).

The serum guselkumab concentration at Week 16, 20, 48 and 52 will be summarized by quartile of the change from baseline score for PPPASI total score (same visit point) for subjects randomized to gusekumab at Week 0 (combined guselkumab 100 mg and 200 mg groups), for each schedule visit. Also, the serum guselkumab concentration at Week 20, 48 and 52 will be summarized by quartile of the change from baseline score for PPPASI total score (same visit point) for subjects randomized to placebo as Week 0 for each schedule visit after combined guselkumab 100 mg and 200 mg group.

This relationship will be also explored graphically by drawing a bar-chart whose height represents the median of serum guselkumab concentration for each quartile of the change from baseline score for PPPASI total score (\leq 1st quartile, $>$ 1st quartile and \leq 2nd quartile, $>$ 2nd quartile and \leq 3rd quartile, $>$ 3rd quartile).

The difference in guselkumab concentration over time between responder and non-responder of following endpoints will be also assessed for PK/PD analysis set by summarizing serum guselkumab concentrations over time through Week 20/52 by scheduled visit, the four treatment groups (described in 2.4) and following response status of endpoints. The difference in guselkumab concentration over time between response status will be also explored graphically by drawing a median (IQ range) of serum guselkumab concentration time profiles through Week 20/52/ with nominal sampling time, by the treatment group and following response status of endpoints.

- PPPASI-50 responder/no responder at Week 20/52
- PPPASI-75 responder/no responder at Week 20/52

If the data is collected without the visit time window as indicated in the TIME AND EVENTS SCHEDULE in protocol, these data will be excluded from PK/PD analyses described in this section.

7.4. Biomarker Analyses

Biomarker samples will be used to generate serum markers and gene expression for computational analyses.

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

REFERENCES

1. 池田俊也, 白岩健, 五十嵐中, 能登真一, 福田敬, 齋藤信也, 下妻晃二郎. 日本語版 EQ-5D-5L におけるスコアリング法の開発. 保健医療科学 2015 Vol.64 No.1 p.47-55
2. Fukuhara S, Suzukamo Y. Manual of SF-36v2 Japanese version: Institute for Health Outcome & Process Evaluation research, Kyoto, 2004

APPENDIX 1 – REFERENCE SAS CODES FOR MMRM ANALYSIS

For primary analysis

```
PROC MIXED DATA=<data> METHOD=reml;  
CLASS usubjid trt week;  
MODEL chg_pppasi = pppasi_b trt week trt*week / residual CL SOLUTION DDFM=kr;  
REPEATED week / TYPE=UN SUBJECT=usubjid;  
LSMEANS trt*week / DIFF CL;  
ODS OUTPUT Tests3=t3fe LSMeans=lsmean Diffs=lsmdif;  
RUN;
```

For subgroup analysis

```
PROC MIXED DATA=<data> METHOD=reml;  
CLASS usubjid trt week sex;  
MODEL chg_pppasi = pppasi_b trt week sex sex*week sex*trt trt*week sex*trt*week/  
residual CL SOLUTION DDFM=kr;  
REPEATED week / TYPE=UN SUBJECT=usubjid;  
LSMEANS sex*trt*week / DIFF CL;  
ODS OUTPUT Tests3=t3fe LSMeans=lsmean Diffs=lsmdif;  
RUN;
```

APPENDIX 2 – UNBLINDING PLAN

Primary endpoints of this study will be evaluated at Week 16. Long-term safety and efficacy of guselkumab will continue being evaluated after Week 16. At the Week 16 DBL, pre-defined selected analyses will be performed to support sponsor's decision. At Week 24 DBL, Clinical Study Report (CSR) and Common Technical Documents (CTD) for CNTO 1959 palmoplantar pustulosis (PPP) submission will be developed and submitted to health authorities. Investigators and subjects will be blinded to the subject's allocation until the last subject has completed the Week 60 visit. However, the data will be unblinded to limited sponsor personnel for analysis at Week 16 DBL. During the period from Week 16 DBL until the last subject's Week 60 visit of the study, in order to maintain the blindness of subjects and investigators to protect the trial integrity and minimize the potential influence on the behavior of the subjects and investigators who still participate this trial, access to the unblinded data will be protected as defined in this unblinding plan.

This unblinding plan details who will be unblinded and the level of unblinding^a at Week 16 DBL. In principle, medical monitors from sponsor or Contract Research Organization (CRO) will continue to be blinded to all data, especially the subject-level data, until the last subject's Week 60 visit of the study. The responsibilities and personnel to be unblinded in each group involved in the CNTO 1959 PPP submission are as follows:

1. Sponsor

The following sponsor personnel are considered as default unblinders who are permitted to have access to subject-level data:

CNTO 1959 PPP JCoT (Japan Compound Team): CNTO 1959 PPP JCoT is a sponsor organization that is responsible for preparing the submission to health authorities. CNTO 1959 PPP JCoT members will be unblinded to subject-level data to clean/analyze the data, develop CNTO 1959 PPP CSR/CTD and make decisions.

Other CSR/CTD writers/reviewers/supporters for CNTO 1959 PPP submission: Upon CNTO 1959 PPP JCoT members' judgment, sponsor personnel other than CNTO 1959 PPP JCoT members who need to access to subject-level data to write/review/support CNTO 1959 PPP CSR/CTD can also be the default unblinders.

Default unblinders are required to give their consent ([Form 1](#)) to declare not to disclose any subject-level data to any non-default-unblinders to maintain the data integrity of this trial. The sponsor study statistician will keep a running log ([Form 2](#)) of personnel who have been unblinded to subject-level data and the date of unblinding.

^a Levels of unblinding are subject level and group level. Subject-level unblinding is defined as unblinded to individual subject treatment assignments. Group-level unblinding is defined as unblinded to aggregate treatment assignments at the treatment group level without knowledge of individual treatment assignments.

Any sponsor personnel other than the above default unblinders will not have access to subject-level data. However, group-level data may be unblinded as necessary for sponsor's decision making. When unblinding the group-level data to any sponsor personnel other than the above default unblinders, it should be clearly noted that "it's an ongoing study and all the study results disclosed are required to be confidential from the investigators and subjects of this study." and all related documentation including the log of who received the group-level data with the reasons should be kept appropriately in a sponsor Sharepoint accessible to default unblinders only. For example, when distributing the topline results (TLR) based on sponsor SOP-10292 (Preparation and Communication of Topline Results), the note of "Confidential and forwarding is strictly prohibited" should be included to avoid further dissemination, or when pursuing the advice from sponsor management team on dose selection through a meeting, notes should be conveyed in advance of presenting the group-level data.

2. Contract Research Organization:

Personnel from CRO companies who are responsible for producing the data displays or writing CNTO 1959 PPP CSR/CTD will be unblinded to subject-level data as the default unblinders. CNTO 1959 PPP JCoT members will be responsible for authorizing CRO personnel access to unblinded data. Default unblinders are required to give their consent to declare not to disclose any subject-level data to any non-default-unblinders to maintain the data integrity of this trial. The sponsor study statistician will keep a running log of personnel who have been unblinded to subject level data and the date of unblinding.

3. Health Authority

Health authorities will review CNTO 1959 PPP submission packages and therefore health authorities will have access to subject-level data.

FORM 1 UNBLINDED INFORMATION HANDLING AGREEMENT**CNTO1959PPP3001 Study: Agreement on the Unblinded Information Handling**

CNTO1959PPP3001 study is a randomized, double-blind, placebo-controlled and Japan-local study. Primary endpoints of this study will be evaluated at Week 16. Long-term safety and efficacy of guselkumab will continue being evaluated after Week 16.

Investigators and subjects will be blinded to the subject's allocation until the last subject has completed the Week 60 visit. Medical monitors from sponsor or Contract Research Organization (CRO) will also continue to be blinded to all data, especially the subject-level data^a, until the last subject's Week 60 visit of the study. During the period from Week 16 DBL until the last subject's Week 60 visit of the study, in order to maintain the blindness of subjects, investigators and medical monitors to protect the trial integrity and minimize the potential influence on the behavior of the subjects and investigators who still participate this trial, access to the unblinded subject-level data will be strictly limited to the default unblinders who have signed this agreement. A list of all default unblinders will be provided by the sponsor study statistician.

To be a default unblinders of this study, you need to fully understand the above and agree as follows:

- Not sharing any subject-level data of CNTO1959PPP3001 study with other than the default unblinders in any manner.
- Not printing any subject-level data of CNTO1959PPP3001 study.
- Immediately reporting any potential deviations from this agreement occurred in any default unblinders to sponsor study statistician of this study.
- Immediately reporting to sponsor study statistician of this study if any existing default unblinder is replaced by other responsible personnel.

This agreement shall become effective from the date of Week 16 DBL and remain valid until the last subject of this study has completed the Week 60 visit.

I consent to take special care to protect the integrity.

(Signature)

^a Levels of unblinding are subject level and group level. Subject-level unblinding is defined as unblinded to individual subject treatment assignments. Group-level unblinding is defined as unblinded to aggregate treatment assignments at the treatment group level without knowledge of individual treatment assignments.

FORM 2 RUNNING LOG OF DEFAULT UNBLINDERS

Affiliation/ Company	Function/ Department	Name	Email address	Start date (Agreement signed date)	End date	Remark