Janssen Pharmaceutical K.K.

Clinical Protocol

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 CNTO 1959 PPP3001; Phase 3
AMENDMENT 2

CNTO 1959 (guselkumab)

Status: Approved
Date: 15 December 2017
Prepared by: Janssen Pharmaceutical K.K.
EDMS number: EDMS-ERI-104552067, 4.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issued Date
Original Protocol	03 Jul 2015
Amendment INT-1	01 Sep 2015
Amendment 2	15 Dec 2017

Amendments are listed beginning with the most recent amendment.

Amendment 2 (15 December 2017)

The overall reason for the amendment: Procedure for reporting adverse events from Week 72 to 84 was changed. From Week 72 to 84, AEs considered associated with the use of the drug will be reported in order to ensure the safety of subjects and to evaluate CNTO 1959 safety throughout the study. In addition, a minor formatting and typographical errors have been corrected to improve the clarity and accuracy of the protocol text.

Applicable Section(s)	Description of Change(s)
Rationale: Error was noted.	
Protocol Amendments	Issued Date of INT-1 was corrected.
Rationale: To ensure the safety of subjects throughout the study.	
SYNOPSIS Overview of Study Design 3.1 Overview of Study Design	The following sentence was modified. Efficacy and safety will be evaluated at Week 72, and ~~also~~ the durability of clinical response and safety at Week 84.
TIME AND EVENTS SCHEDULE	The following table was modified, and the following sentence was added.

Ongoing Subject Review				
Smoking status	X	X	X----------X	
Concomitant therapy	X	X	X----------X	
Tuberculosis evaluation	X	X	X----------X	
Adverse events[m]	X	X	X----------X	X

m. All AEs will be reported from the time a signed and dated ICF is obtained until 12 weeks after the last dose of study drug (Week 72 visit or early termination visit). From Week 72 to 84, AEs considered associated with the use of the drug will be reported.

12.3.1 All Adverse Events	The following sentences were modified and added. From Week 72 to 84, AEs considered associated with the use of the drug, whether serious or non-serious, will be reported. SAEs, including those spontaneously reported to the investigator through Week 84 ~~within 12 weeks after the last dose of the study drug~~ must be reported using the Serious Adverse Event Form.
Rationale: To clarify the analyses for safety.	
11.7 Safety Analyses	The following sentence was modified. Safety data, including but not limited to, AEs, serious adverse events

	(SAEs) , infections, serious infections, mortality, changes in laboratory assessments, and changes in vital signs through Week 72 will be summarized.
11.7 Safety Analyses Adverse Events	The following sentence was added. Analysis methods for those AEs reported during after Week 72 visit will be detailed in SAP.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-1 (1 September 2015)

The overall reason for the amendment: The patient population with a history of immunotherapy in allergy became able to participate in the clinical trial. The blood sample volume were reassessed and changed. In addition a minor formatting and typographical errors have been corrected to improve the clarity and accuracy of the protocol text.

Applicable Section(s)	Description of Change(s)
Rationale: Because it was determined that the administration of Guselkumab is less likely to increase a risk related to the safety in the patients with a history of immunotherapy in allergy, the patient population with a history of immunotherapy in allergy are able to participate in a clinical trial.	
Section 4.2. Exclusion Criteria number 30	The paragraph of exclusion criteria was deleted. The paragraph number of exclusion criteria 31-39 were moved up to 30-38.
Rationale: The lower limit of the blood volume required of clinical laboratory tests was reassessed, the blood sample volume were changed.	
9.1.1. Overview	The total blood volume, etc. were changed.
Attachment 7	The total blood volume, etc. were changed.
Rationale: Minor formatting and typographical errors have been corrected to improve the clarity and accuracy of the protocol text.	
Section 8.1.2. Concomitant Medications for Conditions Other than Palmoplantar Pustulosis	It was clarified that topical medication to body area other than palms and soles of the steroid is not limited.
Section 9.6. Safety Evaluations	*vital signs* The title of the paragraph related to vital signs was changed. *ECG testing* The description of the visit schedule for ECG testing was corrected.
Section 10.2. Discontinuation of Study Treatment Throughout the protocol	It was clarified that it isn't limited to medication treatment that use is prohibited on the protocol. Minor formatting and typographical errors have been corrected to improve the clarity and accuracy of the protocol text.

SYNOPSIS

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

CNTO 1959 (guselkumab) is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that binds to the p19 protein subunit of human interleukin (IL)-23 with high specificity and affinity. The binding of CNTO 1959 to the IL-23p19 subunit blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23 specific intracellular signaling and subsequent activation and cytokine production. In this manner, CNTO 1959 inhibits the biological activity of IL-23 in all in vitro assays examined.

OBJECTIVES AND HYPOTHESISES

Primary Objectives

The primary objectives of this study are:

- To evaluate the efficacy of CNTO 1959 for the treatment of subjects with palmoplantar pustulosis.
- To assess the safety and tolerability of CNTO 1959 in subjects with palmoplantar pustulosis.

Secondary Objectives

The secondary objectives of this study are:

- 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 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

The exploratory objectives of this study are:

- 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.

Hypothesis

The primary hypothesis is that CNTO1959 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.

OVERVIEW OF STUDY DESIGN

This is a Phase 3, randomized, double-blind, multicenter placebo-controlled study in subjects with palmoplantar pustulosis. 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)

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 CNTO 1959 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 active treatment groups at Week 16. Stratification factors will be PPPASI total score range at baseline (≤ 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 the durability of clinical response and safety 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 (DBLs) will occur at Weeks 16, 24, 52 and 84. Additional DBLs may also occur after Week 52 DBL during the study.

An Independent Data Monitoring Committee (IDMC) will be constituted for safety monitoring and interim analysis review of this study.

SUBJECT POPULATION

The target population is adult men or women who must have inadequate response to conventional therapies (topical treatment, and/or phototherapy, and/or systemic treatment), 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.

DOSAGE AND ADMINISTRATION

A 100 mg/ mL solution of CNTO 1959 in a single-use prefilled syringe (PFS) assembled with the UltraSafe PLUS™ Passive Needle Guard (PFS-U) device will be used. Liquid placebo for CNTO 1959 will also be supplied as a PFS assembled with the PFS-U. During the study, all subjects will subcutaneously receive two syringes for each dose.

All study drug administrations will be given at the study site. The dose regimens are as follows:

- **Group I**: Two syringes of CNTO 1959 100 mg at Weeks 0, 4, 12 and q8w thereafter through Week 60, 2 syringes of placebo for CNTO 1959 100 mg at Week 16 to maintain the blind.
- **Group II**: A syringe of CNTO 1959 100 mg and a syringe of placebo for CNTO 1959 100 mg at Weeks 0, 4, 12 and q8w thereafter through Week 60, 2 syringes of placebo for CNTO 1959 100 mg at Week 16 to maintain the blind.

- **Group III**: Two syringes of placebo for CNTO 1959 100 mg at Weeks 0, 4 and 12 to maintain the blind. At Week 16, placebo subjects will be randomized in a 1:1 ratio to CNTO 1959 200 mg arm (Group IIIa) or 100 mg arm (Group IIIb). Group IIIa subjects will receive 2 syringes of CNTO 1959 100 mg at Weeks 16, 20 and q8w thereafter through Week 60. Group IIIb subjects will receive a syringe of CNTO1959 100mg and a syringe of placebo for CNTO1959 100mg at Weeks 16, 20 and q8w thereafter through Week 60.

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 EVALUATIONS/ENDPOINTS

Efficacy evaluations include PPPASI, Palmoplantar Pustulosis Severity Index (PPSI), Physician's Global Assessment (PGA), Dermatology Life Quality Index (DLQI), 36-Item Short form Health Assessment Questionnaire (SF-36), EuroQOL five dimensions questionnaire (EQ-5D), Magnetic Resonance Imaging (MRI), and Photographs.

Primary Endpoints

- Change from baseline in PPPASI total score at Week 16, comparing the CNTO 1959 groups and the placebo group.

Major Secondary Endpoints

- Change from baseline in PPSI total score at Week 16
- Proportion of subjects who achieve a PPPASI-50 at Week 16

Other Secondary Endpoints

- Change from baseline in PPPASI total score over time
- Change from baseline in PPSI total score over time
- Proportion of subjects who achieve a PPPASI-50 over time
- Proportion of subjects who achieve a PPPASI-75, PPPASI-90, PPPASI-100 over time.
- Proportion of subjects who achieve a PPSI-50, PPSI-75, PPSI-90, PPSI-100 over time.
- Change from baseline in PGA score over time.
- Proportion of subjects who achieve a PGA score of cleared (0) or minimal (1) over time.
- Proportion of subjects who achieve a PGA score of cleared (0) or minimal (1) and have at least a 2-grade improvement from baseline over time.
- Change from baseline in DLQI score over time.
- Change from baseline in SF-36 score over time.
- Change from baseline in EQ-5D score over time.

Exploratory Endpoints

- Change from baseline in EQ-5D score in PAO subjects over time.

PHARMACOKINETIC EVALUATIONS

Blood samples will be collected for the measurement of serum CNTO 1959 concentrations.

IMMUNOGENICITY EVALUATION

Blood samples will be collected for the measurement of antibodies to CNTO 1959.

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS

If data permit, the relationships between serum CNTO 1959 concentration and efficacy may be analyzed graphically. If any visual trend is observed, a suitable population PK/PD model may be developed to describe the exposure-response relationship.

BIOMARKER EVALUATIONS

Biomarker samples will be used to generate serum markers.

SAFETY EVALUATIONS

Safety and tolerability will be assessed by collecting information on adverse events (AEs), clinical laboratory tests, electrocardiogram (ECG), vital signs (axillary temperature, pulse rate, blood pressure), physical examinations, concomitant medication review, injection-site evaluations, allergic reactions, and early detection of tuberculosis (TB).

STATISTICAL METHODS

Sample size determination

This study is designed to evaluate the efficacy of CNTO 1959 versus placebo in subjects with palmoplantar pustulosis at Week 16. 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 of 50 patients per group was chosen to achieve at least 90% power to detect treatment difference between CNTO 1959 group 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).

Interim Analysis

Since the assumptions used for determining the sample size may or may not be upheld in this study, an interim analysis is planned to re-estimate the sample size and determine whether to stop the study early for futility based on the approach introduced by Mehta and Pocock.[16]

This interim analysis will be conducted when approximately 40% of the 150 randomized subjects have completed Week 16 visit or have ended study participation before Week 16 visit. Conditional power and the sample size required for satisfying the 90% conditional power will be calculated by an independent Statistical Support Group (SSG). The IDMC will compare the calculated results with the pre-specified sample size adaptation rules to determine the final sample size for the study. The maximum sample size for the study is capped at 75 patients per group (225 in total).

Efficacy

Primary endpoint of this study is change from baseline in PPPASI total score at Week 16. In the primary efficacy analyses, data from all randomized subjects will be analyzed according to their assigned treatment group. In this primary analysis, 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. Un-imputed data 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 least-square (LS) means of the differences. The p-values for the LS mean differences along with the 2-sided 95% confident intervals (CIs) will be presented.

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

- The change from baseline in PPSI through Week 16 will be analyzed using the same MMRM model as described for the primary analysis, 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 least-square (LS) means of the differences. The p-values for the LS mean differences along with the 2-sided 95% CIs will be presented. The change from baseline in PPSI through Week 16 will also be summarized by treatment group and week using descriptive statistics.
- 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 ($\leq$ 20, 21-30, $\geq$ 31) and smoking status (smoking or non-smoking). The proportion through Week 16 will also be summarized by treatment group and week using frequencies and percentages with 95% CI.
- For other secondary endpoints (including exploratory endpoints), the continuous variables will be summarized by treatment group and week using descriptive statistics, which will include the number of subjects (N), mean, SD, median, minimum, and maximum and the measurements through Week 16 will be analyzed using an MMRM model where there are repeated measurements; or an analysis of variance model based on appropriate rank scores or ANCOVA model where there is no repeated measurement. The categorical variables will be summarized by treatment group and week using frequencies and percentages. The binary variables through Week 16 will be compared using stratified CMH chi-square test or Fisher's exact test.

Pharmacokinetic

Serum CNTO 1959 concentrations will be summarized for each treatment group over time. Descriptive statistics, including arithmetic mean, standard deviation (SD), median, interquartile range, minimum, and maximum will be calculated at each sampling timepoint. If feasible, a population PK analysis using nonlinear mixed effects model (NONMEM) will be used to characterize the disposition characteristics of CNTO 1959 in the current study. If needed, other studies data may be combined.

Immunogenicity

The incidence and titers of antibodies to CNTO 1959 will be summarized for all subjects who receive at least 1 dose of CNTO 1959 and have appropriate samples for detection of antibodies to CNTO 1959. If NAbs are measured, the incidence of NAbs to CNTO 1959 will be summarized for subjects who are positive for antibodies to CNTO 1959 and have samples evaluable for NAbs.

Pharmacokinetic/Pharmacodynamic

If data permit, the relationships between serum CNTO 1959 concentration and efficacy may be analyzed graphically. If any visual trend is observed, a suitable population PK/PD model may be developed to describe the exposure-response relationship.

Biomarker

Biomarker samples will be used to generate serum markers.

Safety

Routine safety evaluations will be performed. Adverse events (AEs), serious adverse events (SAEs), and infections by Week 16 will be summarized by treatment group. Additional summary tables of AEs during the entire treatment period will be generated for all CNTO 1959 treated subjects including those who switched from placebo at Week 16.

Laboratory data will be summarized by type of laboratory test. National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grades (specified in the Statistical Analysis Plan [SAP]) will be used in the summary of laboratory data. Descriptive statistics will be calculated for selected laboratory analytes at baseline and at each scheduled time point. A listing of subjects with post-baseline abnormal laboratory results based on CTCAE grades will also be provided.

TIME AND EVENTS SCHEDULE

Phase	Screening[a]	Treatment Period																Observational Period	
Week		0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	60	72(ET[b])	84
Allowance (day)			±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Study Procedures[c]																			
Screening/Administrative																			
Informed consent (ICF)	X																		
Medical history and demographics	X																		
Inclusion/exclusion criteria	X	X																	
Study Drug Administration																			
Randomization		X					X												
Study agent administration		X		X		X	X	X		X		X		X		X	X		
Safety Assessments																			
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height		X																	
Weight		X					X									X		X	
12-lead ECG	X						X									X		X	
Chest radiograph (Chest CT or Chest X-ray: both posterior-anterior and lateral views)	X						X									X		X	
Urine pregnancy test[e]		X		X		X	X	X		X		X		X		X	X	X	
Efficacy Assessments																			
PPPASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PPSI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLQI[f]		X					X				X					X		X	X

Phase	Screening[a]	Treatment Period																Observational Period	
Week		0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	60	72(ET[b])	84
Allowance (day)			±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Study Procedures[c]																			
SF-36[f]		X					X				X					X		X	X
EQ-5D[f]		X					X				X					X		X	X
MRI[g]	X[g]															X			
Photographs[h]	X	X					X				X					X		X	X
Clinical Laboratory Assessments[i, j]																			
Hematology	X	X	X	X	X	X	X	X	X	X		X		X		X		X	
Chemistry	X	X	X	X	X	X	X	X	X	X		X		X		X		X	
Lipid panel[j]		X																	
Serology / other screening	X																		
Pharmacokinetics / Immunogenicity[k]																			
Serum sample collection for PK		X		X	X	X	X	X	X	X		X		X	X	X	X	X	
Serum sample collection for population PK							← X[l] →												
Serum sample collection for immunogenicity		X		X			X								X	X	X	X	
Biomarkers																			
Serum sample collection		X					X								X		X	X	
Ongoing Subject Review																			
Smoking status	X	X	X----------X																
Concomitant therapy	X	X	X----------X																
Tuberculosis evaluation	X	X	X----------X																
Adverse events[m]	X	X	X----------X																X

Footnotes

a. The screening period is planned to allow approximately 6 weeks.

b. ET: Early Termination. For subjects who withdraw from study participation, every effort should be made to conduct final efficacy and safety assessments which are listed in Week72.

c. All study procedures and evaluations are to be completed before study drug injection.
d. Axillary temperature, Pulse rate, Blood pressure
e. Women of childbearing potential must have a negative urine pregnancy test before randomization and at all study visits before study drug administration.
f. Indicated assessments should be performed before any tests, procedures, or other consultations (PPPASI, PPSI, and PGA) for that visit.
g. To be performed only for those subjects who had a diagnosis of PAO at screening. Screening MRI is to be completed before study drug injection.
h. To be performed in a subset of subjects who have consented to be taken photography of their lesions. See separate Photography manual.
i. Laboratory tests are listed in Section 9.7, Sample Collection and Handling.
j. Subjects must fast (ie, no food or beverages [except water]) for at least 8 hours before blood is drawn for lipid panel. All other visits can be nonfasting.
k. Venous blood samples (approximately 6 mL each) will be collected from all subjects in the study. Each sample will be split into 3 aliquots (1 aliquot for serum CNTO 1959 concentration, 1 aliquot for antibodies to study drug, and 1 aliquot as a back-up). The samples for PK and immunogenicity assessments must be collected before study drug administration at visits when a study drug administration is scheduled.
l. One additional venous blood sample (approximately 4 mL) will be collected from all subjects at any time between Weeks 16 to 20 (other than the scheduled visit at Weeks 16 or 20). This sample must be collected at least 24 hours after the scheduled study drug administration at Week 16 and at least 24 hours before the scheduled visit at Week 20. Each serum sample will be split into 2 aliquots (1 aliquot for serum CNTO 1959 concentration and 1 aliquot as a back-up).
m. All AEs will be reported from the time a signed and dated ICF is obtained until 12 weeks after the last dose of study drug (Week 72 visit or early termination visit). From Week 72 to 84, AEs considered associated with the use of the drug will be reported.

ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BCG	Bacille Calmette-Guérin
BQL	below quantification limit
CD	cluster of differentiation
CI	confident interval
CL	clearance
CMH	Cochran-Mantel-Haenszel
CRF	case report form (paper or electronic as appropriate for this study)
DBL	database lock
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EQ-5D	EuroQOL Five Dimensions Questionnaire
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBc	hepatitis B core
HBs	hepatitis B surface
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HR	heart rate
HTLV	human T-cell lymphotropic virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN-γ	interferon-gamma
IGRA	interferon gamma release assay
IL	interleukin
IM	intramuscular
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
mAb	monoclonal antibody
MMRM	mixed-model for repeated measures
MTX	methotrexate
NAb	neutralizing antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NONMEM	nonlinear mixed effects model
PAO	pustulotic arthro-osteitis
PD	pharmacodynamic
PFS	prefilled syringe
PFS-U	Prefilled syringe assembled with the UltraSafe Plus™ Passive Needle Guard
PGA	Physician's Global Assessment
PK	pharmacokinetic
PPP	palmoplantar pustulosis
PPPASI	Palmo-Plantar Area and Siverity Index
PPSI	Palmo-Planter Severity Index

PQC	Product Quality Complaint
PRO	patient-reported outcome
PSO	psoriasis
QOL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SF-36	36-Item Short Form Health Assessment Questionnaire
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
Th	helper T cell
TNF-α	tumor necrosis factor-alpha

1. INTRODUCTION

Guselkumab (CNTO 1959) is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that binds to the p19 protein subunit of human interleukin (IL)-23 with high specificity and affinity. The binding of CNTO 1959 to the IL-23p19 subunit blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23 specific intracellular signaling and subsequent activation and cytokine production. In this manner, CNTO 1959 inhibits the biological activity of IL-23 in all in vitro assays examined.

For the most comprehensive nonclinical and clinical information regarding CNTO 1959, refer to the latest version of the Investigator's Brochure.

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

1.1. Background

Nonclinical Studies

Pharmacologic Profile

CNTO 1959 has been shown to be pharmacologically active and binds to the p19 subunit of IL-23, preventing binding of extracellular IL-23 to the cell surface IL-23R and subsequent activation of intracellular signaling pathways. In vitro studies have demonstrated that CNTO 1959 inhibits the biological activity of human, guinea pig, and non-human primate IL-23.

Toxicology

A 3-week (25 day) non-Good Laboratory Practice (GLP) toxicology study was conducted in male Hartley guinea pigs administered subcutaneous (SC) doses of 10 mg/ kg, 50 mg/ kg, or 100 mg/ kg CNTO 1959 twice a week. No CNTO 1959 related effects were noted during the study, indicating that the maximum tolerated dose is considered to be ≥ 100 mg/ kg.

A 5-week/24-week GLP toxicology study was conducted in cynomolgus monkeys with once per week administration of CNTO 1959 subcutaneously at doses of 10 mg/ kg or 50 mg/ kg for up to 24 weeks or intravenously at a dose of 50 mg/ kg for 5 weeks. Toxicological evaluations in this study have shown that once weekly SC (24 weeks) or intravenous (IV) (5 weeks) administration of 50 mg/ kg CNTO 1959 was well tolerated, with no observed clinical or anatomic findings related to CNTO 1959.

In vitro tissue human and cynomolgus monkey cross-reactivity studies revealed specific cytoplasmic staining of striated myocytes in cardiac and skeletal muscle by CNTO 1959. This is considered not to be relevant to in vivo administration as antibodies are too large to diffuse across plasma membranes and do not gain access to the intracellular environment. Additional in vitro studies demonstrated that CNTO 1959 did not bind to either human or porcine myosin.

A cardiovascular safety pharmacology study with CNTO 1959 (10 or 50 mg/ kg, IV) was conducted in cynomolgus monkeys to evaluate any potential adverse effects of CNTO 1959 on

cardiac function. Tissue samples examined by immunohistochemistry (IHC) revealed no binding of CNTO 1959 to cardiovascular or skeletal muscle tissues, indicating the cytoplasmic binding observed during in vitro studies may not be relevant to in vivo studies. This study revealed no treatment-related effects on blood pressure. A mild reduction in both heart rate (HR; 16 beats per minute or up to -9.9% compared to vehicle) and body temperature (0.3°C or up to -0.8% compared to vehicle) was observed from approximately 6 hours to 12 hours after the 50 mg/ kg dose of CNTO 1959 and was considered non-adverse. No adverse effects were observed in electrocardiogram (ECG) parameters, including corrected QT (QTc) measures.

Cardiovascular safety pharmacology parameters were also evaluated as part of a CNTO 1959 5-week/24-week GLP toxicity study conducted in cynomolgus monkeys and revealed no treatment related adverse cardiovascular effects. Anatomic pathology conducted after 5-weeks of SC or IV administration or 24-weeks of SC administration at doses up to 50 mg/ kg revealed no treatment related effects on heart weight or histomorphologic effects on the heart or skeletal muscles.

The cynomolgus monkey was selected as a pharmacologically relevant species for toxicological evaluation as CNTO 1959 binds to cynomolgus monkey IL-23 and inhibits pharmacological activity. In vitro tissue cross reactivity studies with both biotinylated-CNTO 1959 and CNTO 1959 showed similar staining profiles for cynomolgus monkey and human tissues.

The toxicology data indicate that the no observed adverse effect level (NOAEL) for CNTO 1959 in cynomolgus monkeys is at least 50 mg/ kg/week and supports the administration of CNTO 1959 to subjects for up to 6 months by SC administration or 1 month by IV administration.

CNTO 1959 also binds and neutralizes guinea pig IL-23; therefore, a toxicology study was performed using the guinea pig as a first step in assessing the feasibility of using the guinea pig for fertility studies. The guinea pig was demonstrated to be a successful model for evaluating mating and fertility parameters. A high dose of 50 mg/ kg of CNTO 1959 was well tolerated in guinea pigs. In the GLP female fertility study in guinea pigs, pregnancy rates for female guinea pigs that delivered a litter and mated postpartum were comparable between the drug-treated and control groups, and there was no effect on fertility. In the GLP male fertility study, there were no effects on fertility in the males including no impact on sperm count or motility, and no macroscopic/microscopic findings.

Pharmacokinetic Profile

Single-dose studies with CNTO 1959 were conducted in cynomolgus monkeys for both IV and SC routes of administration with SC doses at 1, 5, 10 and 50 mg/ kg, and IV doses at 1 mg/ kg and 50 mg/ kg. Following SC administration of CNTO 1959, the observed time to maximal concentration (T_{max}) was 1 to 5 days. In general, the systemic exposure of CNTO 1959 increased in an approximately dose-proportional manner. The mean half-life ($T_{1/2}$) ranged from 6 to 12 days. The absolute bioavailability (F%) for SC administration was estimated to be in the range of 70 to 100%.

Following weekly SC administrations of CNTO 1959 (10 mg/ kg and 50 mg/ kg) in cynomolgus monkeys, the systemic exposure of CNTO 1959 also increased in an approximately dose-proportional manner. There were no apparent gender-related differences in the pharmacokinetics of CNTO 1959.

Immunogenicity Profile

Of the 50 cynomolgus monkeys treated with either IV (n = 13) or SC (n = 37) injections of CNTO 1959 in 3 pharmacokinetic/toxicokinetic (PK/TK) studies, one (2.0%) in the 50 mg/ kg IV dose group developed antibodies to CNTO 1959 and exhibited accelerated systemic clearance of CNTO 1959. None of the animals in the SC groups tested positive for antibodies to CNTO 1959.

Clinical Studies

The following are complete studies of CNTO 1959; more details about the individual studies are provided in the Investigator's Brochure.

- CNTO1959PSO1001 was the first-in-human study for CNTO 1959 which was evaluated in both healthy subjects and subjects with moderate to severe proriasis.
- CNTO1959PSO1002 was a Phase 1 study of CNTO 1959 in Japanese subjects with moderate to severe plaque psoriasis in Japan.
- CNTO1959PSO2001 was a Phase 2 randomized, placebo- and active-comparator-controlled, parallel group, multicenter dose-ranging study of CNTO 1959 in subjects with moderate to severe plaque psoriasis.
- CNTO1959NAP1001 was a Phase 1 study to assess PK comparability of 2 formulations and to evaluate the PK comparability of CNTO 1959 delivered by 2 different devices in healty subjects.
- CNTO1959PPP2001, a Phase 2 study in subjects with PPP in Japan.
- CNTO1275ARA2001, a Phase 2 study of CNTO 1959 and ustekinumab (STELARA®) in subjects with active rheumatoid arthritis (RA) despite concomitant methotrexate (MTX) therapy.

CNTO1959PSO3004 study for the treatment of subjects with psoriasis and CNTO1959PSO3005 study for the treatment of subjects with Generalized Pustular Psoriasis or Erythrodermic Psoriasis are ongoing in Japan.

Phase 1 Pharmacokinetic Results

In the Phase 1 studies in subjects with psoriasis (CNTO1959PSO1001 [Part 2] and CNTO1959PSO1002) and in healthy subjects (CNTO1959PSO1001 [Part 1] and CNTO1959NAP1001), CNTO 1959 was slowly absorbed into the systemic circulation, with a median T_{max} of approximately 3 to 6 days after a single SC administration. Systemic exposure (C_{max} and AUC) increased in an approximately dose-proportional manner after a single IV administration at doses ranging from 0.03 to 10 mg/ kg or after a single SC administration at doses ranging from 10 to 300 mg. After a single IV administration, mean V_z values were

approximately 6.7 to 10.1 L (98 to 123 mL/ kg) and mean CL values were approximately 0.288 to 0.479 L/day (3.6 to 6.0 mL/day/ kg). The mean $T_{1/2}$ values ranged [redacted] approximately 14.7 to 17.2 days after a single SC administration. The mean absolute bioavailability (F%) of CNTO 1959 after a single 100 mg SC administration was approximately 47.6% to 54.9%.

In CNTO1959PSO1001 (Part 2), CNTO 1959 SC was generally safe and well tolerated, with no dose-dependent response in the incidence of Adverse Events (AEs); all AEs were considered to be mild to moderate in intensity by the investigator. In CNTO1959PSO1002, administration of CNTO 1959 SC was generally safe and well tolerated. No dose-dependent response in the incidence of AEs was observed, and all AEs were considered mild in severity by the investigator.

Phase 2 Study (CNTO1959PPP2001)

CNTO1959PPP2001 is complete Phase 2, randomized, double-blind, placebo-controlled, parallel group, multicenter study of CNTO 1959 in subjects with PPP in Japan. Approximately 50 subjects were to be randomly assigned in a 1:1 ratio to receive either 200 mg CNTO1959 SC or placebo SC at Week 0 and Week 4 and will be followed through Week 24. Eligible subjects must have (Week 0), including active lesion on the palms or soles.

1.2. Overall Rationale for the Study

IL-23 is a member of the IL-12 family of heterodimeric cytokines. IL-23 shares the p40 subunit with IL-12. However, in contrast to IL-12, which is formed from p40/p35 heterodimers, the p40 subunit is paired with a p19 subunit to form IL-23.[1] Although IL-12 and IL-23 are closely related cytokines, which are expressed by antigen-presenting cells such as dendritic cells, increasing evidence suggests that these 2 cytokines drive divergent immunological pathways. IL-12 induces the production of interferon γ-(IFN-γ) producing T helper 1 (Th1) cells, which are important in host defense to intracellular pathogens by promoting cytotoxic, antimicrobial, and antitumor responses. IL-23, alone or in combination with other cytokines (transforming growth factor β [TGF-β] and IL-6 or IL-1β), drives the expansion and/or maintenance of mouse and human CD4+ IL-17 producing T helper 17 (Th17) cells. Th17 cells produce the pro-inflammatory cytokines, IL-17A, IL-17F, IL-22, IL-6, and tumor necrosis factor-alpha (TNFα).[2, 3, 4]

CNTO 1959, a human mAb directed against the p19 subunit of IL-23 specifically targets IL-23. A rapidly growing body of literature suggests that the IL-23/IL-17 pathway contributes to the chronic inflammation underlying the pathophysiology of many immune-mediated diseases,[5, 6] including psoriasis,[7] multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, AS, psoriatic arthritis (PsA) and palmoplantar pustulosis (PPP).[8, 9, 10] In addition, susceptibility to psoriasis, PsA, and inflammatory bowel disease has been shown to be associated with genetic polymorphisms in IL-23/IL-23R components.[11, 12, 13, 14, 15] Finally, CNTO 1959 demonstrated efficacy and was well-tolerated in a Phase 2 study of palmoplantar pustulosis. The results of this Phase 2 study support further investigation of the efficacy and safety of CNTO 1959 for the treatment of palmoplantar pustulosis in this Phase 3 clinical study.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objectives

The primary objectives of this study are:

- To evaluate the efficacy of CNTO 1959 for the treatment of subjects with palmoplantar pustulosis.
- To assess the safety and tolerability of CNTO 1959 in subjects with palmoplantar pustulosis.

Secondary Objectives

The secondary objectives of this study are:

- 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

The exploratory objectives of this study are:

- 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.

2.2. Hypothesis

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.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a Phase 3, randomized, double-blind, multicenter placebo-controlled study in subjects with palmoplantar pustulosis. The target population is adult men or 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 $\geq$ 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.

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

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.

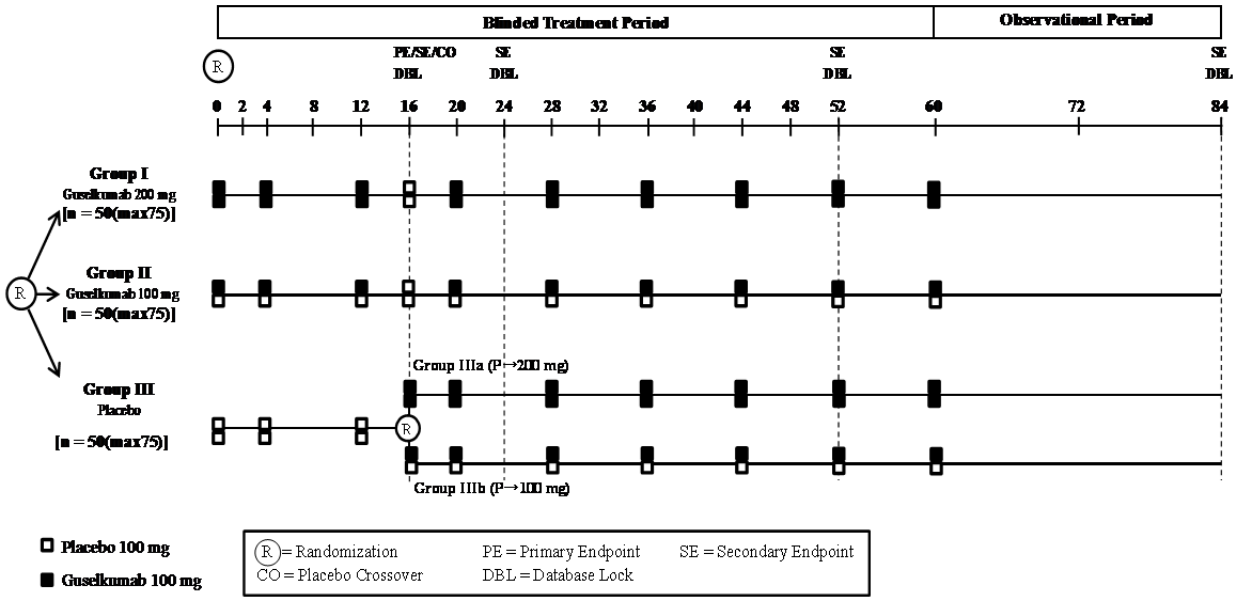
Subject will be assigned to 1 of 3 treatment groups using a stratified block randomization method in a 1:1:1 ratio at Week 0 and Group III subjects will be allocated in a 1:1 ratio to 1 of 2 treatment groups at Week 16. Stratification factors will be PPPASI total score range (≤20 score, 21-30 score, ≥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 the durability of clinical response and safety 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 design



3.2. Study Design Rationale

As described in Section 1.2, there is substantial scientific and clinical evidence supporting the critical role of IL-23 in the pathogenesis of palmoplantar pustulosis. Specifically, the clinical response to CNTO 1959 observed in Phase 2 palmoplantar pustulosis study provides compelling evidence of the specific importance of this cytokine and supports further investigation in Phase 3 clinical studies. The dose justification for this study is described in Section 3.3 and the reasons for considering inclusion of an interim analysis are described in Section 11.8.

Blinding, Control, Study Phase/Periods, Treatment Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment. Comparisons are planned between CNTO 1959 groups and placebo group at Week 16, which is within the range that has been used in previous studies of biologic therapies for palmoplantar pustulosis (8 to 24 weeks). In addition to placebo control, two CNTO 1959 doses are selected to determine the appropriate dose level for palmoplantar pustulosis. These two doses will be evaluated for efficacy and safety through one year for two reasons: 1) palmoplantar pustulosis is a chronic disease that often requires chronic treatment, such that longer-term outcomes are clinically important, and 2) CNTO 1959 is

expected to achieve maximal efficacy by Week 20 to 24 of treatment, so these later evaluations will evaluate maintenance doses after reaching steady state and/or maximal responses.
Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Biomarker Collection

Biomarker samples will be collected to evaluate the mechanism of action of CNTO 1959 or help to explain inter-individual variability in clinical outcomes or may help to identify population subgroups that respond differently to a drug. The goal of the biomarker analyses is to evaluate the PD of CNTO 1959 and aid in evaluating the drug-clinical response relationship.

Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

3.3. Dose Rationale

Two dose regimens of CNTO 1959 were selected for the Phase 3 CNTO 1959 PPP study: 200 mg and 100 mg at Weeks 0 and 4 and every 8 weeks (q8w) thereafter. These dose regimens were chosen based on clinical results and pharmacokinetics/pharmacodynamics (PK/PD) modeling of the Phase 2 study (CNTO1959PPP2001) in subjects with PPP. By PK/PD modeling 200 mg appears to be the plateau. Therefore 100 mg will be tested as the lower dose.

- Statistically improvement of Palmoplantar Pustulosis Severity Index (PPSI) total score and PPPASI total score from the baseline in subjects in 200 mg CNTO 1959 treatment group than in the placebo group was seen at Week 16 (PPSI total score change; -3.3 in CNTO 1959 group, -1.8 in placebo group, PPPASI total score change; -11.12 in CNTO 1959 group, -5.47 in placebo group).
- No dose-related safety or tolerability issues were observed with the 200 mg at Week 0 and 4 doses.
- A dose-response relationship from 50 mg q8w, 100 mg q8w and 200 mg q8w was predicted by PK/PD modeling and the efficacy will be expected also at 200 mg q8w and 100 mg q8w.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within approximately 6 weeks before administration of CNTO 1959.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study.

4.1. Inclusion Criteria

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

1. Be a man or a woman at least 20 years of age.

2. Has a diagnosis of palmoplantar pustulosis (with or without pustulotic arthro-osteitis, concurrent extra-palmoplantar lesions) for at least 24 weeks before screening.

3. Has a ≥ 12 PPPASI total score at screening and at baseline.

4. Has a moderate or more severe pustules/vesicle on the palms or soles (≥ 2 PPPASI severity score) at screening and baseline.

5. Has inadequate response to the treatment with topical steroid and/or topical vitamin D3 derivative preparations and/or the phototherapy and/or systemic etretinate prior to or at screening. Inadequate response is defined as a case judged by the investigator.

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

   - Not of childbearing potential: premenarchal; postmenopausal (> 45 years of age with amenorrhea for at least 52 weeks or any age with amenorrhea for at least 24 weeks and a serum follicle stimulating hormone [FSH] level > 40 IU/L); permanently sterilized (eg, bilateral tubal occlusion [which includes tubal ligation procedures as consistent with local regulations], hysterectomy, bilateral salpingectomy, bilateral oophorectomy); or otherwise be incapable of pregnancy.
   - Of childbearing potential and practicing a highly effective method of birth control, consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS); barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject).

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

7. A woman of childbearing potential must have a negative serum β-human chorionic gonadotropin (β-hCG) test at screening and a negative urine pregnancy test at Week 0.

8. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 12 weeks after receiving the last administration of CNTO 1959.

9. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control (eg, either a condom with spermicidal foam/gel/film/cream/suppository or a partner with an occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository), during the study and for at least 12 weeks after receiving the last administration of CNTO 1959. All men must also agree to not donate sperm during the study and for at least 12 weeks after receiving the last administration of CNTO 1959.

10. Is considered eligible according to the following tuberculosis (TB) screening criteria:

    - Has no history of latent or active TB before screening. An exception is made for subjects who have a history of latent TB and are currently receiving treatment for latent TB, will initiate treatment for latent TB before the first administration of study drug, or have documentation of having completed appropriate treatment for latent TB within 5 years before the first administration of study drug. It is the responsibility of the investigator to verify the adequacy of previous anti-tuberculosis treatment and provide appropriate documentation.
    - Has no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
    - Has had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB at least 3 weeks before the first administration of study drug.
    - Within 8 weeks before the first administration of study drug, has a negative interferon gamma release assays (IGRAs) result, or have a newly identified positive IGRAs result (Attachment 9) in which active TB has been ruled out and for which appropriate treatment for latent TB (Attachment 9) has been initiated at least 3 weeks before the first administration of study drug. A subject whose first IGRA result is indeterminate should have the test repeated. In the event that the second IGRA result is also indeterminate, the subject should be excluded from the study.

      Note : The IGRA and the tuberculin skin test are not required at screening for subjects with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment as described above; subjects with documentation of having completed adequate treatment as described above are not required to initiate additional treatment for latent TB.
    - Has a chest radiograph (posterior-anterior and lateral views, or substitutable with chest computed tomography [CT]), taken within 12 weeks before the first administration of study drug and read by a qualified radiologist or pulmonologist, with no evidence of current, active TB or old, inactive TB.

11. Agrees not to receive a live virus or live bacterial vaccination during the study, or within 12 weeks after the last administration of study drug. For information on Bacille Calmette-Guérin (BCG) vaccination, see Inclusion Criterion 12.

12. Agrees not to receive a BCG vaccination during the study, or within 52 weeks after the last

administration of study drug.

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

    - Hemoglobin ≥ 10 g/dL (SI: ≥100 g/L)
    - White blood cells ≥ 3.5 x 10^3/µL (SI: ≥3.5 GI/L)
    - Neutrophils ≥ 1.5 x 10^3/µL (SI: ≥1.5 GI/L)
    - Platelets ≥ 100 x 10^3/µL (SI: ≥100 GI/L)
    - Serum creatinine ≤ 1.5 mg/dL (SI: ≤129 µmol/L)

    Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase levels must be ≤ 2 × upper limit of normal (ULN) for the laboratory conducting the test.

14. Agrees to avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet (UV) light sources to the palms and soles during study.

15. Agrees that every effort should be made to stop smoking.

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

17. Signs an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study. The subject will be excluded if he or she:

1. Has a diagnosis of plaque-type psoriasis.

2. Has obvious improvement during screening (≥ 5 PPPASI total score improvement during the screening).

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

4. Has unstable cardiovascular disease, defined as a recent clinical deterioration (eg, unstable angina, rapid atrial fibrillation) in the last 12 weeks or a cardiac hospitalization within the last 12 weeks before screening.

5. Currently has a malignancy or has a history of malignancy within 5 years before screening (with the exception of a nonmelanoma skin cancer that has been adequately treated with no

evidence of recurrence for at least 12 weeks before screening or cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 12 weeks before screening).

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

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

8. Has or has had a serious infection (eg, sepsis, pneumonia or pyelonephritis) , or has been hospitalized or received IV antibiotics for an infection during the 8 weeks before screening.

9. Has a history of active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening. Refer to Inclusion Criterion 10 for information regarding eligibility with a history of latent TB.

10. Has a chest radiograph within 12 weeks before the first administration of study drug that shows an abnormality suggestive of a malignancy or current active infection, including TB.

11. Has persistently indeterminate (indeterminate on repeat sampling) IGRA results.

12. Has ever had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystosis, aspergillosis).

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

14. Has or has had herpes zoster within the 8 weeks before screening.

15. Is infected with human immunodeficiency virus (HIV, positive serology for HIV infection) or human T-lymphotropic virus-1 (HTLV-1, positive serology for HTLV-1 infection).

16. Tests positive for hepatitis B virus (HBV) infection or who are seropositive for antibodies to hepatitis C virus (HCV) at screening (Attachment 10).

17. Has a transplanted organ (with exception of a corneal transplant >12 weeks before the first administration of study drug).

18. Subject has had major surgery, (eg, requiring general anesthesia) within 8 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study (52 weeks).

    Note: subjects with planned surgical procedures to be conducted under local anesthesia

may participate.

19. Has current drug-induced palmoplantar pustulosis (eg, a new onset of palmoplantar pustulosis or an exacerbation of palmoplantar pustulosis from beta blockers, calcium channel blockers, lithium, or biologic therapy including infliximab, adalimumab or etanercept etc.).

20. Is pregnant, nursing, or planning a pregnancy (both men and women) within 20 weeks following the last administration of study drug.

21. Has previously received CNTO 1959.

22. Has received focal infection treatment (e.g., tonsillectomy and dental therapy) within 24 weeks of the first administration of any study agent.

23. Has received any anti-TNFα biologic therapy within 12 weeks or 5 half-lives of the first administration of study drug, whichever is longer.

24. 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]).

25. 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.

26. 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.

27. 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.

28. 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.

29. 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.

30. 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.

31. 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.

32. Has known allergies, hypersensitivity, or intolerance to CNTO 1959 or its excipients (refer to Investigator's Brochure).

33. Has received, or is expected to receive, any live virus or bacterial vaccination within 12 weeks before the first administration of study drug. For BCG vaccine, see Exclusion Criterion 35.

34. Has had a BCG vaccination within 52 weeks of screening.

35. Is known to have had a substance abuse (drug or alcohol) problem within the previous 52 weeks before screening.

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

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

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

Note : Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study.

4.3. Prohibitions and Restrictions

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

1. If a woman of childbearing potential is heterosexually active, she must remain on a highly effective method of birth control (see inclusion criteria 6) during the study and for 12 weeks after receiving the last dose of any study agent.

2. If a man who has not had a vasectomy and is sexually active with a woman of childbearing potential must use a barrier method of birth control, eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the study and for 12 weeks after receiving the last dose of study drug.

3. Must agree not to receive a live virus or bacterial vaccination during the study or up to 12 weeks after the last administration of any study agent.

4. Must agree not to receive a BCG vaccination during the study or up to 52 weeks after the last administration of any study agent.

5. Must comply with restrictions on prestudy and concomitant medications (see Section 8).

6. Must avoid prolonged sun exposure and avoid use of tanning booths or other UV light sources to the palms and soles during study.

7. Must agree that every effort should be made to stop smoking.

8. Must agree not to participate in other clinical study which will collect the skin biopsy samples during the study and for 12 weeks after receiving the last dose of any study agent.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

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).

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.

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.

6. DOSAGE AND ADMINISTRATION

A 100 mg/ mL solution of CNTO 1959 in a single-use prefilled syringe (PFS) assembled with the UltraSafe PLUS™ Passive Needle Guard (PFS-U) device will be used. Liquid placebo for CNTO 1959 will also be supplied as a PFS assembled with the PFS-U. During the study, all subjects will subcutaneously receive two syringes for each dose.

All study drug administrations will be given at the study site. The dose regimens are as follows:

- **Group I**: Two syringes of CNTO 1959 100 mg at Weeks 0, 4, 12 and q8w thereafter through Week 60, 2 syringes of placebo for CNTO 1959 100 mg at Week 16 to maintain the blind.
- **Group II**: A syringe of CNTO 1959 100 mg and a syringe of placebo for CNTO 1959 100 mg at Weeks 0, 4, 12 and q8w thereafter through Week 60, 2 syringes of placebo for CNTO 1959 100 mg at Week 16 to maintain the blind.
- **Group III**: Two syringes of placebo for CNTO 1959 100 mg at Weeks 0, 4 and 12 to maintain the blind. At Week 16, placebo subjects will be randomized in a 1:1 ratio to CNTO 1959 200 mg arm (Group IIIa) or 100 mg arm (Group IIIb). Group IIIa subjects will receive 2 syringes of CNTO 1959 100 mg at Weeks 16, 20 and q8w thereafter through Week 60. Group IIIb subjects will receive a syringe of CNTO 1959 100 mg and a syringe of placebo for CNTO 1959 100 mg at Weeks 16, 20 and q8w thereafter through Week 60.

7. TREATMENT COMPLIANCE

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

The Week 2 and 4 visits should occur within ± 3 days of the scheduled visit date. All the other study visits should occur within ± 7 days of the scheduled visit date. 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).

Information regarding study drug administrations that are administered outside of the scheduled windows or missed will be recorded. Subject charts and worksheets will be reviewed and compared with the data entries on the eCRFs to ensure accuracy. Although it is understood that treatment may be interrupted for many reasons, compliance with the treatment schedule is strongly encouraged.

8. CONCOMITANT THERAPY

Any concomitant therapy that could affect palmoplantar pustulosis or the efficacy evaluation and would be used for serious adverse events must be recorded throughout the study from screening until the study end. Other concomitant therapies must be recorded throughout the study from screening and continuing until 12 weeks after the last dose of study drug for randomized subjects.

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

8.1. Week 0 through Week 60

8.1.1. Concomitant Medications for Treatment of Palmoplantar Pustulosis

8.1.1.1. Topical Therapy

Topical therapies that could affect palmoplantar pustulosis or the efficacy evaluation (eg, corticosteroids, vitamin D3 derivatives, tacrolimus, and antibiotics) are not permitted. The only allowable concomitant treatments for palmoplantar pustulosis throughout the study are topical moisturizers including horny softener. Subjects should not use moisturizers on the day of a study visit.

8.1.1.2. Focal infection treatment, Phototherapy or Systemic medications for Palmoplantar Pustulosis

Focal infection must be carefully assessed in all subjects, and the focal infection treatment should be completed before starting the study. Focal infection treatments for palmoplantar pustulosis (e.g., tonsillectomy) are not permitted at any time during the study. If tooth abscess and/or tooth cavity is newly recognized after starting the study, dental therapy could be allowed.

The use of phototherapy or systemic medications for palmoplantar pustulosis are not permitted at any time during the study. These medications include those targeted for reducing TNF (including but not limited to infliximab, adalimumab or etanercept), drugs targeted for reducing IL-12, IL-17, or IL-23 (including but not limited to ustekinumab, tildrakizumab [MK3222], secukinumab [AIN457], ixekizumab [LY2439821], or brodalumab [AMG827]), alpha-4 integrin antagonists (including but not limited to natalizumab), steroids, any conventional systemic therapy that could affect palmoplantar pustulosis or the efficacy evaluation (including but not limited to vitamin D3 derivatives, antibiotics, biotin, MTX, cyclosporine, etretinate), herbal treatments, or traditional Taiwanese, Korean, or Chinese medicines, and any other biological agent or other systemic medication that could affect palmoplantar pustulosis or the efficacy evaluation.

8.1.1.3. Concomitant Medications for PAO

The use of nonsteroidal anti-inflammatory drugs for PAO is allowed.

The use of corticosteroids for PAO should be limited to situations for which, in the opinion of the treating physician, there are no adequate alternatives. They should be used on a short-term

basis, preferably for ≤ 2 weeks. Longer-term use of corticosteroids should be discussed with the medical monitor or designee and may require discontinuation of study drug.

Any other therapies that could affect palmoplantar pustulosis or the efficacy evaluation (eg, bisphosphonates, immunosuppressants [eg, methotrexate, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, tacrolimus]) or anakinra are not permitted.

8.1.2. Concomitant Medications for Conditions Other than Palmoplantar Pustulosis

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

The use of nonsteroidal anti-inflammatory drugs is allowed. However, disease-modifying agents such as MTX, sulfasalazine, or IM gold are prohibited during the study. Antimalarial agents, with the exception of chloroquine, may be used after Week 60.

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

8.2. After the week 60

After the Week 60 visit, there is no limitation on concomitant therapies.

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

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The TIME AND EVENTS SCHEDULE summarizes the frequency and timing of efficacy, pharmacokinetic, immunogenicity, biomarker, safety, clinical laboratory and other measurements applicable to this study.

Study visit dates are scheduled relative to the Week 0 visit date. The study visits scheduled postrandomization should occur at the times delineated in the TIME AND EVENTS SCHEDULE. The Week 2 and 4 visits should occur within ± 3 days of the scheduled visit date. All the other study visits should occur within ± 7 days of the scheduled visit date.

All visit-specific patient-reported outcome (PRO) assessments should be conducted/completed before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions.

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

The total blood volume for the study is approximately 214.0 mL (83.5 mL for Safety, 84.0 mL for PK immunogenicity, 4.0 mL for Population PK, 42.5 mL for Biomarkers). (Attachment 7)

9.1.2. Screening Phase

All subjects will have a screening visit that will occur within approximately 6 weeks before their first drug administration (Week 0). The screening phase is designed to assess inclusion/exclusion criteria and establish baseline characteristics for a subject’s palmoplantar pustulosis.

The subjects will be asked to sign the consent form at the screening visit before any study related procedures are conducted.

Adverse events and concomitant medication recording will start after the signing of the informed consent and will continue until the last study-related procedure.

Subjects with a negative IGRA result are eligible to continue with prerandomization procedures. Subjects with a newly identified positive IGRA result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients (see Attachment 9).

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

Subjects must undergo testing for TB (Attachment 9) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The subject should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing.

Subjects will undergo screening for HBV (Attachment 10) and antibodies to HCV, HIV, and HTLV-1.

Screen Failure/Rescreening

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

If the result of a test does not meet all enrollment criteria, the test may be performed a second time at the discretion of the investigator. In such cases, the first test result will not constitute a screening failure; however, the result of second test that also does not meet all enrollment criteria will be considered a screening failure. A subject will not be randomly assigned to treatment if results of a test performed at screening or baseline, or if applicable, results of a second test indicate that the subject is ineligible to participate.

In general, if a subject is a screen failure, but at some point after screening meets all of the subject eligibility criteria, the rescreening may be performed after new informed consent has been obtained. Subjects who are rescreened will be assigned a new subject number and will restart a new screening phase.

9.1.3. Treatment Phase

Week 0/Day of Randomization

At Week 0, subjects who satisfy all inclusion and exclusion criteria will be randomized. All required tests and evaluations must be conducted before start of study drug administration.

Randomization visit procedures will be performed as specified on the TIME AND EVENTS SCHEDULE.

Post-randomization Visit (Week 2 through Week 60)

All visit procedures will be performed as specified in the TIME AND EVENTS SCHEDULE.

9.1.4. Observational Period (Week 60 through Week 84)

At Week 72, Subjects will be followed for safety and PK and immunogenicity information, Subjects will be followed for safety, and maintenance of efficacy information during the observational period (Week 60 through Week 84) as per the TIME AND EVENTS SCHEDULE.

9.1.5. Safety follow-up after Early Termination

For subjects who withdraw from study participation, every effort should be made to conduct final efficacy and safety assessments at 12 weeks after the last administration of the study drug, which are the same as Week 72.

9.2. Efficacy

9.2.1. Evaluations

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

- Palmoplantar Pustulosis Area and Severity Index (PPPASI)
- Palmoplantar Pustulosis Severity Index (PPSI)
- Physician's Global Assessment (PGA)

- Dermatology Life Quality Index (DLQI)
- 36-item short-form health survey (SF-36)
- EuroQOL five dimensions questionnaire (EQ-5D)
- Magnetic Resonance Imaging (MRI)
- Photographs

Efficacy assessments (PPPASI, PPSI, PGA) will be performed at the site by an efficacy assessor trained by the sponsor at the appropriate visits as outlined by the TIME AND EVENTS SCHEDULE.

The PRO assessments will be completed at the site by subjects at the appropriate visits as outlined by the TIME AND EVENTS SCHEDULE. All visit-specific PRO assessments during a visit should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions.

9.2.1.1. Palmoplantar Pustulosis Area and Severity Index (PPPASI)

The PPPASI assesses the severity of palmoplantar pustulosis lesions and their response to therapy (see Attachment 1). 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.

9.2.1.2. Palmoplantar Pustulosis Severity Index (PPSI)

The PPSI assesses the severity of palmoplantar pustulosis lesions and their response to therapy with a score ranging from 0 to 12 (see Attachment 2). 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.

9.2.1.3. Physician's Global Assessment (PGA)

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

9.2.1.4. Patient-Reported Outcome (PRO)

9.2.1.4.1. 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, daily activities, leisure, work or school performance, personal relationships, and treatment. The DLQI produces a numeric score that can range from 0 to 30. A higher score indicates more severe disease.

9.2.1.4.2. 36-item short-form health survey (SF-36)

The SF-36 consists of 8 multi-item scales: 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. A physical component summary (PCS) scores and mental component summary (MCS) score can be derived. The concepts measured by the SF-36 are not specific to age, disease or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments.

9.2.1.4.3. EuroQOL five dimensions questionnaire (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 Index. EQ-5D index scores in this analysis will be derived based on the Japanese population.

9.2.1.5. Magnetic Resonance Imaging (MRI)

MRI image of Pustulotic Arthro-Osteitis (PAO) will be taken and should be provided to the sponsor (only for subjects with PAO at screening). MRI image of PAO will be centrally evaluated. Subjects with contraindication in MRI image (eg, claustrophobia, metal implant) are not allowed to undergo MRI. The details will be provided in a separate PAO Central Evaluation charter.

9.2.1.6. Photographs

Overview photographs of the palms and soles will be taken at a subset of study sites in patients who provide an additional consent. See Trial Center File for photography instructions.

9.2.2. Endpoints

Primary Endpoint

Change from baseline in PPPASI total score at Week 16, comparing the CNTO 1959 groups and the placebo group.

Major Secondary Endpoints

- Change from baseline in PPSI total score at Week 16
- Proportion of subjects who achieve a PPPASI-50 at Week 16

Other Secondary Endpoints

- Change from baseline in PPPASI total score over time
- Change from baseline in PPSI total score over time
- Proportion of subjects who achieve a PPPASI-50 over time
- Proportion of subjects who achieve a PPPASI-75, PPPASI-90, PPPASI-100 over time.
- Proportion of subjects who achieve a PPSI-50, PPSI-75, PPSI-90, PPSI-100 over time.
- Change from baseline in PGA score over time.
- Proportion of subjects who achieve a PGA score of cleared (0) or minimal (1) over time.
- Proportion of subjects who achieve a PGA score of cleared (0) or minimal (1) and have at least a 2-grade improvement from baseline over time.
- Change from baseline in DLQI score over time.
- Change from baseline in SF-36 score over time.
- Change from baseline in EQ-5D score over time.

Exploratory Endpoints

- Change from baseline in EQ-5D score in PAO subjects over time.

9.3. Pharmacokinetics and Immunogenicity

Blood samples will be collected for the measurement of serum CNTO 1959 concentrations and detection of antibodies to CNTO 1959 at the timepoints presented in the TIME AND EVENTS SCHEDULE. Blood samples will also be collected at the final visit from subjects who terminate study participation early.

9.3.1. Evaluations

Venous blood samples of approximately 6 mL will be collected for determination of serum concentrations of CNTO 1959 and antibodies to CNTO 1959.

Samples will be used to evaluate the pharmacokinetics, as well as the immunogenicity of CNTO 1959 (antibodies to CNTO 1959). Venous blood samples will be collected and serum samples will be divided into 3 aliquots (1 aliquot for CNTO 1959 concentration, 1 aliquot for antibodies to CNTO 1959, and 1 aliquot as back-up samples may be used as spare samples for sample loss for CNTO 1959 concentration and antibodies to CNTO 1959).

Samples collected for analyses of CNTO 1959 serum concentration and antibody to CNTO 1959 may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period for the evaluation of relevant biomarkers.

At visits where serum concentration and antibodies to CNTO 1959 will be evaluated, 1 blood draw of sufficient volume can be used.
Samples must be collected at study visits before study drug is administered. The exact dates and times of blood sampling must be recorded in the laboratory requisition form.
See the Laboratory Manual for further information regarding collection, handling, and shipment of biological samples.

9.3.2. Analytical Procedures

Serum samples will be analyzed to determine concentrations of serum CNTO 1959 using a validated, specific, and sensitive electrochemiluminescence immunoassay (ECLIA) method by the sponsor's bioanalytical facility or under the supervision of the sponsor. The sponsor, or its designee, under conditions in which the subjects' identity remains blinded, will assay these samples.

9.3.3. Pharmacokinetic Parameters

If feasible, the apparent clearance (CL/F) and apparent volume of distribution (V/F) will be estimated using a nonlinear mixed effects modeling (NONMEM) approach.

9.3.4. Immunogenicity Assessments Antibodies to CNTO 1959

The presence of antibodies to CNTO 1959 in serum will be detected using a validated ECLIA method by the sponsor's bioanalytical facility or under the supervision of the sponsor.

Serum samples that test positive for antibodies to CNTO 1959 will be further characterized to determine if antibodies to CNTO 1959 could neutralize the biological effects of CNTO 1959 in vitro (ie, neutralizing antibodies [NAbs] to CNTO 1959).

9.4. Pharmacokinetic/Pharmacodynamic Evaluations

If data permit, the relationships between serum CNTO 1959 concentration and efficacy may be analyzed graphically. If any visual trend is observed, a suitable population PK/PD model may be developed to describe the exposure-response relationship.

9.5. Biomarkers

Biomarker samples will include serum according to the TIME AND EVENTS SCHEDULE. Serum samples will be analyzed for the presence of serum markers related to Palmoplantar Pustulosis and/or inflammation. For biomarkers, known proteins related to Palmoplantar Pustulosis or CNTO 1959 (for example, IL-17, IL-23) will be measured after completion of the study. Instructions for the collection and shipment of these samples can be found in the appropriate Laboratory Manual.

9.6. Safety Evaluations

Safety and tolerability will be assessed by collecting information on AEs, Clinical Laboratory Testing (Attachment 10), ECG, vital signs (axillary temperature, pulse rate, blood pressure),

physical examinations, concomitant medication review, injection-site evaluations, allergic reactions, and early detection of TB (TB evaluation).

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached, or when investigators determine follow-up to be unnecessary.

The study will include the following evaluations of safety and tolerability according to the time points provided in the TIME AND EVENTS SCHEDULE:

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally-acceptable representative) for the duration of the study. Adverse events will be followed by the investigator.

Clinical Laboratory Tests

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

The following tests will be performed:

- Hematology Panel

-Hemoglobin	-WBC with differential [a]
-Hematocrit	-Lymphocytes
-RBC	-Monocytes
-Platelets	-Neutrophils
	-Eosinophils
	-Basophils

a. If other hematocytes are detected, then their result will be provided.

- Serum Chemistry Panel

-Albumin	-Chloride
-Alkaline phosphatase	-Creatinine
-ALT/SGPT	-Glucose
-AST/SGOT	-HbA1c
-Total CO_2	-Potassium
-Total bilirubin	-Total protein
-Urea	-Sodium
-Calcium	- hsCRP

- Lipid Panel

-Total cholesterol	-Total cholesterol to HDL ratio
-LDL	-Triglycerides
-HDL	

- Serology/other screening

-HBV [b,c]	-IGRAs (T-SPOT.TB test or QuantiFERON-TB Gold)
-Antibodies to HCV	-Serum β-hCG, Qualitative [d]
-Antibodies to HIV	-FSH [e]
-Antibodies to HTLV-1	

b. Includes HBV serology and HBV DNA testing. (See Attachment 10 for criteria of HBV DNA quantitative test required)
c. If core antibody (anti-HBc) and/or surface antibody (anti-HBs) are positive and the HBV DNA test is negative, HBV DNA quantitation should be monitored at least every 3 months or shorter.
d. Woman of childbearing potential only.
e. Necessary female subject only. (see Inclusion Criterion 7)

Electrocardiogram (ECG)

A supine 12-lead ECG will be performed at screening and at Weeks 16, 52 and 72, as specified in the TIME AND EVENTS SCHEDULE. A full 12-lead ECG will be recorded and the data will be stored in digital format and will be read at a central site as per the ECG Manual.

Vital Signs

Measurement of vital signs (axillary temperature, pulse rate, blood pressure) will be performed at the time points specified in the TIME AND EVENTS SCHEDULE.

If any clinically significant changes in vital signs are noted, they must be reported as AEs and followed to resolution, or until reaching a clinically stable endpoint.

Physical Examination

Physical examinations will be performed by the investigator. The timepoints of these examinations are specified in the TIME AND EVENTS SCHEDULE.

Any abnormalities or changes in severity noted during the review of body systems should be documented in the source document and recorded on the AE page of the eCRF.

A new, clinically significant finding (in the opinion of the investigator) not noted at screening must be captured as an AE. In addition, resolution of any abnormal findings during the study will be noted in the source document and in the eCRF.

Height and Weight

Height and weight will be measured at visits noted in the TIME AND EVENTS SCHEDULE. Subjects will be instructed to remove shoes and outdoor apparel and gear.

Injection Site Evaluation

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

Allergic Reactions

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

Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at scheduled visits. The following series of questions are suggested for use during the evaluation:

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

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

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

Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph (both posterior-anterior and lateral views,

substitutable with chest CT), a repeat IGRA, and, if possible, referral to a physician specializing in TB to determine the subject's risk of developing active TB and whether treatment for latent TB is required.

If the IGRA result is indeterminate, the test should be repeated. Subjects should be encouraged to return for all subsequent scheduled study visits according to the protocol.

Pregnancy Testing

Urine pregnancy testing is required for all women of childbearing potential at all study drug administration visit. Pregnancy tests must be completed and the result must be negative before the administration of any study drug for that visit. All pregnancy test results must be recorded in study source documents.

9.7. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. Refer to the TIME AND EVENTS SCHEDULE for the timing and frequency of all sample collections.

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

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the study if he or she has completed assessments at Week 60 of the treatment phase. Subjects who prematurely discontinue study treatment for any reason before completion of the treatment phase will not be considered to have completed the study.

10.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study.

A subject's study treatment should be discontinued if:

- The investigator believes that for safety reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment.
- The subject becomes pregnant.
- The subject is diagnosed with a malignancy, with the exception of no more than 2 localized basal cell skin cancers that are treated with no evidence of recurrence or residual disease.
- The subject is deemed ineligible according to the following TB screening criteria:

  - A diagnosis of active TB is made.
  - A subject has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination, or has had recent close contact with a person with active TB, and cannot or will not continue to undergo additional evaluation.
  - A subject undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive IGRA result, unless active TB can be ruled out and appropriate treatment for latent TB can be initiated prior to the next administration of study drug and continued to completion. Indeterminate IGRA results should be handled as in Section 9.1.2, Screening Phase. Subjects with persistently indeterminate IGRA results may continue without treatment for latent TB if active TB is ruled out, their chest radiograph (both posterior-anterior and lateral views, substitutable with chest CT) shows no abnormality suggestive of TB (active or old, inactive TB) and the subject has no additional risk factors for TB as determined by the investigator and medical monitor.
  - A subject receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.
- The subject initiates a protocol-prohibited therapy (unless previously agreed to by the medical monitor).
- The subject withdraws consent for administration of study drug.
- The subject is unable to adhere to the study visit schedule or comply with protocol requirements.
- The subject develops a severe allergic reaction such as bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension that occurs following a study drug administration.
- The subject has a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an injection of study drug. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.

Discontinuation of study treatment should be considered for subjects who develop a serious or opportunistic infection, congestive heart failure, demyelinating disease, lupus-like syndrome, cytopenias (including pancytopenia) and liver abnormalities.

Discontinuation of study treatment should also be considered for subjects who have shown no response with up to 28 weeks of treatment.

If a subject discontinues study treatment before the end of the double-blind treatment phase, every effort should be made to conduct final efficacy and safety assessments at 12 weeks after the last administration of the study drug, which are the same as Week 72.

Subjects who decide to discontinue study drug administration must be interviewed by the investigator to determine if a specific reason for discontinuing study drug can be identified. Subjects should be explicitly asked about the contribution of possible AEs to their decision to discontinue study drug; investigators should confirm that any AE information elicited has been

documented. If a subject elects to discontinue study drug due to an AE, the event should be recorded as the reason for study drug discontinuation, even if the investigator's assessment is that the AE would not require study drug discontinuation. The reason for study drug discontinuation must be documented in the eCRF and in source documents. Study drug assigned to a subject who discontinues may not be assigned to another subject.

10.3. Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent
- Death
- The investigator or sponsor believes (eg, that for safety or tolerability reasons such as an AE) it is in the best interest of the subject to discontinue treatment.
- The investigator deems the subject should initiate the protocol-prohibited medications/treatment due to lack of efficacy or other reason.

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

If a subject withdraws from the study before the end of the double-blind phase, early termination assessments (which are the same as Week 72) should be obtained wherever possible. The subject should be encouraged to conduct the safety follow-up visits for up to 12 weeks after the last dose of study drug. If a subject elects to terminate participation in the study, every effort should be made to schedule an early termination visit as soon as possible.

11. STATISTICAL METHODS

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

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

Analyses suitable for categorical data (eg, chi-square tests or Cochran-Mantel-Haenszel (CMH) chi-square tests or Fisher’s exact test, as appropriate) will be used to compare the proportions of subjects achieving selected endpoints (eg, PPPASI-50). Continuous response parameters will be analyzed using a mixed-model for repeated measures (MMRM) (for repeated measurements) or

an analysis of variance (ANOVA) or covariance (ANCOVA). If the normality assumption is in question, an ANOVA or ANCOVA on the van der Waerden normal scores will be used.

Subject baseline data, demographic and baseline clinical disease characteristics will be summarized. The baseline measurement is defined as the closest measurement taken at or before the time of the Week 0 administration.

11.1. Subject Information

For all subjects who are randomly assigned to study drug, descriptive statistics by the randomized treatment group based on all randomized subjects will be provided for subject dispositions, demographics, baseline disease characteristics, and prior and concomitant medications.

11.2. Sample Size Determination

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	

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).

Table 2: Power for a fixed sample size (47 subjects/treatment) at alpha = 0.05 with different assumptions about the change from baseline in PPPASI score at Week 16

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).

11.3. Efficacy Analysis

11.3.1. Analysis Data Set

For the efficacy analyses, all randomized subjects will be included. Subjects will be analyzed according to the treatment group to which they were randomized, regardless of the treatment they actually received.

Summaries and analyses of most of the secondary endpoints will be based on the subset of subjects with evaluable measurements according to their randomized treatment group. For subjects randomized to placebo, only subjects crossed over to receive CNTO 1959 at Week 16 will also be included in the efficacy summaries after Week 16 (from Week 20).

11.3.2. Efficacy Definitions

Treatment Failure: Subjects who discontinue study treatment due to lack of efficacy or an AE of worsening of Palmoplantar Pustulosis, or who started a protocol-prohibited medication/therapy during the study that could improve Palmoplantar Pustulosis are considered treatment failures. The treatment failure rules and handlings of efficacy data for patients with treatment failure will be documented in detail in the SAP.

PPPASI 50 Responders: Subjects with ≥ 50% improvement in PPPASI from baseline will be considered PPPASI 50 responders.

PPPASI 75 Responders: Subjects with ≥ 75% improvement in PPPASI from baseline will be considered PPPASI 75 responders.

PPPASI 90 Responders: Subjects with ≥ 90% improvement in PPPASI from baseline will be considered PPPASI 90 responders.

PPPASI 100 Responders: Subjects with 100% improvement in PPPASI from baseline will be considered PPPASI100 responders (ie, PPPASI score = 0).

11.3.3. Primary Analysis

Primary endpoint of this study is change from baseline in PPPASI total score at Week 16. In the primary efficacy analyses, data from all randomized subjects will be analyzed according to their assigned treatment group. In this primary analysis, 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. Un-imputed data 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 least-square (LS) means of the differences. The p-values for the LS mean differences along with the 2-sided 95% CIs will be presented.

Sensitivity analyses for primary endpoint (change from baseline in PPPASI total score at Week 16) will be performed 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 with and without imputation of last observation carry forward (LOCF). The last available post-baseline PPPASI total score will be carried forward to impute the PPPASI total score that are missing after discontinuation of treatment up to Week 16 of the double-blind treatment period.

Furthermore, subgroup analyses will be performed to evaluate consistency of the primary endpoints over demographics and baseline disease characteristics as appropriate. The exploratory analyses for the primary endpoints to evaluate the dose-response may be performed if deemed appropriate. Additional efficacy analyses may also be performed and will be documented in the SAP.

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.

11.3.4. Major Secondary Analyses

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

- The change from baseline in PPSI through Week 16 will be analyzed using the same MMRM model as described for the primary analysis, 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 least-square (LS) means of the differences. The p-values for the LS mean differences along with the 2-sided 95% CIs will be presented. The change from baseline in PPSI through Week 16 will also be summarized by treatment group and week using descriptive statistics.
- 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). The proportion through Week 16 will also be summarized by treatment group and week using frequencies and percentages with 95% CI.

11.3.5. Other Efficacy Analyses

For other secondary endpoints (including exploratory endpoints), the continuous variables will be summarized by treatment group and week using descriptive statistics, which will include the number of subjects (N), mean, SD, median, minimum, and maximum and the measurements through Week 16 will be analyzed using an MMRM model where there are repeated measurements; or an analysis of variance model based on appropriate rank scores or ANCOVA model where there is no repeated measurement. The categorical variables will be summarized by treatment group and week using frequencies and percentages. The binary variables through Week 16 will be compared using stratified CMH chi-square test or Fisher's exact test.

Other secondary endpoints are as follows:

- Change from baseline in PPPASI total score over time
- Change from baseline in PPSI total score over time
- Proportion of subjects who achieve a PPPASI-50 over time
- Proportion of subjects who achieve a PPPASI-75, PPPASI-90, PPPASI-100 over time
- Proportion of subjects who achieve a PPSI-50, PPSI-75, PPSI-90, PPSI-100 over time
- Change from baseline in PGA score over time
- Proportion of subjects who achieve a PGA score of cleared (0) or minimal (1) over time
- Proportion of subjects who achieve a PGA score of cleared (0) or minimal (1) and have at least a 2-grade improvement from baseline over time
- Change from baseline in DLQI score over time
- Change from baseline in SF-36 score over time
- Change from baseline in EQ-5D score over time

Exploratory endpoints are as follows:

- Change from baseline in EQ-5D score in PAO subjects over time

11.3.6. Criteria for Endpoints

Primary and major secondary endpoints will be evaluated based on the analyses specified in the efficacy analysis section. The effectiveness of CNTO 1959 treatment in this study will be reached if at least the CNTO 1959 high dose group is shown to be superior to placebo group for the primary efficacy analysis.

11.4. Pharmacokinetic and Immunogenicity Analysis

11.4.1. Analysis Data Set

PK and immunogenicity analyses will be performed based on the population which includes all subjects who received at least 1 administration of CNTO 1959 and have at least 1 observed post-dose PK and immunogenicity data point, respectively, after administration of CNTO 1959.

11.4.2. Pharmacokinetic Analysis

Serum CNTO 1959 concentrations over time will be summarized for each treatment group. Descriptive statistics, including arithmetic mean, SD, median, interquartile range, minimum, and maximum will be calculated at each sampling timepoint. All concentrations below the lowest quantifiable sample concentration of the assay (BQL) or missing data will be labeled as such in the concentration data listing or statistical analysis system (SAS) dataset. The BQL concentrations will be treated as zero in the summary statistics.

If feasible, a population PK analysis using a NONMEM approach will be used to characterize the disposition characteristics of CNTO 1959 in the current study. Data may be combined with those of other selected studies to support a relevant structural model. The CL/F and V/F values will be estimated. The influence of important variables (such as body weight, antibodies to CNTO 1959, and concomitant medications) on the population PK parameter estimates may be evaluated. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate technical report.

11.4.3. Immunogenicity Analysis

The incidence and titers of antibodies to CNTO 1959 will be summarized for all subjects who receive at least 1 dose of CNTO 1959 and have appropriate samples for detection of antibodies to CNTO 1959 (ie, subjects with at least 1 sample obtained after their first dose of CNTO 1959). A listing of subjects who are positive for antibodies to CNTO 1959 will be provided in the clinical study report.

If NAbs are measured, the incidence of NAbs to CNTO 1959 will be summarized for subjects who are positive for antibodies to CNTO 1959 and have samples evaluable for NAbs.

11.5. Pharmacokinetic/Pharmacodynamic Analyses

If data permit, the relationships between serum CNTO 1959 concentration and efficacy may be analyzed graphically. If any visual trend is observed, a suitable population PK/PD model may be developed to describe the exposure-response relationship. Details will be given in a population

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

11.6. 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.

11.7. Safety Analyses

Safety data, including but not limited to, AEs, serious adverse events (SAEs) , infections, serious infections, mortality, changes in laboratory assessments, and changes in vital signs through Week 72 will be summarized. Treatment-emergent AEs will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms. Details will be specified in the SAP.

Safety Definitions

Injection Site Reactions

An injection site reaction is any unfavorable or unintended sign that occurs at an injection site and will be recorded as an AE.

Safety Analyses

All safety analyses will be based on the population of subjects who received at least 1 injection of study drug; subjects will be summarized by the treatment they actually received. Routine safety evaluations will be performed. AEs, SAEs, and infections by Week 16 will be summarized by treatment group. Additional summary tables of AEs during the entire treatment period will be generated for all CNTO 1959 treated subjects including those who switched from placebo at Week 16.

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

- The incidence and type of AEs
- The incidence and type of SAEs
- The incidence and type of infection
- The incidence and type of related AEs
- The incidence and type of injection site reactions
- The laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry)
- The incidence of markedly abnormal laboratory parameters (hematology and chemistry)

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are AEs with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe or an SAE. Analysis methods for those AEs reported during after Week 72 visit will be detailed in SAP.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test (eg, hematology, serum chemistry). National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grades (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for selected laboratory analyses at baseline and at each scheduled time point. A listing of subjects with post-baseline abnormal laboratory results based on CTCAE grades will also be provided.

Electrocardiogram (ECG)

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Abnormal findings will also be summarized.

Vital Signs

The observed value and change from baseline of vital signs parameters will be summarized descriptively by visit and treatment group.

Physical Examination

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

11.8. Interim Analysis

The sample size proposed in Section 11.2, Sample Size Determination was estimated based on previous Phase 2 results. The assumptions of an expected treatment difference and variability may or may not be upheld in this study. As a result, an unblind interim analysis is planned to re-estimate sample size, and, if necessary, increase the sample size to achieve the desired conditional power while maintaining control of the overall Type I error rate. In addition, a

futility analysis of the primary analysis will be performed, based on the approach introduced by Mehta and Pocock.[16]

A rigorous IDMC statistical analysis plan and IDMC charter will be developed detailing the algorithm for a sample size increase based on the interim data, the futility boundary and how the interim analysis will be executed, and how potential operational bias will be minimized. An independent, Statistical Support Group (SSG) will perform the interim analysis and will make recommendations to the Chair of the IDMC for futility and any sample size adjustment based on the rules defined in the IDMC SAP. Any changes to sample size will be communicated by the IDMC Chair to SSG who will coordinate with the interactive web response system (IWRS) vendor to ensure that the appropriate number of subjects is enrolled in the trial. To prevent back-calculation of the effect size, none of the sponsor members, subjects or staff members at the investigational sites conducting this clinical trial will be informed of the specific sample size adjustment resulting from this interim analysis (i.e., neither the recommendation to increase the sample size or not, nor the overall total increase in sample size). Moreover, the total accrual information (i.e., the total numbers of screened, randomized or dosed patients) will be kept confidential from subjects, investigators and site staffs during the entire period from FPI (first patient in) to the DBL at Week 16.

Before the DBL at Week 16, the interim analysis will be conducted when approximately 40% of the 150 randomized subjects have completed Week 16 visit or have ended study participation before Week 16 visit. The data accrued up to the interim analysis will be used to calculate the conditional power based on the analysis of change from baseline in PPPASI total score at Week 16 in Group I (CNTO 1959 200 mg) and placebo.

The values of attainable conditional power will be partitioned into 4 zones – futility, unfavorable promising, and favorable. If the conditional power falls in the futility zone, the study will stop for futility; if the conditional power falls in the promising zone, the sample size will be increased according to a pre-specified sample size adaptation rule to attain the 90% conditional power in Group I, subject not exceeding the maximum 75 patients per group; otherwise the study will continue with sample size unadjusted. Note that the new adjusted sample size computed out by the data in Group I will be applied for both doses of CNTO 1959. This study does not allow for stopping a dose based on the results of the interim analysis and the numbers of subjects per group for the second stage will be identical across the treatment groups. Details of the plan for the interim analysis will be specified in the IDMC statistical analysis plan document before the time at which the interim analysis is performed.

Gao, Ware and Mehta[17] have shown that if the chosen boundary value of unfavorable zone is not so small, the method employed in this interim analysis will not inflate the overall Type I error. In light of the capped number of patients (about 1.5 times of the original one) and the timing of the interim analysis (when about 40% of the randomized subjects data are available), the boundary value of unfavorable zone set for this study at 42% (see Table 1 in Metha and Pocock[16]) satisfies the requirement that protects the overall Type I error rate and the conventional final inference can be performed at the end of the study.

11.9. Independent Data Monitoring Committee

An IDMC will be 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 committee will meet to review the safety and interim data. After the review, the IDMC will make recommendations regarding the continuation of the study. The details will be provided in a separate IDMC charter.

The IDMC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The IDMC responsibilities, authorities, and procedures will be documented in its charter.

12. ADVERSE EVENT REPORTING

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

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

Serious Adverse Event

A SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death

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

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For CNTO 1959, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Event Associated With the Use of the Drug

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

12.1.2. Attribution Definitions

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

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

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

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

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

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

12.2. Special Reporting Situations

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

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

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

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations (Section 12.2), whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 12 weeks after the last dose of study drug (Week 72 visit or early termination visit). From Week 72 to 84, AEs considered associated with the use of the drug, whether serious or non-serious, will be reported. SAEs, including those spontaneously reported to the investigator through Week 84 must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- The investigator believes that it is not necessary
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

All events that meet the definition of a SAE will be reported as SAE, regardless of whether they are protocol-specific assessments.

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

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

SAEs relating to lack of efficacy (eg, events attributed to "Palmoplantar Pustulosis") or progression of the disease under study will not be individually unblinded for expedited reporting. These cases will still be individually reviewed in an unblinded fashion by the IDMC (Section 11.9), and along with all events (including those assessed as unrelated by investigators), collectively assessed at study database locks and/or periodic full IDMC meetings. If such a review concludes that an association with CNTO 1959 is at least reasonably possible, that assessment would result in changes to the ICF and/or the protocol consistent with assessment of the AE as an unanticipated problem and/or an adverse drug reaction to CNTO 1959. This assessment as well as any resultant ICF or protocol changes would be communicated promptly to appropriate global health authorities and IEC/IRB under whose auspices this protocol is being conducted.

All SAEs and nonserious AEs that represent any of the following diagnoses or any symptoms associated with the following diagnoses (eg, chest pain, dizziness) must be reported to the sponsor and will require efforts to obtain additional medical records:

- myocardial infarction
- stroke
- cardiovascular death
- unstable angina
- coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery)
- transient ischemic attack
- venous and peripheral arterial vascular thrombotic events (ie, deep vein thrombosis and pulmonary embolism)
- congestive heart failure
- cardiac arrhythmia
- syncope of a cardiovascular origin
- severe/accelerated hypertension leading to hospitalization

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

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

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

12.3.2. Serious Adverse Events

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

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to

the sponsor within 24 hours. The initial and follow-up reports of a SAE should be made by facsimile (fax) or electronic mail.

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

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

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

- Surgery or procedure planned before entry into the study (must be documented in the eCRF).

  Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

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

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

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

12.3.4. Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first administration of study drug(s) in subjects participating in this clinical study must be reported by the investigator according to the procedures in Section 12.3.2, Serious Adverse Events. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE.

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

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

13.1. Procedures

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

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

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

A 100 mg/1 mL solution of CNTO 1959 in an aqueous medium of 10 mM L-histidine 8.5% [w/v] sucrose, and 0.055% [w/v] polysorbate 80 at pH5.8 in a PFS-U will be used. Liquid placebo for CNTO 1959 containing an aqueous medium of 10 mM L-histidine 8.5% [w/v]

sucrose, and 0.055% [w/v] polysorbate 80 at pH5.8 will also be supplied as a PFS assembled with the PFS-U.

14.2. Packaging

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

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

All CNTO 1959 and placebo must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C) and protected from exposure to light. The sterile product does not contain preservatives and is designed for single use only. Protection from light is not required during dose preparation or administration of CNTO 1959.

Refer to the pharmacy manual/study site investigational product manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug (CNTO 1959 or placebo) received at the site is inventoried and accounted for throughout the study. CNTO 1959 administered to the subject must be documented on the drug accountability form. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

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

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids should be disposed of immediately in safe manner and therefore will not be retained for drug accountability purposes. The immediate destruction of these drug supplies should be documented in the drug accountability on-site.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The

investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure
- Study site investigational product manual
- Laboratory manual
- PRO questionnaires
- Study Card
- Codebreak procedure

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled. Vulnerable populations (ie, persons in detention) are not eligible for this study.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the Japan Red Cross (400 mL of blood for donation).

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

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

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug

- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

At least once a year, the IEC/IRB will be asked to review and reapprove this study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

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

16.2.3. Informed Consent

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

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

evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

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

In order to properly implement the evaluation of this study, it is possible to use previous data obtaining informed consent.

16.2.4. Privacy of Personal Data

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

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

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

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

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

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by

the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

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

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable

- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

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

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)

17.3. Subject Identification, Enrollment, and Screening Logs

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

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

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

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

Subject-and investigator-completed scale and assessments designated by the sponsor will be recorded and will be considered electronic source data.

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

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

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

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. Study site personnel must complete the eCRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

Every effort should be made to ensure that all subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the eCRFs are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the eCRF (if applicable) and complete the query.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

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

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

17.7. Record Retention

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

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator (or designee)/institution as to when these documents no longer need to be retained.

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

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

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the

monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

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

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

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last visit and study assessment for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit and assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

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

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

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

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

17.10. On-Site Audits

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

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

17.11. Use of Information and Publication

All information, including but not limited to information regarding CNTO 1959 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of CNTO 1959, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

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

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data

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

Registration of Clinical Studies and Disclosure of Results

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

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Attachment 1: PPPASI (Palmo-Plantar Pustular Area and Severity Index)

The PPPASI is a system used for assessing and grading the severity and area of palmoplantar pustulosis lesions and their response to therapy. The PPPASI produces a numeric score that can range from 0 to 72. The severity of the disease is calculated as follows.

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% of the total body BSA of the palms and soles, respectively. Each of these areas is assessed separately for erythema, pustules and desquamation, which are each rated on a scale of 0 to 4.

The scoring system for the signs of the disease (erythema, pustules/vesicle and desquamation /scale) is: 0 = none, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.

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

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

The PPPASI formula is:

PPPASI = (E + P + D) Area×0.2 (right palm) + (E + P + D) Area×0.2 (left palm) + (E + P + D) Area×0.3 (right sole) + (E + P + D) Area×0.3 (left sole)

Where E = erythema, P = pustular/vesicle and D = desquamation/scale

References

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Attachment 2: Palmo-Planter Severity Index (PPSI)

The PPSI is a system used for assessing and grading the severity of palmoplantar pustulosis lesions and their response to therapy. The PPSI produces a numeric score that can range from 0 to 12.

In the PPSI system, evaluation sites are identified either palms or soles, which has the most severe skin lesion at screening. And identified site will be assessed at all subsequent visits.
Evaluation site are assessed separately for erythema, pustules/vesicle and desquamation/scale, which are each rated on a scale of 0 to 4.

The severity of the disease is calculated as follows.
The scoring system for the signs of the disease (erythema, pustules/vesicle and desquamation/scale) is:
0 = none, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe.

The PPSI formula is: PPSI total score= (E + P + D)

Where E = erythema, P = pustular/vesicle and D = desquamation/scale

References

PMDA assessment report of Oxarol (Maxacalcitol) Ointmnet 25 μg/g and Lotion 25 μg/g, October 2008

Attachment 3: PGA (Physician's Global Assessment)

The PGA is used to determine the subject's overall palmoplantar pustulosis lesions at a given time point.

<PGA>
Overall lesions will be graded based on the scales below.
0 = clear
1 = almost clear
2 = Mild
3 = Moderate
4 = Severe
5 = Very severe

Attachment 4: Dermatology Life Quality Index (DLQI)

The questionnaire used in this study is written in Japanese and not included here since the web posting requirements don't allow Japanese language in the documents. Information regarding the original version and Japanese version is provided in the reference below:

References

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. Clin Exp Dermatol, 1994; 19: 210-216.
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Attachment 5: 36-Item Short Form Health Assessment Questionnaire (SF-36)

The questionnaire used in this study is written in Japanese and not included here since the web posting requirements don't allow Japanese language in the documents. Information regarding the original version and Japanese version is provided in the reference below:

References

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Attachment 6: EuroQOL five dimensions questionnaire (EQ-5D)

The questionnaire used in this study is written in Japanese and not included here since the web posting requirements don't allow Japanese language in the documents. Information regarding the original version and Japanese version is provided in the reference below:

References

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Attachment 7: Blood Volume Requirements by Assessment

Volume of Blood to be Collected From Each Subject

Type of Sample	Volume per Sample (mL)	No. of Tests per Subject	Total Volume of Blood (mL)[a, b]
Safety			
- Chemistry/Lipids/other	2.5	12	30.0
	5.0	1	5.0
	7.5	1	7.5
		(total 14)	42.5
- Hematology	2.0	14	28.0
- Serology	10.0	1	10.0
- HBV DNA testing	6.0	as needed	—[c]
- TB testing	3.0[d]	1	3.0
Pharmacokinetic/Immunogenicity samples	6.0	14	84.0
Population PK sample	4.0	1	4.0
Biomarker sample	8.5	5	42.5
Total			214.0

a. Calculated as number of samples multiplied by amount of blood per sample during the study.
b. The following visits are not included in the total volume: RETEST, FOLLOW-UP 12 WKS AFTER LA, HBV DNA
c. Not included in the total volume
d. 3.0 mL for the QuantiFERON-TB Gold test (the central laboratory) or 6.0 - 8.0 mL for T-SPOT.TB test (the study site or local laboratory)

Attachment 8: Central Laboratory Testing

Hematology	Lipids	Serum Chemistry
• Hemoglobin • Hematocrit • RBC • WBC with differential[a] • Lymphocytes • Monocytes • Neutrophils • Eosinophils • Basophils • Platelets	• Total cholesterol • LDL • HDL • Total cholesterol to HDL ratio • Triglycerides	• Albumin • Alkaline phosphatase • ALT/SGPT • AST/SGOT • Total CO_2 • Total bilirubin • Urea • Calcium • Chloride • Creatinine • Glucose • HbA1c • Potassium • Total protein • Sodium • hsCRP
Serology / other screening		
• HBV[b,c] • Antibodies to HCV • Antibodies to HIV • Antibodies to HTLV-1 • IGRAs (T-SPOT.TB test or QuantiFERON-TB Gold) • Serum β-hCG, Qualitative[d] • FSH[e]		

a. If other hematocytes are detected, then their result will be provided.
b. Includes HBV serology and HBV DNA testing. (See Attachment 10 for criteria of HBV DNA quantitative test required)
c. If core antibody (anti-HBc) and/or surface antibody (anti-HBs) are positive and the HBV DNA test is negative, HBV DNA quantitation should be monitored at least every 3 months or shorter.
d. Woman of childbearing potential only.
e. Necessary female subject only. (see Inclusion Criterion 7)

Attachment 9: Tuberculosis Screening

QuantiFERON-TB Gold Test

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

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

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

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

Performing the QuantiFERON-TB Gold Test

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

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

laboratory will perform an ELISA to quantify the amount of IFN-γ present in the plasma using spectrophotometry and computer software analysis.

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

T-SPOT.TB test

The T-SPOT.TB test is an in vitro diagnostic test for the detection of effector T cells that respond to stimulation by M. tuberculosis-specific antigens ESAT-6 and CFP 10 by capturing IFN-γ.

The immune response to infection with M. tuberculosis is mediated predominantly through T cell activation. As part of this response, T cells are sensitized to M. tuberculosis antigens and the activated effector T cells produce the cytokine IFN-γ when stimulated by these antigens (Arend et al, 2000; Lalvani et al, 2001).

The T-SPOT.TB test uses the enzyme-linked immunospot (ELISPOT) methodology to enumerate M. tuberculosis-sensitized T cells by capturing IFN-γ in the vicinity of T cells from which it was secreted (NCCLS document I/LA26-A).

The T-SPOT.TB test uses M. tuberculosis-specific antigens ESAT-6 and CFP 10. ESAT-6 and CFP10 are absent from all BCG strains and from most non-tuberculous mycobacteria with the exception of M. kansasii, M. szulgai, M. gordonae, and M. marinum , and it is therefore possible that a positive T-SPOT.TB test result may be due to infection with any of the four mycobacteria.

In a Japanese clinical study, the sensitivity and specificity of the T-SPOT.TB test were 97.5% and 99.1%, respectively.

Data from a limited number of published studies examining the performance of the IGRAs in immunosuppressed populations suggest that the T-SPOT.TB test is more sensitive than the QuantiFERON-TB Gold test in the diagnosis of high-risk individuals, such as immunosuppressed patients and children (Ferrara et al, 2006).

Performing the T-SPOT.TB test

The investigator can choose the T-SPOT.TB test instead of the QuantiFERON-TB Gold test. The T-SPOT.TB test can be performed at the study site or local laboratory in accordance with each laboratory's procedure. Subjects who have an indeterminate result should have the test repeated.

In case result is incomplete, the investigator can consider as negative, if the subject's chest radiograph or lung computed tomography (CT) shows no abnormality suggestive of TB (active or old, inactive TB), and he/she has no additional clinical risk factors for TB as determined by the investigator and medical monitor.

Adherence to Local Guidelines

In Japan, oral isoniazid (INH: 300 mg daily, in principle, but adjusted to 5 mg/ kg/day for low-weight subjects) will be administered to subjects for 6 to 9 months from 3 weeks before the initiation of investigational treatment. If subjects cannot take INH, Rifampicin (RFP: 600 mg daily, in principle, but adjusted to 10 mg/ kg/day for low-weight subjects) will be administered to subjects for 4 to 6 months (The Japanese Society for Tuberculosis, 2013).

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Attachment 10: Hepatitis B Virus Screening

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

Subjects who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this study.

Subjects who test **positive** for surface antigen (HBsAg+) ***are not eligible*** for this study, regardless of the results of other hepatitis B tests.

Subjects who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and/or*** surface antibody (anti-HBs+) must undergo further testing for hepatitis B deoxyribonucleic acid (HBV DNA test). If the HBV DNA test is **positive**, the patient ***is not eligible*** for this study. If the HBV DNA test is **negative**, the patient ***is eligible*** for this study. In the event the HBV DNA test cannot be performed, the patient ***is not eligible*** for this study. If core antibody (anti-HBc) and/or surface antibody (anti-HBs) are positive and the HBV DNA test is negative, HBV DNA quantitation should be monitored at least every 3 months or shorter.

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

Reference;

Japan College of Rheumatology: Recommendations on Immunosuppressive Therapy in Patients with Rheumatic Disease and Hepatitis B Virus Infection, Revised Version; Oct. 18. 2011.

INVESTIGATOR AGREEMENT

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

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

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Kenji Nonaka

Institution: Janssen Pharmaceutical K.K.

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

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