

**Janssen Pharmaceutical K.K.**

**Clinical Protocol**

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**A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Efficacy, Safety and Tolerability of CNTO 1959, a Human Anti-IL-23 Monoclonal Antibody, following Subcutaneous Administration in Subjects with Palmoplantar Pustulosis**

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**Protocol CNTO1959PPP2001; Phase 2**

**CNTO 1959**

**Status:** Approved  
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**Prepared by:** Janssen Pharmaceutical K.K.  
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**GCP Compliance:** This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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## **SYNOPSIS**

A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Efficacy, Safety and Tolerability of CNTO 1959, a Human Anti-IL-23 Monoclonal Antibody, following Subcutaneous Administration in Subjects with Palmoplantar Pustulosis

CNTO 1959 is a fully human immunoglobulin G1 lambda (IgG1 $\lambda$ ) monoclonal antibody 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 subsequent binding of extracellular IL-23 to the cell surface IL-23 receptor (IL-23R), inhibiting IL-23 specific intracellular signaling and subsequent activation and cytokine production.

## **OBJECTIVES AND HYPOTHESES**

### **Primary Objectives**

The primary objectives of this study are to evaluate the efficacy of CNTO 1959 in the treatment of subjects with palmoplantar pustulosis at Week 16, and to assess the safety and tolerability of CNTO 1959 in subjects with palmoplantar pustulosis.

### **Major Secondary Objectives**

The major secondary objectives of this study are:

- To assess the pharmacokinetics and immunogenicity of CNTO 1959 following subcutaneous (SC) administration in subjects with palmoplantar pustulosis
- To assess the impact of treatment with CNTO 1959 on the health related quality of life (QOL) measurements in subjects with palmoplantar pustulosis at Week 16
- To assess the possible time point with maximum clinical response of CNTO 1959 after two dose injection

### **Exploratory Objectives**

The exploratory objectives of this study are:

- To explore biomarkers following CNTO 1959 administration in subjects with palmoplantar pustulosis
- To explore the impact of treatment with CNTO 1959 on pustulotic arthro-osteitis (PAO) in the subset of subjects with PAO at screening
- To explore possible overall process of clinical response of CNTO 1959 over time.

### **Hypothesis**

The primary hypothesis of this study is that CNTO 1959 treatment, 200 mg SC injection at Week 0 and Week 4, is superior to placebo in terms of the change from baseline of Palmoplantar Pustulosis Severity Index (PPSI) total score at Week 16.

## **OVERVIEW OF STUDY DESIGN**

This is a phase 2, randomized, double-blind, placebo-controlled, parallel group, multicenter study of CNTO 1959 in subjects with palmoplantar pustulosis. Approximately 50 subjects will be randomly assigned to 1 of 2 treatment groups (CNTO 1959 200 mg SC or placebo SC) in a 1:1 ratio and will receive study drug at Week 0 and Week 4. After randomization (Week 0), subjects will return to the

study site for 9 evaluation visits (Week 1, 2, 4, 6, 8, 12, 16, 20 and 24). The total duration of subject participation will be approximately 30 weeks, which includes a screening period of about 6 weeks before dosing. Completion of the Week 24 assessment constitutes the subject's completion of the study.

### **SUBJECT POPULATION**

Subjects are men or women 20 years of age or older with palmoplantar pustulosis as defined by a PPSI score of 7 or greater at screening and baseline (Week 0), including active lesions on the palms or soles. Subject must have inadequate response to the treatment with topical steroid and/or topical vitamin D<sub>3</sub> derivative preparations and/or the phototherapy and/or systemic etretinate prior to or at screening. Subject must agree to avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet (UV) light sources to the palms and soles during study.

### **DOSAGE AND ADMINISTRATION**

All subjects randomized will receive 2 injections of 1 mL each as SC injections at each administration (two 1 mL SC injection containing placebo or CNTO 1959) at Week 0 and Week 4.

### **EFFICACY EVALUATIONS/ENDPOINTS**

Efficacy evaluations include PPSI, PPPASI (Palmo-Plantar Pustulosis Area and Severity Index), PGA (Physician's Global Assessment of palmoplantar pustulosis lesion), PA (Physician's Assessment of each skin lesions) and Patient's Visual Analogue Scale Assessment of Palmoplantar Pustulosis Severity (Patient's VAS-PPP severity), Subjects with concurrent PAO at screening will also be evaluated using a Physician's Visual Analogue Scale Assessment of Pustulotic Arthro-Osteitis Activity (Physician's VAS-PAO activity) and a Patient's Visual Analogue Scale Assessment of Pustulotic Arthro-Osteitis Activity and Pain (Patient's VAS-PAO activity and pain) in order to explore the efficacy of CNTO 1959 in the treatment of PAO. In addition, the Dermatology Life Quality Index (DLQI) score and SF-36 score will be used to assess the impact of treatment on disease and subject's QOL, respectively. 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, either both palms or both soles, which has the most severe skin lesion at screening will be identified as the evaluation sites. Evaluation sites are assessed separately for erythema, pustules/vesicle and desquamation/scale, which are each rated on a scale of 0 to 4. PPPASI is a system used for assessing and grading the severity of palmoplantar pustulosis lesions and their response to therapy. The PPPASI produces a numeric score that can range from 0 to 72. The PGA documents the Physician's Global assessment of the subject's palmoplantar overall skin lesions status. The Visual Analogue Scale assessment will be recorded on a 10-cm VAS.

### **Primary Endpoint**

The primary efficacy endpoint is the change from baseline in PPSI total score at Week 16.

### **Major Secondary Endpoints**

- Change from baseline in PPSI total score over time
- Change from baseline in PPPASI total score at Week 16 and over time
- Proportion of subjects who achieve a PPPASI-50 at Week 16 and over time
- Proportion of subjects who achieve a PGA score of 1 or less at Week 16 and over time

### **Other Secondary Endpoints**

- Proportion of subjects who achieve a PPPASI-75 at Week 16 and over time

- Change from baseline in PA (each score) at Week 16 and over time
- Change from baseline in Patient's VAS-PPP severity at Week 16 and over time
- Change from baseline in Physician's VAS-PAO activity at Week 16 and over time
- Change from baseline in Patient's VAS-PAO activity and pain at Week 16 and over time
- Change from baseline in DLQI at Week 16 and over time
- Change from baseline in SF-36 at Week 16 and over time

### **PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS**

Samples will be collected according to the Time and Events Schedule and used to evaluate the pharmacokinetics, as well as the immunogenicity of CNTO 1959 (antibodies to CNTO 1959). If deemed necessary, pharmacokinetic data may be combined with those of other clinical studies of CNTO 1959 when population PK analysis is performed.

### **BIOMARKER EVALUATIONS**

Serum biomarkers of inflammation such as, but not limited to, IL-23p19, IL-17, IL-6, IL-8, IL-22, tumor necrosis factor alpha (TNF $\alpha$ ), and IL-12p40 will be evaluated from all subjects according to the Time and Events Schedule. Total ribonucleic acid (RNA) will be isolated from whole blood samples and used for differential gene expression analyses and microRNA analyses to better understand the pathological mechanisms involved in palmoplantar pustulosis and to identify a treatment response signature to CNTO 1959. Skin biopsy samples for gene expression analyses may include, but are not limited to, IL-23-associated proteins, such as IL-23 receptor, IL-17A, IL-17F, IL-17 receptor, IL-6, IL-12p40, IL-12p35, IL-20R, IL-22RI, IL-8, GM-CSF, VEGF and TNF $\alpha$  will be collected from subjects who consent separately to participate in biopsy assessment.

### **SAFETY EVALUATIONS**

The safety and tolerability of study drugs (placebo, CNTO 1959) will be monitored by physical examinations, detection of injection site and allergic reactions, ECGs, clinical laboratory tests, vital signs, concomitant medications and adverse events (AEs) according to the Time and Events Schedule.

### **STATISTICAL METHODS**

#### Sample size determination

In the phase 3 double blind controlled study for Maxacalcitol (topical vitamin D<sub>3</sub>) that is approved for a treatment of palmoplantar pustulosis in Japan, the mean change from baseline of skin observation total score for Maxacalcitol was -3.7 (standard deviation [SD] = 2.1, number of patients [N] = 94) and -1.9 (SD = 1.9, N=93) for placebo group, as results of the primary endpoint. Based on these results, 25 subjects per group (total of 50 subjects) are considered as appropriate for this study in consideration to uncertainty for the estimates with varying assumptions. The sample size of 25 subjects has an 84% power to detect a significant difference between the CNTO 1959 treatment group and the placebo group at a two-sided alpha level of 0.05, assuming a treatment difference in the change from baseline of PPSI total score at Week 16 of 1.8 with a SD of 2.1.

#### Efficacy

In this primary analysis, the change from baseline in PPSI total score at Week 16 will be analyzed using an analysis of covariance (ANCOVA) model which includes treatment as factors and baseline score as a covariate. Treatment effect of CNTO 1959 versus placebo will be estimated based on least-square (LS) means of the difference. The p-value for the treatment difference along with the 2-sided 95% CI will be presented. The last available post-baseline PPSI total score will be carried forward to impute the PPSI



total score that are missing after discontinuation of treatment up to Week 16 of the double-blind treatment period. If a subject meets one of the criteria of a treatment failure, the subject will be designated a treatment failure for primary endpoint at all visits starting from the visit after the treatment failure and the last available post-baseline PPSI total score value will be assigned regardless of the actual observed data. To evaluate sensitivity of the results to the imputation method, the impact of missing data would be explored through various analysis methods.

For major secondary endpoints, the change from baseline in PPSI total score will also be summarized over time by treatment group using descriptive statistics. If the evaluation visit with larger difference between treatment groups than that of Week 16 is observed, same analysis will be performed for that visit as described for the primary analysis, to assess possible time point with maximum clinical response of CNTO 1959. The change from baseline in PPPASI at Week 16 will be analyzed using an ANCOVA model. Treatment effect of CNTO 1959 versus placebo will be estimated based on LS means of the difference. The p-value for the treatment difference along with the 2-sided 95% CI will be presented. The change from baseline in PPPASI will also be summarized over time by treatment group using descriptive statistics. The proportion of subjects who achieve a PPPASI-50 at Week 16 and the proportion of subjects who achieve a PGA score of 1 or less at Week 16 will be compared between the CNTO 1959 treatment group and placebo group using Fisher's exact test.

For other secondary endpoints, the continuous variables will be summarized by treatment group using descriptive statistics, which will include the number of subjects (N), mean, SD, median, minimum, and maximum and will be analyzed using an analysis of variance model based on appropriate rank scores or ANCOVA model. The categorical variables will be summarized by treatment group using frequencies and percentages. The binary variables will be compared using Fisher's exact test. These other secondary endpoints at other evaluation visits than Week 16 might be summarized as described above, if necessary.

#### Pharmacokinetics

Serum CNTO 1959 concentrations will be summarized with descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, maximum, 25% quantile and 75% quantile at each sampling time. Mean or median serum CNTO 1959 concentration time profiles will be plotted after the first dose of study drug.

Population PK analysis of serum concentration-time data of CNTO 1959 will be performed using nonlinear mixed-effects model. Data may be combined with those of other clinical studies of CNTO 1959 to conduct the population PK analysis. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

#### Immunogenicity

The incidence of antibodies to CNTO 1959 during the study will be summarized for all subjects who receive an administration 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).

#### Safety

The verbatim terms used in the electronic case report form (eCRF) by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the treatment phase (ie, treatment-emergent AEs, and AEs that have worsened since baseline) will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

For other safety data (e.g., laboratory test, vital sign, and electrocardiogram [ECG]) will be summarized using descriptive statistics and frequency table.

**TIME AND EVENTS SCHEDULE**

Phase	Screening period	Double-blind period											Safety follow-up after ET		
		Day 1 <sup>j</sup> (Week 0)	Day 8 (Week 1)	Day 15 (Week 2)	Day 29 <sup>j</sup> (Week 4)	Day 43 (Week 6)	Day 57 (Week 8)	Day 85 (Week 12)	Day 113 (Week 16)	Day 141 (Week 20)	Day 169 (Week 24)	ET	4, 8 weeks after LA	12 weeks after LA	
<b>Allowance</b>															
Screening/Administrative															
Informed consent	X														
Demographics	X														
Eligibility criteria	X	X													
Medical and medication history	X														
Height	X														
Weight	X	X							X		X	X		X	
Chest X-ray (both posterior-anterior and lateral views, substitutable with chest CT)	X										X			X	
Serology/other screening test <sup>b</sup>	X														
Serum pregnancy test <sup>c</sup>	X														
Urine pregnancy test <sup>c</sup>		X													
Discontinue systemic phototherapy / medications <sup>d</sup>	X														
Discontinue topical treatments <sup>e</sup>	X														
<b>Study Drug Administration</b>															
Randomization		X													
Study drug administration <sup>f</sup>		X			X										
<b>Safety Assessments</b>															
Vital signs <sup>g</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Supine 12-lead ECG <sup>h</sup>	X	X	X	X	X				X		X	X	X		X
<b>Efficacy Assessments</b>															
PPSI, PPPASI, PGA, PA-pustule, PA-vesicle	X	X	X	X	X	X	X	X	X	X	X	X			
PA-nail	X	X							X		X	X			
Patient's VAS-PPP severity		X	X	X	X	X	X	X	X	X	X	X			
Physician's VAS-PAO activity <sup>i</sup>		X					X		X		X	X			
Patient's VAS-PAO activity and pain <sup>j</sup>		X					X		X		X	X			
DLQI		X	X	X	X	X	X	X	X	X	X	X			
SF-36		X					X		X		X	X			
MRI <sup>k</sup>	X								X		X	X			
Photographs	X	X	X	X	X	X	X	X	X	X	X	X			

Phase	Screening period	Double-blind period										Safety follow-up after ET		
		Day 1 <sup>j</sup> (Week 0)	Day 8 (Week 1)	Day 15 (Week 2)	Day 29 <sup>j</sup> (Week 4)	Day 43 (Week 6)	Day 57 (Week 8)	Day 85 (Week 12)	Day 113 (Week 16)	Day 141 (Week 20)	Day 169 (Week 24)	ET	4, 8 weeks after LA	12 weeks after LA
<b>Allowance</b>			±3 day	±3 day	±3 day	±3 day	±3 day	±7 day	±7 day	±7 day	±7 day			
<b>Clinical Laboratory Assessments</b>														
Serum chemistry <sup>b</sup>	X	X		X	X	X	X	X	X	X	X	X	X	X
Hematology <sup>b</sup>	X	X			X		X	X	X	X	X	X	X	X
Lipid panel <sup>b</sup>		X							X		X	X		X
Urinalysis <sup>b</sup>	X	X			X		X	X	X	X	X	X	X	X
<b>Pharmacokinetics/Immunogenicity</b>														
Serum sample for CNTO 1959 concentration <sup>k</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X
Serum sample for antibodies to CNTO 1959 <sup>k</sup>		X									X	X <sup>m</sup>		X
<b>Biomarkers</b>														
Serum sample for biomarker analysis		X			X				X					
Whole blood sample for biomarker analysis		X			X				X					
Skin biopsy <sup>l</sup>		X							X					
<b>Ongoing Subject Review</b>														
Physical examination	X	←	←	←	←	←	←	←	←	←	←	←	X	←
Concomitant medication monitoring	X	←	←	←	←	←	←	←	←	←	←	←	X	←
Adverse event monitoring	X	←	←	←	←	←	←	←	←	←	←	←	X	←

- a. Screening visit must occur within 6 weeks of study drug administration.
  - b. See Attachment 5 for list of required laboratory tests.
  - c. Female subjects of childbearing potential.
  - d. Discontinue at least 4 weeks prior to study drug administration.
  - e. Discontinue at least 2 weeks prior to study drug administration.
  - f. Subjects will be observed for symptoms of allergic reactions for at least 30 minutes after the SC injection of study drug at the study site.
  - g. Vital signs include temperature, resting pulse rate, and blood pressure.
  - h. During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures are desirable to be performed in the following order: ECG(s), vital signs, blood draw.
  - i. Only for subjects with PAO at screening.
  - j. Before start of study drug administration.
  - k. Serum from a single blood draw may be used to test CNTO 1959 concentration and antibodies to CNTO 1959.
  - l. Subjects who have consented separately to participate in biopsy assessment.
  - m. Only for subjects who terminate 12 weeks after last study drug administration.
- ET: Early Termination, LA: Last Administration

**ABBREVIATIONS**

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BCG	Bacille Calmette-Guérin
BSA	Body Surface Area
CL	Clearance
DBL	database lock
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
F%	absolute bioavailability
FDA	Food and Drug Administration (United States)
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
hsCRP	high sensitivity C-reactive protein
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IgG1 $\lambda$	immunoglobulin G1 lambda
IHC	immunohistochemistry
IL	interleukin
IL-23R	interleukin 23 receptor
IU	International unit
IV	intravenous
LS	least-square
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NOAEL	no observed adverse effect level
NSAIDs	nonsteroidal anti-inflammatory drugs
PAO	pustulotic arthro-osteitis
PASI	Psoriasis Area and Severity Index
PGA	Physician's Global Assessment of palmoplantar lesion
PK	pharmacokinetic(s)
PQC	product quality complaint
QOL	quality of life
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
T <sub>1/2</sub>	half-life
TB	tuberculosis
Th17	T helper 17
TK	toxicokinetics
T <sub>max</sub>	observed time to maximal concentration
TNF $\alpha$	tumor necrosis factor alpha
ULN	upper limit of normal
USA	United States America

UV	ultraviolet
VAS	Visual Analogue Scale
V <sub>z</sub>	volume of distribution during the terminal phase
WBC	white blood cell



[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

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[Redacted]

[Redacted]


### **Clinical Studies**

CNTO1959PSO1001 was the first-in-human study for CNTO 1959 and is the only study completed thus far in humans. In Part 1 of the CNTO1959PSO1001 study, 47 healthy subjects received a single dose of CNTO 1959 or placebo, and they were followed for 16 weeks. Of the 47 subjects, 30 subjects received a single IV infusion of CNTO 1959 (0.03, 0.1, 0.3, 1, 3, or 10 mg/kg), 6 subjects received a SC injection of 3 mg/kg CNTO 1959, and 11 subjects received placebo (10 IV and 1 SC). In Part 2, 24 subjects with moderate to severe psoriasis received a single SC dose (10, 30, 100 or 300 mg) of CNTO 1959 (20 subjects) or placebo (4 subjects), and they were followed for 24 weeks. Currently, two studies (CNTO1959PSO2001 and CNTO1275ARA2001) are ongoing outside Japan. CNTO1959PSO2001 is a Phase 2 dose-ranging study in subjects with psoriasis. Approximately 280 subjects will be randomized and will continue dosing through Week 40 with a subsequent efficacy and safety follow-up at Week 52. There are 5 dose groups for CNTO 1959 (5 mg every 12 weeks [q12w], 15 mg every 8 weeks [q8w], 50 mg q12w, 100 mg q8w and 200 mg q12w). Subjects CNTO1275ARA2001 is a phase 2 study in subjects with active rheumatoid arthritis. Approximately 250 subjects will be randomized. The study duration will be 72 weeks, including a 28-week placebo-controlled period, and 20 week follow-up period between the last injection of study agent and the last visit. There are 2 dose groups for CNTO 1959 (200 mg at Weeks 0, 4, then q8 weeks, or 50 mg at Weeks 0, 4, then q8 weeks). In Japan, a single dose Phase 1 study in Japanese subjects with psoriasis (CNTO1959PSO1002) is ongoing. Approximately 24 subjects will be included in this study. There are 4 dosing cohorts (10, 30, 100, 300 mg single SC injection) and follow-up through 24 weeks.

### ***Human Pharmacokinetics and Immunogenicity***

The pharmacokinetics of CNTO 1959 was evaluated in the first-in-human Study CNTO1959PSO1001. CNTO 1959 exhibited linear pharmacokinetics at doses ranging from 0.03 mg/kg to 10 mg/kg following IV administration and from 10 mg to 300 mg following SC administration in subjects with moderate to severe psoriasis. Following a single IV administration of 0.03 mg/kg to 10 mg/kg CNTO 1959 to healthy subjects, mean values of clearance (CL) and volume of distribution ( $V_z$ ) ranged from 3.62 to 6.03 mL/day/kg and 99.38 to 123.22 mL/kg, respectively; the mean  $T_{1/2}$  values ranged from 12.3 to 19.1 days. The absolute SC bioavailability (F%) of CNTO 1959 was estimated to be 32.6%. Following a single SC administration of 10 to 300 mg CNTO 1959 to subjects with psoriasis, median  $T_{max}$  values ranged from 3.2 to 6.0 days; the mean  $T_{1/2}$  was 14.7 to 16.9 days, which is consistent with that in



healthy subjects. The pharmacokinetics of CNTO 1959 were generally comparable between healthy subjects and subjects with psoriasis.

The immunogenicity of CNTO 1959 was also evaluated in Study CNTO1959PSO1001. Following IV administration of CNTO 1959 to healthy subjects, 1 (3.3%) of 30 subjects tested positive for antibodies to CNTO 1959. None of 6 healthy subjects treated with SC CNTO 1959 tested positive for antibodies to CNTO 1959. Following SC administration of CNTO 1959 to subjects with psoriasis, 1 (5.0%) of 20 subjects tested positive for antibodies to CNTO 1959.

### ***Efficacy/Safety Studies in Patient With Plaque Psoriasis***

In the CNTO1959PSO1001 study part 2, efficacy was assessed by Psoriasis Area and Severity Index (PASI) and Physician's Global Assessment (PGA) throughout the 24-week follow-up period in subjects with psoriasis. Improvements in PASI scores were observed in all dose groups. The maximum clinical response was observed between Weeks 8 and 16 in all dose groups. At Week 12, a PASI 75 response was achieved by 50.0%, 60.0%, 60.0%, and 100.0% of subjects in the 10 mg, 30 mg, 100 mg, and 300 mg dose groups, respectively whereas 0% in the placebo group. With the exception of the 100 mg dosing group, evidence of a dose-response relationship was observed for the 10 mg, 30 mg and 300 mg dose groups in which the PASI 75 response was maintained through Week 24. PGA scores were generally consistent with results of the PASI analysis.

The safety results from this study show that CNTO 1959 or placebo administered either via IV infusion or SC injection in healthy subjects or by SC injection in subjects with moderate to severe psoriasis was generally safe and well tolerated. There was no dose-dependent response in the incidence of adverse events (AEs) and all AEs were considered to be mild to moderate in intensity by the investigator. In healthy subjects, the most common AEs were headache (9 [25.0%] of 36 subjects treated with CNTO 1959 and 3 [27.3%] of 11 subjects treated with placebo), and upper respiratory tract infection (5 [13.9%] of 36 subjects treated with CNTO 1959 and 1 [9.1%] of 11 subjects treated with placebo). In subjects with psoriasis, the most common AEs were upper respiratory tract infection and vomiting (each in 2 [10.0%] of 20 subjects treated with CNTO 1959) which were not observed in subjects who received placebo (n = 4). One subject with psoriasis who received CNTO 1959 10 mg experienced a serious adverse event (SAE) of traumatic brain injury secondary to motor vehicle accident, which was considered unrelated to study drug by the investigator. No trends or dose related changes in vital signs, physical examinations, ECGs, or laboratory values were observed. No subjects terminated study participation due to AEs.

Thus, the Phase 1 data demonstrate that CNTO 1959 may be efficacious in the treatment of subjects with moderate to severe psoriasis with a good emerging safety profile. These results support further investigation of CNTO 1959 in Phase 2 studies.

## **1.2. Overall Rationale for the Study**

Palmoplantar pustulosis is a chronic and intensely inflammatory skin disease with pustules, erythema and scaling localized to the palms and soles. Palmoplantar pustulosis is an

inflammatory hyperkeratosis that appears most commonly in middle-aged men and women, particularly those who are smokers<sup>9</sup>. As clinical features of palmoplantar pustulosis, multiple vesicles occur on the thenar and antithenar regions of the palms and arches of feet, and these become pustular. Erythema develops at the periphery of the lesions and fuses into plaques. Itching may be present. Punctate depressions and thickening occur frequently in the nails. Pustules recur in 2- to 4-week cycles and progress chronically. They may appear on the knees, lower extremities and scalp. In 10% of palmoplantar pustulosis cases, sternocostoclavicular ossification accompanied by chest pain develops as a complication<sup>10</sup>. This disease shares some common features with other pustular forms of psoriasis and is often classified as a localized form of pustular psoriasis. Quality of Life (QOL) is lower because the presence of painful lesions on the soles and the palms can significantly impair the patient's ability to walk and use their hands<sup>12</sup>. Commonly-used treatment options are limited to topical treatments such as corticosteroids, or active vitamin D<sub>3</sub> ointments, and phototherapy (ultraviolet [UV] radiation therapy). These therapies are modestly effective and can take up to 5-7 years before there is a significant clearance of lesions. T helper 17 (Th17) cells and IL-23 may play a role in promoting the inflammation observed in palmoplantar pustulosis<sup>2, 3, 7</sup>. The lesions of patients with palmoplantar pustulosis show an infiltration of neutrophils and Th17 cells as well as increased expression of IL-8, IL-17, IL-22, and IL-23. In addition, dendritic cells and keratinocytes demonstrate increased production of IL-23, a key cytokine which plays a role in- the stabilization and proliferation of Th17 cells<sup>1, 3, 5</sup>. IL-23 also stimulates Th17 cells within the dermis to produce IL-17A, IL-17F, and IL-22, which, in turn, stimulates IL-8 production from keratinocytes. IL-8 promotes infiltration of neutrophils to the skin, promoting pustule formation<sup>5</sup>. These observations suggest that blockade of IL-23-mediated inflammation by CNTO 1959 (anti-IL-23 mAb) could provide therapeutic benefit to patients with palmoplantar pustulosis.

## **2. OBJECTIVES AND HYPOTHESIS**

### **2.1. Objectives**

#### **Primary Objectives**

The primary objectives of this study are:

- To evaluate the efficacy of CNTO 1959 in the treatment of subjects with palmoplantar pustulosis at Week 16
- To assess the safety and tolerability of CNTO 1959 in subjects with palmoplantar pustulosis

#### **Major Secondary Objectives**

The major secondary objectives of this study are:

- To assess the pharmacokinetics and immunogenicity of CNTO 1959 following SC administration in subjects with palmoplantar pustulosis
- To assess the impact of treatment with CNTO 1959 on the health related QOL measurement in subjects with palmoplantar pustulosis at Week 16

- To assess possible time point with maximum clinical response of CNTO 1959 after two dose injection.

### **Exploratory Objectives**

The exploratory objectives of this study are:

- To explore biomarkers following CNTO 1959 administration in subjects with palmoplantar pustulosis
- To explore the impact of treatment with CNTO 1959 on pustulotic arthro-osteitis (PAO) in the subset of subjects with PAO at screening
- To explore possible overall process of clinical response of CNTO 1959 over time.

### **2.2. Hypothesis**

The primary hypothesis of this study is that CNTO 1959 treatment, 200 mg SC injection at Week 0 and Week 4, is superior to placebo in terms of the change from baseline of Palmoplantar Pustulosis Severity Index (PPSI) total score at Week 16.

## **3. STUDY DESIGN AND RATIONALE**

### **3.1. Overview of Study Design**

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel group, multicenter study of CNTO 1959 in subjects with palmoplantar pustulosis. Approximately 50 subjects will be randomly assigned to 1 of 2 treatment groups (CNTO 1959 200 mg SC or placebo SC) in a 1:1 ratio and will receive study drug at Week 0 and Week 4. After randomization (Week 0), subjects will return to the study site for 9 evaluation visits (Weeks 1, 2, 4, 6, 8, 12, 16, 20 and 24). The overall study schema is provided in [Figure 1](#).

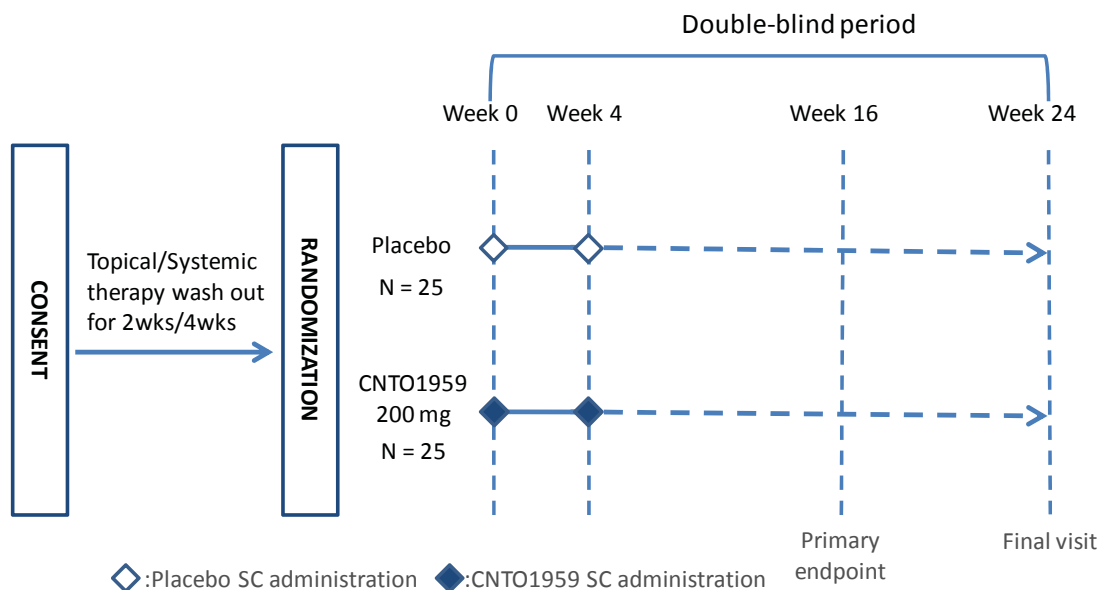
The target population consists of moderate to severe subjects with palmoplantar pustulosis defined as that subject has pathognomonic skin manifestation of palmoplantar pustulosis on palms and/or soles. Subjects must have had an inadequate response to prior conventional treatment (eg, topical corticosteroids, active vitamin D<sub>3</sub>, etretinate or phototherapy) and must have active lesions at screening and baseline (PPSI score of 7 or greater). Subjects with extra-palmoplantar lesions and/or PAO can be included. See Section “SUBJECT SELECTION” for inclusion and exclusion criteria.

The total duration of subject participation will be approximately 30 weeks, which includes a screening period of about 6 weeks before dosing. Subjects will return to the study site on Weeks 1, 2, 4, 6, 8, 12, 16, 20 and 24. Completion of the Week 24 assessment constitutes the subject’s completion of the study.

Efficacy, safety, pharmacokinetics, immunogenicity and pharmacodynamic (biomarker) assessments will be conducted in this study. Efficacy measurements include PPSI, PPPASI (Palmo-Plantar Pustulosis Area and Severity Index), PGA and the Dermatology Life Quality Index (DLQI). Safety assessments will include AEs, vital signs, laboratory parameters, and

ECGs. Pharmacokinetics and immunogenicity measurements will be made over time. Biomarker measurements include the evaluation of relevant markers in serum and whole blood and skin biopsy biomarkers (only subjects who consent to participate to skin biopsy). One of the goals of the biomarker analyses is to evaluate the pharmacodynamics of CNTO 1959 and aid in evaluating the drug-clinical response relationship. The frequency/timing of all of the above measurements is provided in the Time and Events Schedule Table.

The data from this study will be cleaned and locked for analysis at the Week 16 and Week 24 database locks (DBLs). The purpose of Week 16 DBLs is to perform selected analyses to be used by the sponsor in planning for the CNTO 1959 next phase clinical program.



**Figure 1 Schematic Overview of the Study**

### 3.2. Study Design Rationale

This is the first study of CNTO 1959 administrating in subjects with palmoplantar pustulosis. This is a Phase 2 randomized, placebo-controlled, parallel-group, multicenter study designed to assess the efficacy and safety of CNTO 1959 in adult subjects with palmoplantar pustulosis.

In a Phase 1 study conducted in the USA in both normal healthy volunteers and psoriatic subjects (CNTO1959PSO1001), CNTO 1959 demonstrated acceptable safety and pharmacokinetics in both populations. Currently, there are two ongoing overseas studies (a Phase 2 dose-ranging study in subjects with psoriasis [CNTO1959PSO2001] and a phase 2 study in subjects with active rheumatoid arthritis [CNTO1275ARA2001]). In Japan, a Phase 1 study in Japanese subjects with psoriasis (CNTO1959PSO1002) is now conducting.

The overall design of this study including dose levels and regimens was selected based on the organized psoriasis clinical studies.

**Placebo control, Randomization and Blinding**

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. 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. Limited sponsor personnel will become unblinded to treatment assignment at the Week 16 database lock (DBL). To minimize potential bias in the study even after the Week 16 DBL, treatment assignment blinding will be maintained for study sites, site monitors, and subjects participating in the study after the Week 16 DBL until the final DBL.

**Dose Rationale**

Based upon the clinical experience of psoriasis studies, 200 mg SC dosing at Week 0 and Week 4 was selected for evaluation in this study. Results from the Phase 1 study (CNTO1959PSO1001), demonstrated a trend for a dose-response relationship for the 10 mg, 30 mg and 300 mg dose groups. The clinical efficacy, safety and pharmacokinetic data from CNTO1959PSO1001 study informed the doses selected for the Phase 2 dose-ranging study (CNTO1959PSO2001) in subjects with psoriasis. This ongoing Phase 2 trial is evaluating doses ranging from 5 mg to 200 mg with 200 mg induction dosing at Week 0 and Week 4 as the maximum dose regimen. Based on the modeling analysis, the 200 mg dose is predicted to achieve high levels of efficacy in subjects with psoriasis. In addition, the safety results from the CNTO1959PSO1001 study show that SC CNTO 1959 in psoriasis subjects was generally safe and well tolerated up to a dose of 300 mg. There was no dose-dependent response in the incidence of AEs at dose levels ranging from 10 mg to 300 mg. Thus, CNTO 1959 200 mg is expected to be well tolerated and achieve a high degree of clinical efficacy in psoriasis subjects. Induction dosing at Weeks 0 and 4 will be included to achieve a more rapid onset of clinical response.

Pathogenesis of palmoplantar pustulosis has not been confirmed, however, Th17 cells and IL-23 may play a role in promoting the inflammation observed in palmoplantar pustulosis as same as observed in psoriasis. CNTO1959PPP2001 is the first clinical study of CNTO 1959 in subjects with palmoplantar pustulosis. The goals of this study are to assess efficacy, safety, pharmacokinetics and pharmacodynamics of CNTO 1959 administered as SC injection in subjects with palmoplantar pustulosis. Taking this into consideration, CNTO 1959 200 mg SC administration at Week 0 and Week 4 was selected as the dose regimen in order to demonstrate Proof of Concept for CNTO 1959 in palmoplantar pustulosis.

In addition, in the preliminary data of the ongoing study CNTO1959PSO1002 for Japanese psoriasis subjects, which is single SC dosed 10, 30, 100 or 300 mg, shows no safety concern to date.

**Study period**

Subjects will be followed from the last administration of study drug at Week 4 through the last study visit at Week 24. Primary endpoints evaluation is set at Week 16 based up on psoriasis study experience. In the CNTO1959PSO1001 study, clinical response reached to almost maximum at 12 to 16 weeks after dosing. Based on the results of CNTO1959PSO1001, it was assumed that clinical response will be observed at 16 weeks after dosing in subjects with palmoplantar pustulosis as well. Follow-up will be continued until 24 weeks in order to explore clinical response of CNTO 1959 over time.

Two database locks (DBLs) are planned. The first DBL will occur at the primary end points Week 16 and the second DBL will occur at the end of the study (Week 24). Subject safety will be monitored through the end of the study as delineated in the Time and Events Schedule.

**Assessments**

Subject assessments and evaluations for safety, efficacy, pharmacokinetics, and biomarkers will be performed as delineated in the Time and Events Schedule.

**Biomarker Collection**

Biomarker samples will be collected to evaluate the biological activity of CNTO 1959, help to explain interindividual 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 pharmacodynamics of CNTO 1959 and aid in evaluating the drug-clinical response relationship.

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

**4. SUBJECT POPULATION**

Screening for eligible subjects will be performed within 42 days before administration of the study drug.

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

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

**4.1. Inclusion Criteria**

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

1. Subject must be a man or woman 20 years of age, inclusive.

2. Subject has had a diagnosis of palmoplantar pustulosis at screening (subjects with concurrent extra-palmoplantar lesions [includes plaque-type psoriasis lesions] and/or PAO also can be included).
3. Subject has active lesions on the palms or soles at screening and baseline (Week 0)
4. Subject has inadequate response to the treatment with topical steroid and/or topical vitamin D<sub>3</sub> 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.
5. Subject has a PPSI score of 7 or greater at screening and baseline (Week 0)
6. At screening, the results of the following laboratory tests performed at the central laboratory must be within the limits specified below.
  - a. Hemoglobin  $\geq 10$  g/dL (SI:  $\geq 100$  g/L)
  - b. White blood cells  $\geq 3.5 \times 10^3$  cells/ $\mu$ L (SI:  $\geq 3.5$  GI/L)
  - c. Neutrophils  $\geq 1.5 \times 10^3$  cells/ $\mu$ L (SI:  $\geq 1.5$  GI/L)
  - d. Platelets  $\geq 100 \times 10^3$  cells/ $\mu$ L (SI:  $\geq 100$  GI/L)
  - e. Serum creatinine  $\leq 1.5$  mg/dL (SI:  $\leq 133$   $\mu$ mol/L)
  - f. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase levels must be  $\leq 2 \times$  the upper limit of normal (ULN) for the laboratory conducting the test.
7. Before randomization, a woman must be either:
  - Not of childbearing potential: premenarcheal; postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle stimulating hormone (FSH) level >40 IU/mL; permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy,
  - Of childbearing potential and practicing a highly effective method of birth control, consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (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.

8. A woman of childbearing potential must have a negative serum  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) test at screening and urine pregnancy test at Week 0.
9. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction.
10. 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 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 3 months after receiving the last dose of study drug.
11. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study.
12. Subject are considered eligible according to the following tuberculosis (TB) screening criteria:
  - a. Have no history of latent or active TB prior to screening. An exception is made for subjects currently receiving treatment for latent TB with no evidence of active TB, or who have a history of latent TB and documentation of having completed appropriate treatment for latent TB within 3 years prior to the first administration of any study drug. It is the responsibility of the investigator to verify the adequacy of previous antituberculous treatment and provide appropriate documentation.
  - b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
  - c. Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB has been initiated at least 3 weeks prior to the first administration of any study drug.
  - d. Within 2 months prior to the first administration of study drug, have a negative QuantiFERON-TB Gold test result, or have a newly identified positive QuantiFERON-TB Gold test result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated at least 3 weeks prior to the first administration of study drug. A subject whose first QuantiFERON-TB Gold test result is indeterminate should have



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

#### **Exception text**

The QuantiFERON-TB Gold test is 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.

- e. Have a chest radiograph (both posterior-anterior and lateral views, substitutable with chest CT), taken within 3 months prior to 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.

#### **4.2. Exclusion Criteria**

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

1. Subject has a history of or current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, neurologic, cerebral, or psychiatric disease.
2. Subject has unstable cardiovascular disease, defined as a recent clinical deterioration (eg, unstable angina, rapid atrial fibrillation) in the last 3 months or a cardiac hospitalization within the last 3 months prior to screening.
3. Subject 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 (eg, recurrent pyelonephritis), fungal infection (eg, mucocutaneous candidiasis), or open, draining, or infected skin wounds or ulcers.
4. Subject 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 2 months prior to screening.
5. Subject has or has had herpes zoster within the 2 months prior to screening.
6. Subject 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.
7. Subject has been hospitalized in the past 3 months for asthma, ever required intubation for treatment of asthma, currently require oral corticosteroids for the

- treatment of asthma, or required more than one short-term ( $\leq 2$  weeks) course of oral corticosteroids for asthma within the previous 6 months prior to screening.
8. Subject has a transplanted organ (with exception of a corneal transplant  $> 3$  months prior to the first administration of any study drug).
  9. Subject has a history of active granulomatous infection, including histoplasmosis or coccidioidomycosis, prior to screening. Refer to inclusion criteria for information regarding eligibility with a history of latent TB.
  10. Subject has had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystosis and aspergillosis) within 6 months prior to screening.
  11. Subject has a chest radiograph (substitutable with chest CT) within 3 months prior to the first administration of study drug that shows an abnormality suggestive of a malignancy or current active infection, including TB.
  12. Subject has indeterminate initial and repeat QuantiFERON-TB Gold test results or a newly positive QuantiFERON-TB Gold test and is unwilling or unable to undergo TB prophylaxis treatment.
  13. Subject is known to be infected with human immunodeficiency virus (HIV) or human T-lymphotropic virus-1 (HTLV-1). Tests positive for HIV infection or positive for HTLV-1 infection.
  14. Subject tests positive for hepatitis B virus (HBV) infection (see Attachment 7 for interpretation of Hepatitis B serologies) or has antibodies to hepatitis C virus (HCV) at screening.
  15. Subject has any known malignancy or has a history of malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ of the skin, or cervical carcinoma in situ that has been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years prior to administration of any study drug).
  16. Subject has known allergies, hypersensitivity, or intolerance to placebo, CNTO 1959 or its excipients (refer to Investigator's Brochure).
  17. Subject has known intolerance or hypersensitivity to any biologic medication, or known allergies or clinically significant reactions to murine, chimeric, or human proteins, monoclonal antibodies, or antibody fragments.
  18. Subject has ever previously received CNTO 1959.

19. Subject has received any anti-tumor necrosis factor alpha (TNF $\alpha$ ) biologic therapy within 3 months or 5 half-lives of the first administration of study drug, whichever is longer.
20. Subject has received any therapeutic agent directly targeted to IL-6, IL-12, IL-17, or IL-23, (including but not limited to tocilizumab, ustekinumab, briakinumab [ABT-874], AIN457, and MK3222) within 6 months of the first administration of any study drug.
21. Subject has received natalizumab, efalizumab, or agents that modulate B cells or T cells (eg, rituximab, alemtuzumab, abatacept, alefacept, or visilizumab) within 12 months of the first administration of any study drug.
22. Subject has received any systemic immunosuppressants (eg, methotrexate [MTX], azathioprine, cyclosporine, mercaptopurine, mycophenolate mofetil, hydroxyurea, and tacrolimus) disease-modifying drugs (eg, sulfasalazine, intramuscular gold) or anakinra within 4 weeks of the first administration of any study drug.
23. Subject has received phototherapy or any systemic medications/treatments that could affect palmoplantar pustulosis or efficacy evaluation (including, but not limited to, oral or injectable corticosteroids, retinoids, psoralens, antibiotics, biotin drug, Chinese herbal preparations, and cyclosporine) within 4 weeks of the first administration of any study drug.
24. Subject has received focal infection treatment (eg, tonsillectomy and dental therapy) within 6 months of the first administration of any study drug.
25. Subject has received systemic medications/treatments that could affect PAO or efficacy evaluation PAO except nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, bisphosphonates and MTX) within 4 weeks of the first administration of any study drug.
26. Subject has used topical medications/treatments to the palms and soles that could affect palmoplantar pustulosis or efficacy evaluation (including, but not limited to, corticosteroids, topical vitamin D<sub>3</sub> derivatives, and tacrolimus) within 2 weeks of the first administration of any study drug.
27. Subject is currently receiving lithium or antimalarials, or has received lithium or antimalarials within 4 weeks of the first administration of any study drug.
28. Subject has received, or is expected to receive, any live virus or bacterial vaccination within 3 months (or longer as indicated in the package insert of the relevant vaccine) prior to the first administration of any study drug.
29. Subject has had a Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening.

30. Subject has received an experimental antibody or biologic therapy within the previous 6 months, or received any other experimental therapy or new investigational agent within 30 days or 5 half-lives (whichever is longer) of any study drug administration or is currently enrolled in an investigational study.
31. Subject is a woman who is pregnant, breast-feeding, or planning to become pregnant or is a man who plans to father a child while enrolled in this study or within 3 months after receiving the last administration of any study drug.
32. Subject 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.
33. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.
34. Subject has current drug-induced palmoplantar pustulosis (eg, a new onset of palmoplantar pustulosis or an exacerbation of palmoplantar pustulosis from anti-TNF $\alpha$  drugs).
35. Subject is known to have had a substance abuse (drug or alcohol) problem within the previous 12 months.
36. Subject is unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.

**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 first dose of study drug is given such that they no longer meet all eligibility criteria, they should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

#### **4.3. Prohibitions and Restrictions**

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

1. A woman of childbearing potential who is heterosexually active must remain on a highly effective method of birth control (see inclusion criteria) during the study and for 3 months after receiving the last dose of any study drug.
2. A man who is sexually active with a woman of childbearing potential must use a double-barrier method of birth control (ie, male condom, female diaphragm or cervical cap, or condom) and all men must also not donate sperm during the study and

for 3 months after receiving the last dose of study drug.

3. Subject must agree not to receive a live virus or bacterial vaccination during the study or up to 3 months after the last administration of any study drug.
4. Subject must agree not to receive a BCG vaccination during the study or up to 12 months after the last administration of any study drug.
5. Subject must comply with restrictions on prestudy and concomitant medications (see Section 8).
6. Subject must avoid prolonged sun exposure and avoid use of tanning booths or other UV light sources to the palms and soles during study.
7. Subject must agree to keep subjects on stable condition of smoking habit throughout the study.

## **5. TREATMENT ALLOCATION AND BLINDING**

### **Treatment Allocation**

#### **Procedures for Randomization**

Subjects will be randomly assigned to 1 of 2 treatment groups based on a randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by study site.

#### **Blinding**

With the exception of the unblinded pharmacy staff, the study site personnel, investigators, and the randomized subjects will be blinded to which drug (CNTO 1959 or placebo) throughout the study.

The sponsor medical monitor, site manager and other sponsor personnel will remain blinded throughout the study (subject level treatment assignment and dosing regimen). At the Week 16 DBL, the data will be unblinded for analysis while subjects are still participating in the study. Identification of sponsor personnel who will have access to the unblinded subject level data will be documented prior to unblinding.

#### **Maintenance of the Blind**

The unblinded pharmacy staff (Pharmacists or medically licensed individuals) responsible for the preparation of study drugs at each site will be unblinded to treatment assignment throughout the study and will prepare, dispense, and account for all study drugs. These individuals should have no other contact with the subject during the study other than study drug administration, should not communicate their knowledge of treatment assignment to any other study personnel. An

independent, unblinded drug monitor will monitor any study drug preparation and accountability data.

Randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those subjects included in the interim analysis.

### **Emergency Unblinding**

The investigator will not be provided with randomization codes. The codes will be maintained within the centralized randomization service for this study, 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, treatment allocation) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of DBL and unblinding.

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

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, IRB/IEC 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**

The study drugs are NOT to be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing.

Subjects will be randomized to 1 of the following 2 treatment groups in a 1:1 ratio:

Group 1: Placebo SC at Week 0 and Week 4.

Group 2: CNTO 1959 200 mg SC at Week 0 and Week 4.

All subjects randomized will receive 2 injections of 1 mL each as SC injections at each administration (two 1 ml SC injection containing placebo or CNTO 1959). Details regarding administration method are provided in Drug Administration manual.

Before all injections at the investigational site, the appropriate personnel, medication (eg, epinephrine, inhaled beta-2-agonists and antihistamines), and other requirements to treat severe allergic reactions must be available. A physician must be available onsite during all SC injections of study drug administered at the study site.

## **7. TREATMENT COMPLIANCE**

As study drug is administered at the investigational site, treatment compliance will be controlled by site personnel.

For study drug administrations, information regarding treatments that are administered outside of the scheduled windows will be collected. Information regarding missed administrations will be available. Subject worksheets will be reviewed and compared with the data entries on the eCRFs to ensure accuracy. Compliance with the treatment schedule is strongly encouraged. It is understood that treatment may be interrupted for many reasons.

The Week 4 injection should occur within  $\pm 3$  days of the scheduled visit.

## **8. PRESTUDY AND CONCOMITANT THERAPY**

### **8.1. Prestudy Therapy**

For the prestudy therapies, subjects must comply with restrictions provided in section "SUBJECT POPULATION" in which inclusion and exclusion criteria are listed. These therapies are not permitted throughout the study except as described in the "CONCOMITANT THERAPY" section.

### **8.2. Concomitant Therapy**

Concurrent use of medications/treatments for palmoplantar pustulosis is not permitted during the study except as noted below.

#### ***Topical therapy for palmoplantar pustulosis***

Concurrent use of topical medications/treatments for palmoplantar lesions (eg, corticosteroids keratolytics, vitamin D<sub>3</sub> analogues and topical tacrolimus), intralesional corticosteroids are not permitted for at least 2 weeks prior to the first administration of study drug and throughout the study.



The following therapies are permitted in the indicated time frames:

Topical moisturizers are permitted from screening period to throughout the study; however, subjects should not use these topical agents prior to the medical examinations on the day of a study visit.

***Phototherapy and Systemic Therapy for Palmoplantar pustulosis***

Focal infection treatments to the tonsils and/or dental are not permitted for at least 6 month prior to administration of study drug and throughout the study.

Concurrent use of phototherapy and systemic therapy for palmoplantar pustulosis (eg, PUVA, narrow band UVB, systemic retinoids, biotin drug, Chinese herbal preparations, antibiotics and cyclosporine) is not permitted for at least 4 weeks prior to administration of study drug and throughout the study.

***Therapy for pustulotic arthro-osteitis***

In case of receiving NSAIDs 1 week before starting administration, it is available if dosage is not changed during study period. Dose can be reduced. However it cannot be re-escalated once it was reduced. Any other medications/treatments for PAO (eg, bisphosphonates, MTX, Chinese herbal preparations and antibiotics) are not permitted for at least 4 weeks prior to the administration of study drug and throughout the study.

***Concomitant Medications for Conditions other than Palmoplantar pustulosis***

Every effort should be made to keep subjects on stable concomitant medications. If a 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 NSAIDs for indications other than PAO should be limited to situations where, in the opinion of the treating physician, there are no adequate alternatives for at least 1 week prior to the first administration of study drug and throughout the study. However, systemic immunosuppressants and disease-modifying agents, including, but not limited to, methotrexate, sulfasalazine, or intramuscular gold must be discontinued at least 4 weeks prior to administration of study drug as described in "SUBJECT POPULATION" and are prohibited during the study.

The biologic therapies described in "SUBJECT POPULATION" (anti-TNF $\alpha$ , agents targeting to IL-6, IL-12, IL-17, or IL-23, and agents modulating B cells or T cells) are prohibited during the study.

Corticosteroids should be used only as follows:

- Topical and Intralesional Corticosteroids: Topical or intralesional corticosteroids for the treatment of palmoplantar pustulosis are not allowed within 2 weeks prior to administration of study drug and are prohibited during the study. Using topical or intralesional



corticosteroids (except for strongest potency) for body area other than palms and soles is allowed. Every effort should be made to keep subjects on stable usage.

- Systemic Corticosteroids (oral or IV only; intramuscular steroids are prohibited) : Systemic corticosteroids for the treatment of palmoplantar pustulosis are not allowed within 4 weeks prior to administration of study drug and are prohibited during the study. Systemic corticosteroids for indications other than palmoplantar pustulosis should be limited to situations where, in the opinion of the treating physician, there are no adequate alternatives during the study. They should be used on a short-term basis (in principle,  $\leq 2$  weeks). Longer-term use of systemic corticosteroids should be discussed with the medical monitor or designee and may require discontinuation from study drug.
- Intra-articular and Epidural Corticosteroids: Intra-articular and epidural corticosteroids are not allowed within 4 weeks prior to administration of study drug and are prohibited during the study.
- Other use of corticosteroids, such as inhaled, otic, ocular, nasal, or other routes of mucosal delivery of corticosteroids are allowed during the study.

When a subject applies topical medication, which is prohibited to use for palmoplantar pustulosis, to body area other than palms and soles, the subject should be avoid applying with bare hand (eg, with use of hand glove).

If the administration of any concomitant therapy is necessary, it must be reported in the appropriate section of the eCRF. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

### ***Prophylactic antituberculosis therapy for latent TB***

As a result of the TB screening, if a subject is judged to require prophylactic treatment, the subject has to receive prophylactic antituberculosis agent (isoniazid [INH], in principle) for at least 6 months beginning at least 3 weeks prior to the first study agent administration. The standard dose of INH is 300 mg/day (if subject is low body weight, 5 mg/kg/day will be administrated). Study drug should not be administered in case of discontinuing INH administration due to adverse reactions, etc. within 3 weeks before first dosing. After the study agent administration, if INH treatment cannot be continued due to adverse reactions, etc., such a case will be dealt with after consultation with the specialist.

## **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, clinical laboratory and safety 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 1, 2, 4, 6, 8 visits should occur within  $\pm 3$  days of the scheduled visit. All other study visits should occur within  $\pm 7$  days of the scheduled visit.

The total blood volume for the study is approximately 272 mL (139 mL for safety and efficacy, 85 mL for PK and immunogenicity, 48 mL for biomarkers).

### **9.1.2. Screening Period**

All subjects will have a screening visit that will occur within 6 weeks before their randomization visit (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.

With the exception of subjects with a history of appropriately treated latent TB within 3 years of the first administration of study drug, subjects must undergo testing for TB (see Attachment 6), 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 (both posterior-anterior and lateral views, substitutable with chest CT) results and responses to tuberculin skin or other TB testing.

Subjects with a negative QuantiFERON-TB Gold test result are eligible to continue with prerandomization procedures. Subjects with a newly identified positive QuantiFERON-TB Gold test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients (see Attachment 6).

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

Subjects will undergo screening for HBV (see Attachment 7) and antibodies to HCV.

#### **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 test performed at screening or baseline, or if applicable, at the time 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 in the future meets all of the subject eligibility criteria, the subject may be rescreened after a new informed consent has been obtained. Subjects who are rescreened will be assigned a new subject number and will restart a new screening phase.

### **9.1.3. Double-blind Period**

#### **Week 0/Day of Randomization**

At Week 0, subjects who meet all inclusion criteria and do not demonstrate any exclusion criteria will be randomized. All required tests and evaluations must be conducted before start of study drug administration.

#### **Post-randomization Visit (through Week 24)**

All visit procedures will be performed as specified in the Time and Events Schedule.

#### **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 is suggested for use during the evaluation:

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

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

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

Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph (both posterior-anterior and lateral views, substitutable with chest CT), a repeat QuantiFERON TB Gold test, and, if possible, referral to a physician specializing in TB to determine the subject’s risk of developing active TB and whether treatment for latent TB is warranted. If the QuantiFERON TB Gold test result is indeterminate,

the test should be repeated as outlined in Section 9.1.2. Subjects should be encouraged to return for all subsequent scheduled study visits according to the protocol.

#### **9.1.4. Safety follow-up after Early Termination**

If the subjects withdraw from the study before 12 weeks after last study drug administration, subjects will be followed for safety for up to 12 weeks after last study drug administration as per the Time and Events Schedule.

### **9.2. Efficacy**

#### **9.2.1. Evaluations**

Every effort should be made to ensure that the physician who performs the efficacy evaluations for a subject at baseline also performs the evaluation for that subject at all subsequent visit. The assessments should be performed by the designated individual.

##### **9.2.1.1. Palms and Sole Skin Lesion Evaluations**

###### **9.2.1.1.1. Palmoplantar Pustulosis Severity Index (PPSI)**

The PPSI is a system used for assessing and grading the severity of palmoplantar pustulosis lesions and their response to therapy<sup>11</sup> (see Attachment 1). The PPSI produces a numeric score that can range from 0 to 12. In the PPSI system, either both palms or both soles, which has the most severe skin lesion at screening will be identified as the evaluation sites. And identified site will be assessed at all subsequent visits. Evaluation sites are assessed separately for erythema, pustules/vesicle and desquamation/scale, which are each rated on a scale of 0 to 4.

###### **9.2.1.1.2. Palmo-Plantar Pustulosis Area and Severity Index (PPPASI)**

The PPPASI is a system used for assessing and grading the severity of palmoplantar pustulosis lesions and their response to therapy<sup>1</sup> (see Attachment 2). The PPPASI produces a numeric score that can range from 0 to 72.

###### **9.2.1.1.3. Physician's Global Assessment of palmoplantar pustulosis lesion (PGA)**

The PGA documents the Physician's Global Assessment of the subject's palmoplantar overall skin lesions status (see Attachment 3).

###### **9.2.1.1.4. Physician's Assessment of each skin lesion (PA-pustule, PA-vesicle, PA-nail)**

The PA documents the physician's assessment of the subject's pustule, [vesicle](#) and nail lesions status (see Attachment 4).

###### **9.2.1.1.5. Patient's Visual Analogue Scale assessment of Palmoplantar Pustulosis Severity (Patient's VAS-PPP severity)**

The Patient's Visual Analogue Scale assessment of Palmoplantar Pustulosis Severity will be recorded on a 10-cm VAS.

**9.2.1.2. Pustulotic Arthro-Osteitis Evaluations**

Pustulotic Arthro-Osteitis evaluations will be performed only for subjects with PAO at screening.

**9.2.1.2.1. Physician's Visual Analogue Scale Assessment of Pustulotic Arthro-Osteitis Activity (Physician's VAS-PAO activity)**

Physician's Visual Analogue Scale Assessment of Pustulotic Arthro-Osteitis Activity will be recorded on a 10-cm VAS.

**9.2.1.2.2. Patient's Visual Analogue Scale Assessment of Pustulotic Arthro-Osteitis Activity and Pain (Patient's VAS-PAO activity, Patient's VAS-PAO pain)**

Patient's Visual Analogue Scale Assessment of Pustulotic Arthro-Osteitis Activity and Pain will be recorded on each 10-cm VAS. The investigator will specify the main site for the patient to evaluate of pain. If there are multiple site worth evaluating, additional 2 site could be evaluated.

**9.2.1.3. Quality of Life evaluations****9.2.1.3.1. Dermatology Life Quality Index (DLQI)**

The DLQI is a dermatology-specific QOL instrument designed to assess the impact of the disease on a subject's QOL. It is a 10-item questionnaire that in addition to evaluating overall QOL, can be used to assess 6 different aspects that may affect QOL: symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment.

**9.2.1.3.2. SF-36**

The QOL of the subject will be assessed using the 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. 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<sup>8</sup>.

**9.2.1.4. Other**

- Photography of palms and soles skin lesion will be taken to record as visual observation. If subject has a nail lesion, it should be taken. These photographs should be provided to the Sponsor.
- MRI image of 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.

## **9.2.2. Endpoints**

### **Primary Endpoint**

The primary efficacy endpoint is the change from baseline in PPSI total score at Week 16.

### **Major Secondary Endpoints**

The following are the major secondary endpoints:

- Change from baseline in PPSI total score over time
- Change from baseline in PPPASI total score at Week 16 and over time
- Proportion of subjects who achieve a PPPASI-50 at Week 16 and over time
- Proportion of subjects who achieve a PGA score of 1 or less at Week 16 and over time

### **Other Secondary Endpoints**

- Proportion of subjects who achieve a PPPASI-75 at Week 16 and over time
- Change from baseline in PA (each score) at Week 16 and over time
- Change from baseline in Patient's VAS-PPP severity at Week 16 and over time
- Change from baseline in Physician's VAS-PAO activity at Week 16 and over time
- Change from baseline in Patient's VAS-PAO activity and pain at Week 16 and over time
- Change from baseline in DLQI at Week 16 and over time
- Change from baseline in SF-36 score at Week 16 and over time

## **9.3. Pharmacokinetics and Immunogenicity**

### **9.3.1. Evaluations**

Samples will be used to evaluate the pharmacokinetics, as well as the immunogenicity of CNTO 1959 (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 further characterization of immunogenicity or for the evaluation of relevant biomarkers. At visits where serum concentration and/or antibodies to CNTO 1959 will be evaluated, 1 blood draw of sufficient volume can be used. Venous blood samples will be collected and each serum sample will be divided into 3 aliquots (1 each for PK, antibodies to CNTO 1959, and a back-up).

A sample for pharmacokinetics and immunogenicity (only subjects who terminate 12 weeks after last study drug administration) assessment will be collected at the early termination visit if a subject terminates study participation.

### **9.3.2. Analytical Procedures**

#### **Pharmacokinetics**

Serum samples will be analyzed to determine concentrations of CNTO 1959 using a validated, specific, and sensitive dissociation-enhanced lanthanide fluorescent immunoassay (DELFLIA) method by or under the supervision of the sponsor.

#### **Immunogenicity**

The detection and characterization of antibodies to CNTO 1959 will be performed using a validated assay method by or under the supervision of the sponsor.

### **9.3.3. Pharmacokinetic Parameters**

If deemed necessary, a population pharmacokinetic approach using nonlinear mixed-effects model (NONMEM) will be used to characterize the pharmacokinetic parameters and exposure information of CNTO 1959.

### **9.3.4. Immunogenicity Assessments**

Antibodies to CNTO 1959 will be evaluated in serum samples collected from all subjects according to the Time and Events Schedule. Additionally, serum samples should also be collected at the final visit for subjects who terminate from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to CNTO 1959 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to CNTO 1959 and/or further characterize the immunogenicity of CNTO 1959.

## **9.4. Biomarkers**

Serum biomarkers of inflammation such as, but not limited to, IL-23p19, IL-17, IL-6, IL-8, IL-22, TNF $\alpha$ , and IL-12p40 will be evaluated from all subjects according to the Time and Events Schedule.

Whole blood samples will be collected from all subjects according to the Time and Events Schedule. Total ribonucleic acid (RNA) will be isolated and used for differential gene expression analyses and microRNA analyses to better understand the pathological mechanisms involved in palmoplantar pustulosis and to identify a treatment response signature to CNTO 1959.

Skin biopsy samples for gene expression analyses may include, but are not limited to, IL-23-associated proteins, such as IL-23R, IL-17A, IL-17F, IL-17 receptor, IL-6, IL-12p40, IL-12p35, IL-20R, IL-22RI, IL-8, GM-CSF, VEGF and TNF $\alpha$  will be collected from subjects who consent separately to participate in biopsy assessment.



## 9.5. Safety Evaluations

The safety and tolerability of study drugs (placebo, CNTO 1959) will be monitored by physical examinations, detection of injection site and allergic reactions, ECGs, clinical laboratory tests, vital signs, concomitant medications and AEs according to the Time and Events Schedule. Serum and/or plasma samples collected for pharmacokinetic or pharmacodynamic analyses may additionally be used to evaluate biomarkers of safety that address concerns that arise during or after the study period.

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 has been determined to be unnecessary (see Section 12.3.1).

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 as specified in Section 12, Adverse Event Reporting.

### Clinical Laboratory Tests

Blood samples for serum chemistry and 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 adverse event section of the eCRF. The laboratory reports must be filed with the source documents.

The following tests will be performed:

#### *Hematology Panel*

-hemoglobin	-white blood cell (WBC) count with differential
-hematocrit	-Lymphocytes
-red blood cell (RBC) count	-Neutrophils
-platelet count	-Basophils
	-Eosinophils
	-Monocytes
	-bands <sup>a</sup>

- a. If bands are detected in the microscopic analysis, then a result will be provided.



***Serum Chemistry Panel***

-Sodium	-Alkaline phosphatase
-Potassium	-Creatine kinase (CPK) <sup>b</sup>
-Chloride	-Lactic dehydrogenase (LDH)
-Bicarbonate	-Troponin-I
-Blood urea nitrogen (BUN)	-Calcium
-Creatinine	-Phosphate, inorganic
-Glucose	-Albumin
-AST	-Total protein
-ALT	-C-reactive protein
-Total bilirubin	-Direct bilirubin <sup>c</sup>

b. Assay to isoenzymes if CPK elevated >ULN.

c. Assay direct bilirubin if total bilirubin is elevated >ULN.

***Lipid Panel***

-Total cholesterol	-Low density lipoprotein(LDL)-cholesterol
-Triglycerides	-High density lipoprotein(HDL)-cholesterol

***Urinalysis*** <sup>d</sup>

-Specific gravity	-Protein
-pH	-Occult blood
-Glucose	-Ketones
-Bilirubin	

d. Microscopic examination of RBC, WBC, casts, and bacteria will be conducted if protein and/or blood are detected during urinalysis.

- Serum or urine Pregnancy Testing (Beta hCG) for women of childbearing potential <sup>\*\*</sup>
- Serology (HIV-1/-2 antibody, hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [anti-HBs], hepatitis B core antibody [anti-HBc total], Hepatitis B Viral DNA quantitative <sup>\*</sup> [HBV DNA], and HCV antibody, QuantiFERON-TB, HTLV-1 Antibody, and Serum follicle stimulating hormone [FSH] <sup>\*\*</sup>)

**Electrocardiogram (ECG)**

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

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\* See Attachment 7 for criteria of HBV DNA quantitative test required.

\*\* Female subject only.

**Vital Signs** (axillary temperature, pulse rate, blood pressure)

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

**Physical Examination**

Physical examinations will be performed by the investigator.

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.

**Height and Body Weight**

Measurement of height and body weight will be performed at the time-points specified in the Time and Events Schedule.

**Allergic Reactions**

All subjects will be observed carefully for symptoms of allergic reactions for at least 30 minutes after the SC injection of study drug at the study site. If the reaction is not severe, subsequent injections at the appropriate treatment intervals may be undertaken with caution.

In the case of a severe allergic reaction (eg, anaphylaxis), the investigator will treat a subject with proper treatment at the investigator's discretion and will judge whether subject should discontinue the study treatment or not by their safety perspective. Subjects with severe reactions following an injection such as bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension with a decrease in systolic blood pressure greater than 40 mm Hg will not be permitted to receive any additional study treatment.

**Injection Site Reactions**

An injection site reaction is any unfavorable or unintended sign that occurs at the study drug injection site. All subjects injected at the study site must be carefully observed for symptoms of an injection site reaction. Subjects will be observed for at least 30 minutes after the SC injection of study drug at the study site. 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.

**9.6. Sample Collection and Handling**

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 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 24 of the double-blind period.

### 10.2. Discontinuation of Study Treatment

If the second study drug administration (Week 4) must be discontinued, this will not result in automatic withdrawal of the subject from the study. The subject should return for the remaining regularly scheduled study visits as long as the subject does not withdraw from the study.

A subject's study treatment should be discontinued if:

- The investigator or sponsor's medical monitor 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 (both posterior-anterior and lateral views, substitutable with chest CT) with evidence of current active TB and/or a positive QuantiFERON-TB Gold test 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 QuantiFERON-TB Gold test results should be handled as in Section 9.1.2. Subjects with persistently indeterminate QuantiFERON-TB Gold test 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 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.
- The subject withdraws from the study.

### **10.3. Withdrawal From the Study**

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

- Lost to follow-up
- Death
- Withdrawal of consent
- The investigator or sponsor believes (eg, that for safety or tolerability reasons such as an adverse event) it is in the best interest of the subject to withdraw from the study.
- 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 completing the study, early termination assessments (refer to the Time and Events Schedule) should be obtained wherever possible. The subject should be encouraged to conduct for the safety follow-up visits (refer to the Time and Events Schedule) for up to 12 weeks after his/her last study drug administration. 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.

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

- The collected samples will be retained and used in accordance with the subject's original separate informed consent for optional research samples.
- The subject may withdraw consent for optional research samples, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If

requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

### **Withdrawal From the Optional Research samples While Remaining in the Main Study**

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

## **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. The analyses will be performed 2 times. The first analysis will be performed for subject information, efficacy and adverse events for all subjects who have either completed the Week 16 visit or terminated study participation prior to Week 16. The second analysis will be performed for efficacy and safety items including adverse events for all subjects who have either completed their final visit (24 weeks) or terminated study participation. No interim analysis is planned based on the statistical inference.

### **11.1. Subject Information**

Efficacy analyses will be performed with 2 analysis sets: full analysis set (FAS) and per-protocol set (PPS). The FAS is the population of all randomized subjects who received at least one dose of study drug and had any post-baseline efficacy assessment. The PPS is a subset of the full analysis set. The per-protocol analysis set excludes any subject with any of the major protocol deviations. The subjects meeting any major protocol deviation criteria will be determined prior to DBL and entered into the clinical database deviation dataset.

The safety analysis set is the population of all randomized subjects who received at least one dose of study drug.

For the FAS and the safety analysis set, descriptive statistics will be provided.

All randomized subjects who receive at least 1 dosing of CNTO 1959 and have serum CNTO 1959 concentration data will be included in the pharmacokinetic analysis set.

### **11.2. Sample Size Determination**

In the phase 3 double blind controlled study for Maxacalcitol (topical vitamin D<sub>3</sub>) that is approved for a treatment of palmoplantar pustulosis in Japan, the mean change from baseline of skin observation total score for Maxacalcitol was -3.7 (standard deviation [SD] = 2.1, number of patients [N] = 94) and -1.9 (SD = 1.9, N=93) for placebo group, as results of the primary endpoint. Based on these results, 25 subjects per group (total of 50 subjects) are considered as appropriate for this study in consideration to uncertainty for the estimates with varying assumptions. The sample size of 25 subjects has an 84% power to detect a significant difference between the CNTO 1959 treatment group and the placebo group at a two-sided alpha level of

0.05, assuming a treatment difference in the change from baseline of PPSI total score at Week 16 of 1.8 with a SD of 2.1. Table 1 provide the power for detecting a treatment difference between the CNTO1959 treatment group and the placebo treatment group (for 25 subjects per group) under varying assumptions for the treatment difference of the change from baseline of PPSI total score.

**Table 1 Power to detect a treatment difference based on the change from baseline of PPSI total score**

Mean Difference	Power
1.6	0.752
1.7	0.801
1.8	0.844
1.9	0.880
2.0	0.910

n = 25 for each group  
common SD = 2.1

### 11.3. Efficacy Analyses

#### *Efficacy Definitions*

- Treatment Failure: Subjects who withdraw from the study due to lack of efficacy or an AE of worsening of palmoplantar pustulosis, or who initiated a protocol-prohibited medication/therapy during the study that could improve palmoplantar pustulosis are considered treatment failures.
- PPPASI 50 Responder: Subjects with  $\geq 50\%$  improvement in PPPASI from baseline will be considered PPPASI 50 responders.
- PPPASI 75 Responder: Subjects with  $\geq 75\%$  improvement in PPPASI from baseline will be considered PPPASI 75 responders.

#### *Primary Endpoint*

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

The primary efficacy analysis will be performed using data from FAS. In this primary analysis, the change from baseline in PPSI total score at Week 16 will be analyzed using an analysis of covariance (ANCOVA) model which includes treatment as factors and baseline score as a covariate. Treatment effect of CNTO1959 versus placebo will be estimated based on least-square (LS) means of the difference. The p-value for the treatment difference along with the 2-sided 95% CI will be presented. The last available post-baseline PPSI total score will be carried forward to impute the PPSI total score that are missing after discontinuation of treatment up to Week 16 of the double-blind treatment period. If a subject meets one of the criteria of a treatment failure, the subject will be designated a treatment failure for primary endpoint at all visits starting from the visit after the treatment failure and the last available post-baseline PPSI total score value will be assigned regardless of the actual observed data. To evaluate sensitivity of the results to the imputation method, the impact of missing data would be explored through various analysis methods.

***Major Secondary Endpoints***

Major secondary endpoints of this study are:

- The change from baseline in PPSI total score will also be summarized over time by treatment group using descriptive statistics. If the evaluation visit with larger difference between treatment groups than that of Week 16 is observed, same analysis will be performed for that visit as described for the primary analysis, to assess possible time point with maximum clinical response of CNTO 1959.
- The change from baseline in PPPASI at Week 16 will be analyzed using an ANCOVA model which includes treatment as factors and baseline score as a covariate. Treatment effect of CNTO1959 versus placebo will be estimated based on least-square (LS) means of the difference. The p-value for the treatment difference along with the 2-sided 95% CI will be presented. The change from baseline in PPPASI will also be summarized over time by treatment group using descriptive statistics.
- The proportion of subjects who achieve a PPPASI-50 at Week 16 and the proportion of subjects who achieve a PGA score of 1 or less at Week 16 will be compared between the CNTO 1959 treatment group and placebo group using Fisher's exact test. The proportion will also be summarized by treatment group using frequencies and percentages with 95% CI. Subjects who discontinued 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.

***Other Secondary endpoints***

Other secondary endpoints as follows;

- Proportion of subjects who achieve a PPPASI-75 at Week 16 and over time
- Change from baseline in PA (each score) at Week 16 and over time
- Change from baseline in Patient's VAS-PPP severity at Week 16 and over time
- Change from baseline in Physician's VAS-PAO activity at Week 16 and over time
- Change from baseline in Patient's VAS-PAO activity and pain at Week 16 and over time
- Change from baseline in DLQI at Week 16 and over time
- Change from baseline in SF-36 at Week 16 and over time

For other secondary endpoints, the continuous variables will be summarized by treatment group using descriptive statistics, which will include the number of subjects (N), mean, SD, median, minimum, and maximum and will be analyzed using an analysis of variance model based on appropriate rank scores or ANCOVA model. The categorical variables will be summarized by treatment group using frequencies and percentages. The binary variables will be compared using Fisher's exact test. These Other secondary endpoints at other evaluation visits than Week 16 might be summarized as described above, if necessary.



#### **11.4. Pharmacokinetic Analyses**

Serum CNTO 1959 concentrations will be summarized with descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, maximum, 25% quantile and 75% quantile at each sampling time.

All serum concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the Clinical Study Report.

Mean or median serum CNTO 1959 concentration time profiles will be plotted after the first dose of study drug, and individual serum concentration time profiles may also be plotted.

Population PK analysis of serum concentration-time data of CNTO 1959 will be performed using NONMEM. Data may be combined with those of other clinical studies of CNTO 1959 to conduct the population PK analysis. Available baseline subject characteristics (demographics, laboratory variables, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

#### **11.5. Immunogenicity Analyses**

The incidence of antibodies to CNTO 1959 during the study will be summarized for all subjects who receive an administration 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). The serum titer of confirmed positive samples will be reported.

#### **11.6. Biomarker Analyses**

Changes in the concentration of individual serum markers from baseline to the selected post treatment time points will be summarized in separate technical reports. Additional analyses may be performed following evaluation of the data. Biomarker analyses are considered exploratory and will be summarized in separate technical reports as well.

#### **11.7. Pharmacokinetic and Pharmacodynamic Analysis**

If deemed necessary, exploratory analysis may be conducted in the relationship between pharmacokinetics and pharmacodynamics of CNTO 1959. When exploratory analysis is conducted, the analysis plan and report will be developed as separate documents.

#### **11.8. Safety Analyses**

##### **Adverse Events**

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the



percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. The following analyses will also be used to assess the safety of subjects in the study:

- The incidence of AEs
- The incidence of SAEs
- The incidence of infections
- The incidence of drug related AEs
- The incidence and type of injection site reactions

### **Clinical Laboratory Tests**

Laboratory data will be summarized by type of laboratory test (eg, hematology, clinical chemistry). Selected laboratory parameters will be summarized by treatment group. Markedly abnormal criteria (to be specified in the Statistical Analysis Plan) will be used to identify markedly abnormal laboratory results, which will be summarized by treatment group. A listing of subjects with any markedly abnormal laboratory results will also be provided.

The following parameters will be summarized using descriptive statistics and frequency table:

- Laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry).
- Incidence of markedly abnormal laboratory parameters (hematology and chemistry).
- Lipid parameters and change from baseline in lipid parameters.
- High sensitivity C-reactive protein (hsCRP) and change from baseline in hsCRP.

### **Electrocardiogram (ECG)**

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

### **Vital Signs**

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

## **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 adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event 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 adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

#### **Serious Adverse Event**

A serious adverse event 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 adverse event 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 adverse event 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 adverse event 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.

**12.1.2. Attribution Definitions****Not Related**

An adverse event that is not related to the use of the drug.

**Doubtful**

An adverse event 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 adverse event 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 adverse event 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 adverse event 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 a serious adverse event should be recorded on the serious adverse event page of the eCRF. Refer to Section 12.3.4 for information on Events of Special Interest.

## **12.3. Procedures**

### **12.3.1. All Adverse Events**

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). Serious adverse events, including those spontaneously reported to the investigator within the last visit or 12 weeks after the last dose of study drug whichever is longer 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 adverse events 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 serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, 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 adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all serious adverse events that are unlisted (unexpected) and associated with the use of the study drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Subjects (or their designees, if appropriate) must be provided with a "study card" indicating the following:

- Subject's name
- Study number
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number
- Statement, in the local language(s), that the subject is participating in a clinical study.

### **12.3.2. Serious Adverse Events**

All serious adverse events 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 serious adverse events 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 serious adverse event should be made by facsimile (fax).

All serious adverse events 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 a serious adverse event. 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 a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the 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 serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.

The cause of death of a subject in a study within the last visit or 12 weeks after the last dose of study drug whichever is longer, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

### **12.3.3. Pregnancy**

All initial reports of pregnancy 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, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further administration of study drug.

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. These events are to be considered serious only if they meet the definition of a serious adverse event.

#### **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 serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event 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)**

The CNTO 1959 supplied for this study as a final lyophilized product is a white solid cake supplied in a 2 mL type 1 glass vial closed with a Teflon<sup>®</sup> coated stopper and aluminum seal with a blue plastic flip-off cap. The sterile product does not contain preservatives and is designed for single use only. The reconstituted CNTO 1959 drug product should be a clear solution and essentially free of visible particulate matter. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

The placebo supplied for this study is a liquid in vial. For further details regarding the composition of the placebo, refer to the study site investigational product procedures manual.

#### **14.2. Packaging**

One vial is packed in one box.

#### **14.3. Labeling**

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

#### **14.4. Preparation, Handling, and Storage**

CNTO 1959 and placebo must be stored at controlled temperatures ranging from 2°C to 8°C (36°F to 46°F) and protected from exposure to light. Protection from light is not required during dose preparation or administration of CNTO 1959 and placebo.

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

#### **14.5. Drug Accountability**

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

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

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



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## **15. STUDY-SPECIFIC MATERIALS**

The investigator will be provided with the following supplies:

- Investigator Brochure
- Site investigational product procedures manual
- Laboratory manual
- Drug administration manual
- PRO questionnaires
- Electronic data capture (eDC) Manual
- Code break procedure

## **16. ETHICAL ASPECTS**

### **16.1. Study-Specific Design Considerations**

Rigorous scientific evidence is mandatory, and ethically required to demonstrate that a new treatment is effective, and that its efficacy substantially outweighs any safety risks or problems with tolerability before it can be marketed. Randomized, double-blind, placebo-controlled design was adopted for this study in order to demonstrate effectiveness of CNTO 1959. Subjects have to stop their usual treatments and to be limited using concomitant therapy and must adhere to other prohibitions and restrictions in accordance with the study procedure. However, subjects will be withdrawn from the study in case the investigator or sponsor believes (eg, for safety or tolerability reasons such as an adverse event), it is in the best interest of the subject to withdraw from the study or investigator deems the subject should initiate the protocol-prohibited medications treatment due to lack of efficacy or other reason. And subjects may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. After withdrawal from the study, alternative treatments are available for the subjects and they will not prejudice future treatment.

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 adverse events 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 subjects in this study based upon the standard of the Japan Red Cross (1 pint/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.

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

### **16.2.2. Independent Ethics Committee or Institutional Review Board**

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

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

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), 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 update 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 adverse events 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 research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

## **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 stated with name of the chairman or authorized designee.

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

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

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

### **17.3. Subject Identification, Enrollment, and Screening Logs**

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth.

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 informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; 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 study 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 scales and assessments designated by the sponsor will be recorded and will be considered 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**

eDC will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, 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.

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 a 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 clinical 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). 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.

### **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 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 they have 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, 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 clinical 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 exploratory 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 exploratory 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 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.

**REFERENCES**

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**Attachment 1: Palmoplantar Pustulosis Severity Index (PPSI)<sup>11</sup>**

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, either both palms or both soles, which has the most severe skin lesion at screening will be identified as the evaluation sites.

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) are:

0 = none, 1 = minimal, 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) Ointment 25µg/g and Lotion 25µg/g, October 2008

**Attachment 2: PPPASI (Palmo-Plantar Pustulosis Area and Severity Index)<sup>1</sup>**

The PPPASI is a system used for assessing and grading the severity 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 surface area (BSA) of the palms and soles, respectively. 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 scoring system for the signs of the disease (erythema, pustules/vesicle and desquamation /scale) are:

0 = none, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.

The scale for estimating the area of involvement for palmoplantar pustulosis 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:

$$\text{PPPASI} = (E + P + D) \text{ Area} \times 0.2(\text{right palm}) + (E + P + D) \text{ Area} \times 0.2(\text{left palm}) + (E + P + D) \text{ Area} \times 0.3(\text{right sole}) + (E + P + D) \text{ Area} \times 0.3(\text{left sole})$$

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

**References**

Brushan M, Buerden AD, McElhone K, James R, Vanhoutte FP, Griffiths CE. Oral liarozole in the treatment of palmo plantar pustular psoriasis: a randomized, double-blind, placebo- controlled study. *Br J Dermatol* 2001; 145:546-53.

**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

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**Attachment 4: PA (Physician's Assessment)**

The PA is used to determine the subject's pustule, vesicle and nail lesions, at a given time point.

< PA-Pustule, Vesicle and Nail lesions >

Each of Pustule, Vesicle and Nail will be graded based on the scales below.

0 = clear

1 = almost clear

2 = Mild

3 = Moderate

4 = Severe

5 = Very severe



**Attachment 5: Laboratory Assessments**

Serology / other screening	Urinalysis <sup>a</sup>	Hematology	Serum Chemistry	Lipid Panel
HIV-1/HIV-2 Antibody	Specific gravity	Hemoglobin	Albumin	Total cholesterol
Hepatitis B Surface Antigen	pH	Hematocrit	Alkaline phosphate	Triglycerides
Hepatitis B Surface Antibody	Protein	RBC count	ALT	Low density lipoprotein(LDL)-cholesterol
Hepatitis B Core Antibody	Glucose	WBC count with differential	AST	High density lipoprotein(HDL)-cholesterol
Hepatitis C Antibody	Ketones	Lymphocytes	LDH	
Hepatitis B Viral DNA, Quantitative <sup>f</sup>	Bilirubin	Monocytes	Total bilirubin	
QuantIFERON-TB	Occult blood	Neutrophils	Direct bilirubin <sup>b</sup>	
HTLV-1 Antibody	Pregnancy Test <sup>c</sup>	Eosinophils	BUN	
Serum Beta hCG, Qualitative <sup>c</sup>		Basophils	Calcium	
Serum follicle stimulating hormone (FSH) <sup>c</sup>		Platelets	Troponin-I	
		Bands <sup>d</sup>	CPK <sup>e</sup>	
			Creatinine	
			Glucose	
			Total protein	
			Phosphate, inorganic	
			Sodium	
			Bicarbonate	
			Potassium	
			Chloride	
			C-reactive protein	

a Microscopic examination of RBC, WBC, casts, and bacteria will be conducted if protein and/or blood are detected during urinalysis.

b Assay if total bilirubin is elevated >ULN.

c Female subject only.

d If Bands are detected in the microscopic analysis, then a result will be provided.

e Assay to isoenzymes if CK elevated >ULN.

f See Attachment 7 for criteria of HBV DNA quantitative test required.

**Attachment 6: QuantiFERON-TB Gold Testing**

The QuantiFERON-TB Gold test is one of the interferon- $\gamma$  (IFN- $\gamma$ ) 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- $\gamma$  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- $\gamma$  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- $\gamma$ -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- $\gamma$ -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- $\gamma$  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. The QuantiFERON-TB Gold test can be measured in the study site or local laboratory in accordance with site procedure.

Interpretation of QuantiFERON-TB Gold test result			
Mitogen minus (IU/mL)	TB Antigen minus (IU/mL)	Results	Interpretation
Any	$\geq 0.35$	Positive	<i>M. tuberculosis</i> infection likely
$\geq 0.5$	$\geq 0.1, < 0.35$	Incomplete*	Determine the overall by taking into account for the degree of risk of infection
	$< 0.1$	Negative	<i>M. tuberculosis</i> infection NOT likely
$< 0.5$	$< 0.35$	Indeterminate	Don't perform determination because there is possibility of immunodeficiency

\*In case result is incomplete, the investigator can consider as negative, if their chest radiograph or lung computed tomography (CT) shows no abnormality suggestive of TB (active or old, inactive TB), and the subject 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 (The Japanese Society for Tuberculosis, 2004; Japan College of Rheumatology, 2008).

**References**

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**Attachment 7: 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.

Eligibility based on Hepatitis B virus test results				
Action	Hepatitis B test result			
	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.

**Coordinating Investigator (where required):**

Name (typed or printed): \_\_\_\_\_

Institution and Address: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

(Day Month Year)

**Principal (Site) Investigator:**

Name (typed or printed): \_\_\_\_\_

Institution and Address: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Telephone Number: \_\_\_\_\_

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

(Day Month Year)

**Sponsor's Responsible Medical Officer:**

Name (typed or printed): Katsuya Hisamichi

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.

**LAST PAGE**

## SIGNATURES

**Signed by**

Katsuya Hisamichi

**Date**

06Feb2013, 10:10:57 AM, UTC

**Justification**

Document Approval

**Janssen Pharmaceutical K.K.**

**Clinical Protocol**

---

**A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Efficacy, Safety and Tolerability of CNTO 1959, a Human Anti-IL-23 Monoclonal Antibody, following Subcutaneous Administration in Subjects with Palmoplantar Pustulosis**

---

**Protocol CNTO1959PPP2001; Phase 2  
AMENDMENT INT-3**

**CNTO 1959**

**Status:** Approved  
**Date:** 4 September 2013  
**Prepared by:** Janssen Pharmaceutical K.K.  
**Document No.:** EDMS- ERI-50537544

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

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**Confidentiality Statement**

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.

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Approved, Date: 4 September 2013



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## PROTOCOL AMENDMENTS

Protocol Version	Issued Date
Original Protocol	07 Feb 2013
INT-1	1 Apr 2013
INT-2	24 Apr 2013
INT-3	4 Sep 2013

Amendments are listed beginning with the most recent amendment.

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### **Amendment INT-3** (4 September 2013)

#### **The overall reason for the amendment:**

Minor formatting and typographical errors have been corrected to improve the clarity and accuracy of the protocol text.

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Applicable Section(s)	Description of Change(s)
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**Rationale:** Added specific classes of disallowed medications.

Section 4.2 Exclusion criteria number 23	Added the section for reference to show specific drugs.
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Section 8.2. Concomitant Therapy	<i>Phototherapy and Systemic Therapy for Palmoplantar pustulosis</i> Added specific classes of disallowed medications to phototherapy and systemic therapy for palmoplantar pustulosis
----------------------------------	---

**Rationale:** Added antibiotics as representative examples of topical medications used for lesions on the palms and soles.

Section 4.2 Exclusion criteria number 26	<i>Topical therapy for palmoplantar pustulosis</i> Added antibiotics as representative examples of topical medications used for lesions on the palms and soles.
Section 8.2. Concomitant Therapy	

**Rationale:** Clarified that this provision is applicable only to subjects who also have PAO.

Section 8.2. Concomitant Therapy	<i>Therapy for palmoplantar pustulosis for arthro-osteitis</i> Clarified that this provision is applicable only to subjects who also have PAO, and made a minor change
----------------------------------	---

**Rationale:** Clarified that baseline laboratory data to be obtained on the treatment start day will not be used to assess the subject's eligibility.

Section 4.2 Exclusion criteria NOTE	Clarified that baseline laboratory data to be obtained on the treatment start day will not be used to assess the subject's eligibility.
-------------------------------------	---

**Rationale:** Altered the description in accordance with the recently revised local guideline.

Attachment 6: Interferon Gamma Release Assays (IGRAs)	The description in accordance with the recently revised local guideline was added.
---	--

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Altered the explanation in accordance with the recently revised protocol template.	
Section 9.3.4. Immunogenicity Assessments	Altered the explanation in accordance with the recently revised protocol template.
Section 12.3.1. All Adverse Events	
Section 17.10. On-Site Audits	
<b>Rationale:</b> Made minor changes in wording to maintain clarity and consistency, and made minor formatting changes.	
Synopsis Section 4.1 Inclusion Criteria number 1	Stated that subjects are men or women <u>aged 20 years or older</u> with palmoplantar pustulosis as defined to make a minor change in wording to maintain consistency
Throughout the protocol	Made minor changes in wording to maintain clarity, and made minor formatting changes.

**Amendment INT-2** (24 Apr 2013)

**The overall reason for the amendment:** As a TB screening test, T- SPOT.TB test can also be used as a substitute for QuantiFERON-TB Gold test.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Description of the TB screening test was modified, and the use of T-SPOT.TB test was added.	
Revised sections are listed in the next column.	<p><u>The term “QuantiFERON TB Gold test” was replaced with “Interferon Gamma Release Assay”.</u></p> <p><u>The above revision was made in the following sections:</u></p> <p>Section 4.1 Inclusion Criteria number 12; Section 4.2 Exclusion Criteria, criterion number 12; Section 9.1.2 Screening Period; Section 9.1.3 Double-blind Period; Section 9.5 Safety Evaluations, Clinical Laboratory Tests; Section 10.2 Discontinuation of Study Treatment; Attachment 5 Laboratory Assessments; Attachment 6 QuantiFERON-TB Gold Testing</p>
<b>Rationale:</b> Description of the biomarker evaluations was modified as below to be accurate.	
Synopsis, Biomarker Evaluations	In order to better understand the pathological mechanisms involved in palmoplantar pustulosis and to identify a treatment response signature to CNTO 1959, following biomarkers will be evaluated according to the Time and Events Schedule. Serum samples will be collected from all subjects. The concentration of inflammatory biomarkers (protein) in serum samples will be measured (such as, but not limited to, IL 23p19, IL 17, IL 6, IL 8, IL 22, tumor necrosis factor alpha [TNF $\alpha$ ], and IL 12p40). Whole blood samples will be collected from all subjects. Total ribonucleic acid (RNA) will be isolated from whole blood samples and used for comprehensive mRNA and microRNA expression level analyses. Skin biopsy samples will be collected from subjects who consent separately to participate in biopsy assessment. Total ribonucleic acid (RNA) will be isolated from whole blood samples and used for comprehensive mRNA and microRNA expression level analyses. Studies of variation of DNA and/or RNA using obtained biomarkers sample (eg. identification of DNA and/or RNA sequences) will not be performed.
9.4 Biomarkers	
<b>Rationale:</b> Description about biomarkers sample was added to clarify the statement.	
3.1 Overview of Study Design	The following sentence was added:
9.5 Safety Evaluations	However, studies of variation of DNA and/or RNA using obtained biomarkers sample (eg. identification of DNA and/or RNA sequences) will not be performed.
<b>Rationale:</b> Specific method of how biomarker samples may be used is not defined. In order to avoid confusion, the sentence is deleted.	
3.2 Study Design Rationale	The following statement was deleted: Biomarker samples may also be used to help address emerging safety issues and to enable the development of safer, more effective, and ultimately individualized therapies.
<b>Rationale:</b> Description was added to clarify the statement about donating eggs for the purposes of assisted reproduction.	
4.1 Inclusion Criteria criterion number 9	The underlined statement was added as follows: A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction <u>during the study and for 3 months after receiving the last dose of the study drug.</u>

Applicable Section(s)	Description of Change(s)
	<b>Rationale:</b> On the basis of “T-SPOT.TB test” use for TB screening, the blood sample volume was revised.
9.1.1 Overview	<p><u>The statement below was revised:</u>            “The total blood volume for the study is approximately 272mL (139 mL for safety and efficacy, 85 mL for PK and immunogenicity, 48 mL for biomarkers).”</p> <p><u>Revised statement:</u>            “The total blood volume for the study is approximately 275mL (142 mL [for T-SPOT.TB test] or 139 mL [for QuantiFERON-TB Gold test] for safety and efficacy, 85 mL for PK and immunogenicity, 48 mL for biomarkers).”</p>
	<b>Rationale:</b> Now that both “QuantiFERON-TB Gold test” and “T-SPOT.TB test” are to be used, an explanation about the use of “T-SPOT.TB test” was added. References were added.
Attachment 6 QuantiFERON-TB Gold Test	<u>The title of Attachment 6 was revised from “QuantiFERON-TB Gold Testing” to “Interferon Gamma Release Assays (IGRAs)”.</u> In addition to an explanatory statement about “QuantiFERON-TB Gold Test”, a statement about “T-SPOT.TB test” is added. <u>Seven references were added.</u>

**Amendment INT-1** (1 Apr 2013)

**The overall reason for the amendment:** The overall reason for this amendment is to clarify some of the Serum Chemistry Panel description based on directions from Central Laboratory.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Clarification added on hospitalization for asthma.	
4.2 Exclusion Criteria criterion number 7	Changed text to: Subject has been hospitalized for asthma <u>within the previous 3 months to screening</u> , ever required intubation for treatment of asthma, currently require oral corticosteroids for the treatment of asthma, or required more than one short-term ( $\leq 2$ weeks) course of oral corticosteroids for asthma within the previous 6 months prior to screening.
<b>Rationale:</b> Corrected based on reviewing the measurement items.	
9.5 Safety Evaluations and Attachment 5	Removed "Bands" from Serum Chemistry Panel and corrected the description of footnote.  a. If <u>other hematocytes</u> are detected, then their result will be provided.
<b>Rationale:</b> Modify the description of the Clinical Laboratory Tests Panel to be accurate.	
9.5 Safety Evaluations and Attachment 5	Addition of HIV Antigen to Clinical Laboratory Tests Panel  HIV <u>antigen/antibody</u>  Modified the description of the Urinalysis panel footnote.  d. Microscopic examination of RBC, WBC, casts, bacteria and such will be conducted if protein and/or blood are detected during urinalysis.
<b>Rationale:</b> All of the randomized subjects should have a chest radiograph at the last visit.	
Time and Events Schedule	Chest X-ray (both posterior-anterior and lateral views, substitutable with chest CT) was added at ET (Early Termination) in the Time and Events Schedule table.
<b>Rationale:</b> Clarify interpretation of QuantiFERON-TB Gold test result	
Attachment 6 QuantiFERON-TB Gold Testing	Added a new sentence at the first part of footnote and transcribe them from footnote to body text.  <u>If the qualitative result cannot be obtained from investigational medical institutions or the local laboratory, it will be determined based on the criteria shown in the table below.</u> In case result is incomplete, the investigator can consider as negative, if <u>the subject's</u> chest radiograph or lung computed tomography (CT) shows no abnormality suggestive of TB (active or old, inactive TB), and <u>he/she</u> has no additional clinical risk factors for TB as determined by the investigator and medical monitor.
<b>Rationale:</b> Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.



## **SYNOPSIS**

A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Efficacy, Safety and Tolerability of CNTO 1959, a Human Anti-IL-23 Monoclonal Antibody, following Subcutaneous Administration in Subjects with Palmoplantar Pustulosis

CNTO 1959 is a fully human immunoglobulin G1 lambda (IgG1 $\lambda$ ) monoclonal antibody that binds to the p19 subunit of human interleukin (IL)-23 with high specificity and affinity. The binding of CNTO 1959 to the IL-23p19 subunit blocks the subsequent binding of extracellular IL-23 to the cell surface IL-23 receptor (IL-23R), inhibiting IL-23 specific intracellular signaling and subsequent activation and cytokine production.

## **OBJECTIVES AND HYPOTHESES**

### **Primary Objectives**

The primary objectives of this study are to evaluate the efficacy of CNTO 1959 in the treatment of subjects with palmoplantar pustulosis at Week 16, and to assess the safety and tolerability of CNTO 1959 in subjects with palmoplantar pustulosis.

### **Major Secondary Objectives**

The major secondary objectives of this study are:

- To assess the pharmacokinetics and immunogenicity of CNTO 1959 following subcutaneous (SC) administration in subjects with palmoplantar pustulosis
- To assess the impact of treatment with CNTO 1959 on the health related quality of life (QOL) measurements in subjects with palmoplantar pustulosis at Week 16
- To assess the possible time point with maximum clinical response of CNTO 1959 after two dose injection

### **Exploratory Objectives**

The exploratory objectives of this study are:

- To explore biomarkers following CNTO 1959 administration in subjects with palmoplantar pustulosis
- To explore the impact of treatment with CNTO 1959 on pustulotic arthro-osteitis (PAO) in the subset of subjects with PAO at screening
- To explore possible overall process of clinical response of CNTO 1959 over time.

### **Hypothesis**

The primary hypothesis of this study is that CNTO 1959 treatment, 200 mg SC injection at Week 0 and Week 4, is superior to placebo in terms of the change from baseline of Palmoplantar Pustulosis Severity Index (PPSI) total score at Week 16.

## **OVERVIEW OF STUDY DESIGN**

This is a phase 2, randomized, double-blind, placebo-controlled, parallel group, multicenter study of CNTO 1959 in subjects with palmoplantar pustulosis. Approximately 50 subjects will be randomly assigned to 1 of 2 treatment groups (CNTO 1959 200 mg SC or placebo SC) in a 1:1 ratio and will receive study drug at Week 0 and Week 4. After randomization (Week 0), subjects will return to the

study site for 9 evaluation visits (Week 1, 2, 4, 6, 8, 12, 16, 20 and 24). The total duration of subject participation will be approximately 30 weeks, which includes a screening period of about 6 weeks before dosing. Completion of the Week 24 assessment constitutes the subject's completion of the study.

### **SUBJECT POPULATION**

Subjects are men or women aged 20 years or older with palmoplantar pustulosis as defined by a PPSI score of 7 or greater at screening and baseline (Week 0), including active lesions on the palms or soles. Subject must have inadequate response to the treatment with topical steroid and/or topical vitamin D<sub>3</sub> derivative preparations and/or the phototherapy and/or systemic etretinate prior to or at screening. Subject must agree to avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet (UV) light sources to the palms and soles during study.

### **DOSAGE AND ADMINISTRATION**

All subjects randomized will receive 2 injections of 1 mL each as SC injections at each administration (two 1 mL SC injection containing placebo or CNTO 1959) at Week 0 and Week 4.

### **EFFICACY EVALUATIONS/ENDPOINTS**

Efficacy evaluations include PPSI, PPPASI (Palmoplantar Pustulosis Area and Severity Index), PGA (Physician's Global Assessment of palmoplantar pustulosis lesion), PA (Physician's Assessment of each skin lesions) and Patient's Visual Analogue Scale Assessment of Palmoplantar Pustulosis Severity (Patient's VAS-PPP severity). Subjects with concurrent PAO at screening will also be evaluated using a Physician's Visual Analogue Scale Assessment of Pustulotic Arthro-Osteitis Activity (Physician's VAS-PAO activity) and a Patient's Visual Analogue Scale Assessment of Pustulotic Arthro-Osteitis Activity and Pain (Patient's VAS-PAO activity and pain) in order to explore the efficacy of CNTO 1959 in the treatment of PAO. In addition, the Dermatology Life Quality Index (DLQI) score and SF-36 score will be used to assess the impact of treatment on disease and subject's QOL, respectively. The PPSI assesses the severity of palmoplantar pustulosis lesions and their response to therapy with a score ranging from 0 to 12. In the PPSI system, either both palms or both soles, which has the most severe skin lesion at screening will be identified as the evaluation sites. Evaluation sites are assessed separately for erythema, pustules/vesicle and desquamation/scale, which are each rated on a scale of 0 to 4. PPPASI assesses the severity of palmoplantar pustulosis lesions and their response to therapy with a score ranging from 0 to 72. The PGA documents the Physician's Global assessment of the subject's palmoplantar overall skin lesions status. The Visual Analogue Scale assessment will be recorded on a 10-cm VAS.

#### **Primary Endpoint**

The primary efficacy endpoint is the change from baseline in PPSI total score at Week 16.

#### **Major Secondary Endpoints**

- Change from baseline in PPSI total score over time
- Change in PPPASI total score over time from baseline to Week 16
- Proportion of subjects who achieve a PPPASI-50 over time from baseline to Week 16
- Proportion of subjects who achieve a PGA score of 1 or less over time from baseline to Week 16

#### **Other Secondary Endpoints**

- Proportion of subjects who achieve a PPPASI-75 over time from baseline to Week 16
- Change in physician's assessment of 3 PA lesions over time from baseline to Week 16
- Change in patient's VAS-PPP severity over time from baseline to Week 16

- Change in physician's VAS-PAO activity over time from baseline to Week 16
- Change in patient's VAS-PAO activity and pain over time from baseline to Week 16
- Change in DLQI over time from baseline to Week 16
- Change in SF-36 over time from baseline to Week 16

### **PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS**

Samples will be collected according to the Time and Events Schedule and used to evaluate the pharmacokinetics, as well as the immunogenicity of CNTO 1959 (antibodies to CNTO 1959). If deemed necessary, pharmacokinetic data may be combined with those of other clinical studies of CNTO 1959 when population PK analysis is performed.

### **BIOMARKER EVALUATIONS**

In order to better understand the pathological mechanisms involved in palmoplantar pustulosis and to identify a treatment response signature to CNTO 1959, following biomarkers will be evaluated according to the Time and Events Schedule. Serum samples will be collected from all subjects. The concentration of inflammatory biomarkers (protein) in serum samples will be measured (such as, but not limited to, IL 23p19, IL 17, IL 6, IL 8, IL 22, tumor necrosis factor alpha [TNF $\alpha$ ], and IL 12p40). Whole blood samples will be collected from all subjects. Total ribonucleic acid (RNA) will be isolated from whole blood samples and used for comprehensive mRNA and microRNA expression level analyses. Skin biopsy samples will be collected from subjects who consent separately to participate in biopsy assessment. Total ribonucleic acid (RNA) will be isolated from skin biopsy samples and used for comprehensive mRNA and microRNA expression level analyses. Studies of variation of DNA and/or RNA using obtained biomarkers sample (eg. identification of DNA and/or RNA sequences) will not be performed.

### **SAFETY EVALUATIONS**

The safety and tolerability of study drugs (placebo, CNTO 1959) will be monitored by physical examinations, detection of injection site and allergic reactions, ECGs, clinical laboratory tests, vital signs, concomitant medications and adverse events (AEs) according to the Time and Events Schedule.

### **STATISTICAL METHODS**

#### Sample size determination

In the phase 3 double blind controlled study for Maxacalcitol (topical vitamin D<sub>3</sub>) that is approved for a treatment of palmoplantar pustulosis in Japan, the mean change from baseline of skin observation total score for Maxacalcitol was -3.7 (standard deviation [SD] = 2.1, number of patients [N] = 94) and -1.9 (SD = 1.9, N=93) for placebo group, as results of the primary endpoint. Based on these results, 25 subjects per group (total of 50 subjects) are considered as appropriate for this study in consideration to uncertainty for the estimates with varying assumptions. The sample size of 25 subjects has an 84% power to detect a significant difference between the CNTO 1959 treatment group and the placebo group at a two-sided alpha level of 0.05, assuming a treatment difference in the change from baseline of PPSI total score at Week 16 of 1.8 with a SD of 2.1.

#### Efficacy

In this primary analysis, the change from baseline in PPSI total score at Week 16 will be analyzed using an analysis of covariance (ANCOVA) model with treatment as a factor and baseline score as a covariate. Treatment effect of CNTO 1959 versus placebo will be estimated based on least-square (LS) means of the difference. The p-value for the difference in treatment effect along with the 2-sided 95% CI will be presented. The last available post-baseline PPSI total score will be carried forward to impute the PPSI total scores that are missing after discontinuation of treatment up to Week 16 of the double-blind

treatment period. If a subject meets one of the criteria of a treatment failure, the subject will be designated a treatment failure for primary endpoint at all visits starting from the visit after the treatment failure and the last available post-baseline PPSI total score value will be assigned regardless of the actual observed data. To evaluate sensitivity of the results to the imputation method, the impact of missing data would be explored through various analysis methods.

For major secondary endpoints, the change from baseline in PPSI total score will also be summarized over time by treatment group using descriptive statistics. If a between-group difference larger than that at Week 16 is observed at any visit, the same analysis will be performed for that visit as described for the primary analysis, to assess possible time point with maximum clinical response of CNTO 1959. The change from baseline in PPPASI at Week 16 will be analyzed using an ANCOVA model. Treatment effect of CNTO 1959 versus placebo will be estimated based on LS means of the difference. The p-value for the treatment difference along with the 2-sided 95% CI will be presented. The change from baseline in PPPASI will also be summarized over time by treatment group using descriptive statistics. The proportion of subjects who achieve a PPPASI-50 at Week 16 and the proportion of subjects who achieve a PGA score of 1 or less at Week 16 will be compared between the CNTO 1959 treatment group and placebo group using Fisher's exact test.

For other secondary endpoints, the continuous variables will be summarized by treatment group using descriptive statistics, which will include the number of subjects (N), mean, SD, median, minimum, and maximum and will be analyzed using an analysis of variance model based on appropriate rank scores or ANCOVA model. The categorical variables will be summarized by treatment group using frequencies and percentages. The binary variables will be compared using Fisher's exact test. These other secondary endpoints at other evaluation visits than Week 16 may be summarized as described above, if necessary.

#### Pharmacokinetics

Serum CNTO 1959 concentrations will be summarized with descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, maximum, 25% quantile and 75% quantile at each sampling time. Mean or median serum CNTO 1959 concentration time profiles will be plotted after the first dose of study drug.

Population PK analysis of serum concentration-time data of CNTO 1959 will be performed using nonlinear mixed-effects model. Data may be combined with those of other clinical studies of CNTO 1959 to conduct the population PK analysis. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

#### Immunogenicity

The incidence of antibodies to CNTO 1959 during the study will be summarized for all subjects who receive an administration 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).

#### Safety

The verbatim terms used in the electronic case report form (eCRF) by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the treatment phase (ie, treatment-emergent AEs, and AEs that have worsened since baseline) will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

For other safety data (e.g., laboratory test, vital sign, and electrocardiogram [ECG]) will be summarized using descriptive statistics and frequency table.

**TIME AND EVENTS SCHEDULE**

Phase	Screening period	Double-blind period										Safety follow-up after ET		
		Screening <sup>a</sup>	Day 1 <sup>j</sup> (Week 0)	Day 8 (Week 1)	Day 15 (Week 2)	Day 29 <sup>j</sup> (Week 4)	Day 43 (Week 6)	Day 57 (Week 8)	Day 85 (Week 12)	Day 113 (Week 16) (Week 16)	Day 141 (Week 20)	Day 169 (Week 24)	ET	4, 8 weeks after LA
<b>Allowance</b>			±3 day	±3 day	±3 day	±3 day	±3 day	±7 day	±7 day	±7 day	±7 day			
Screening/Administrative														
Informed consent	X													
Demographics	X													
Eligibility criteria	X	X												
Medical and medication history	X													
Height	X													
Weight	X	X							X		X	X		X
Chest X-ray (both posterior-anterior and lateral views, substitutable with chest CT)	X										X	X <sup>m</sup>		X
Serology/other screening test <sup>b</sup>	X													
Serum pregnancy test <sup>c</sup>	X													
Urine pregnancy test <sup>c</sup>		X												
Discontinue systemic phototherapy / medications <sup>d</sup>	X													
Discontinue topical treatments <sup>e</sup>	X													
Study Drug Administration														
Randomization		X												
Study drug administration <sup>f</sup>		X			X									
Safety Assessments														
Vital signs <sup>g</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Supine 12-lead ECG <sup>h</sup>	X	X	X		X				X		X	X		X
Efficacy Assessments														
PPSI, PPPASI, PGA, PA-pustule, PA-vesicle	X	X	X	X	X	X	X	X	X	X	X	X		
PA-nail	X	X							X		X	X		
Patient's VAS-PPP severity		X	X	X	X	X	X	X	X	X	X	X		
Physician's VAS-PAO activity <sup>i</sup>		X					X		X		X	X		
Patient's VAS-PAO activity and pain		X					X		X		X	X		
DLQI		X	X	X	X	X	X	X	X	X	X	X		
SF-36		X					X		X		X	X		
MRI <sup>l</sup>	X								X		X	X		
Photographs	X	X	X	X	X	X	X	X	X	X	X	X		

Phase	Screening period	Double-blind period										Safety follow-up after ET		
		Day 1 <sup>j</sup> (Week 0)	Day 8 (Week 1)	Day 15 (Week 2)	Day 29 <sup>j</sup> (Week 4)	Day 43 (Week 6)	Day 57 (Week 8)	Day 85 (Week 12)	Day 113 (Week 16)	Day 141 (Week 20)	Day 169 (Week 24)	ET	4, 8 weeks after LA	12 weeks after LA
<b>Allowance</b>			±3 day	±3 day	±3 day	±3 day	±3 day	±7 day	±7 day	±7 day				
<b>Clinical Laboratory Assessments</b>														
Serum chemistry <sup>b</sup>	X	X		X	X	X	X	X	X	X	X	X	X	X
Hematology <sup>b</sup>	X	X		X			X	X	X	X	X	X	X	X
Lipid panel <sup>b</sup>		X							X	X	X	X		X
Urinalysis <sup>b</sup>	X	X			X		X	X	X	X	X	X	X	X
<b>Pharmacokinetics/Immunogenicity</b>														
Serum sample collection for CNTO 1959 concentration <sup>k</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X
Serum sample collection for antibodies to CNTO 1959 <sup>k</sup>		X								X	X <sup>m</sup>			X
<b>Biomarkers</b>														
Serum sample collection for biomarker analysis		X			X				X					
Whole blood sample collection for biomarker analysis		X			X				X					
Skin biopsy <sup>l</sup>		X							X					
<b>Ongoing Subject Review</b>														
Physical examination	X	←	←	←	←	←	←	←	←	←	←	X	←	←
Concomitant medication monitoring	X	←	←	←	←	←	←	←	←	←	←	X	←	←
Adverse event monitoring	X	←	←	←	←	←	←	←	←	←	←	X	←	←

- a. Screening visit must occur within 6 weeks of study drug administration.
  - b. See Attachment 5 for list of required laboratory tests.
  - c. Female subjects of childbearing potential.
  - d. Discontinue at least 4 weeks prior to study drug administration.
  - e. Discontinue at least 2 weeks prior to study drug administration.
  - f. Subjects will be observed for symptoms of allergic reactions for at least 30 minutes after the SC injection of study drug at the study site.
  - g. Vital signs include temperature, resting pulse rate, and blood pressure.
  - h. During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures are desirable to be performed in the following order: ECG(s), vital signs, blood draw.
  - i. Only for subjects with PAO at screening.
  - j. Before start of study drug administration.
  - k. Serum from a single blood draw may be used to test CNTO 1959 concentration and antibodies to CNTO 1959.
  - l. Subjects who have consented separately to participate in biopsy assessment.
  - m. Only for subjects who terminate after 12 weeks of last study drug administration.
- ET: Early Termination, LA: Last Administration

**ABBREVIATIONS**

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BCG	Bacille Calmette-Guérin
BSA	Body Surface Area
CL	Clearance
DBL	database lock
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
F%	absolute bioavailability
FDA	Food and Drug Administration (United States)
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
hsCRP	high sensitivity C-reactive protein
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IgG1 $\lambda$	immunoglobulin G1 lambda
IGRA	Interferon-gamma release assay
IHC	immunohistochemistry
IL	interleukin
IL-23R	interleukin 23 receptor
IU	International unit
IV	intravenous
LS	least-square
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NOAEL	no observed adverse effect level
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PAO	pustulotic arthro-osteitis
PASI	Psoriasis Area and Severity Index
PGA	Physician's Global Assessment of palmoplantar lesion
PK	pharmacokinetic(s)
PQC	product quality complaint
QOL	quality of life
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
T <sub>1/2</sub>	half-life
TB	tuberculosis
Th17	T helper 17
TK	toxicokinetics
T <sub>max</sub>	observed time to maximal concentration
TNF $\alpha$	tumor necrosis factor alpha
ULN	upper limit of normal

USA	The United States of America
UV	ultraviolet
VAS	Visual Analogue Scale
V <sub>z</sub>	volume of distribution during the terminal phase
WBC	white blood cell



## 1. INTRODUCTION

CNTO 1959 is a fully human immunoglobulin G1 lambda (IgG1 $\lambda$ ) monoclonal antibody (mAb) that binds to the p19 subunit of human interleukin 23 (IL-23) with high specificity and affinity, and blocks IL-23 alone without blocking IL-12. Binding of CNTO 1959 to the IL-23 p19 subunit blocks the subsequent binding of extracellular IL-23 to the cell surface IL-23 receptor (IL-23R), inhibiting IL-23-specific intracellular signaling and subsequent activation and cytokine production. CNTO 1959 inhibits the biological activity of IL-23 in all in vitro assays examined. While there is no reported clinical experience with agents that only inhibit IL-23, a rapidly growing body of literature suggests that dysregulated IL-23/IL-17 responses contribute to the chronic inflammation underlying the pathophysiology of many immune-mediated diseases<sup>4,6</sup>, including psoriasis, multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease.

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

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. [REDACTED]

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## Clinical Studies

CNTO1959PSO1001 was the first-in-human study for CNTO 1959 and is the only study completed thus far in humans. In Part 1 of the CNTO1959PSO1001 study, 47 healthy subjects received a single dose of CNTO 1959 or placebo, and they were followed for 16 weeks. Of the 47 subjects, 30 subjects received a single IV infusion of CNTO 1959 (0.03, 0.1, 0.3, 1, 3, or 10 mg/kg), 6 subjects received a SC injection of 3 mg/kg CNTO 1959, and 11 subjects received placebo (10 IV and 1 SC). In Part 2, 24 subjects with moderate to severe psoriasis received a single SC dose (10, 30, 100 or 300 mg) of CNTO 1959 (20 subjects) or placebo (4 subjects), and they were followed for 24 weeks. Currently, two studies (CNTO1959PSO2001 and CNTO1275ARA2001) are ongoing outside Japan. CNTO1959PSO2001 is a Phase 2 dose-ranging study in subjects with psoriasis. Approximately 280 subjects will be randomized and will continue dosing through Week 40 with a subsequent efficacy and safety follow-up through Week 52. There are 5 dose groups for CNTO 1959 (5 mg every 12 weeks [q12w], 15 mg every 8 weeks [q8w], 50 mg q12w, 100 mg q8w and 200 mg q12w). CNTO1275ARA2001 is a phase 2 study in subjects with active rheumatoid arthritis. Approximately 250 subjects will be randomized. The study duration will be 72 weeks, including a 28-week placebo-controlled treatment period, a 24-week blinded active treatment period and a 20-week safety follow-up period between the last injection of study agent and the last visit. There are 2 dose groups for CNTO 1959 (200 mg at Weeks 0, 4, then q8 weeks, or 50 mg at Weeks 0, 4, then q8 weeks). In Japan, a single dose Phase 1 study in Japanese subjects with psoriasis (CNTO1959PSO1002) is ongoing. Approximately 24 subjects will be included in this study. There are 4 dosing cohorts (10, 30, 100, 300 mg single SC injection) and follow-up through 24 weeks.

### *Human Pharmacokinetics and Immunogenicity*

The pharmacokinetics of CNTO 1959 was evaluated in the first-in-human Study CNTO1959PSO1001. CNTO 1959 exhibited linear pharmacokinetics at doses ranging from 0.03 mg/kg to 10 mg/kg following IV administration and from 10 mg to 300 mg following SC

administration in subjects with moderate to severe psoriasis. Following a single IV administration of 0.03 mg/kg to 10 mg/kg CNTO 1959 to healthy subjects, mean values of clearance (CL) and volume of distribution ( $V_z$ ) during the elimination phase ranged from 3.62 to 6.03 mL/day/kg and 99.38 to 123.22 mL/kg, respectively; the mean  $T_{1/2}$  values ranged from 12.3 to 19.1 days. The absolute SC bioavailability (F%) of CNTO 1959 was estimated to be 32.6%. Following a single SC administration of 10 to 300 mg CNTO 1959 to subjects with psoriasis, the median  $T_{max}$  ranged from 3.2 to 6.0 days; the mean  $T_{1/2}$  was 14.7 to 16.9 days, which is consistent with that in healthy subjects. The pharmacokinetics of CNTO 1959 were generally comparable between healthy subjects and subjects with psoriasis.

The immunogenicity of CNTO 1959 was also evaluated in Study CNTO1959PSO1001. Following IV administration of CNTO 1959 to healthy subjects, 1 (3.3%) of 30 subjects tested positive for antibodies to CNTO 1959. None of 6 healthy subjects treated with SC CNTO 1959 tested positive for antibodies to CNTO 1959. Following SC administration of CNTO 1959 to subjects with psoriasis, 1 (5.0%) of 20 subjects tested positive for antibodies to CNTO 1959.

### ***Efficacy/Safety Studies in Patients With Plaque Psoriasis***

In the CNTO1959PSO1001 study part 2, efficacy was assessed by Psoriasis Area and Severity Index (PASI) and Physician's Global Assessment (PGA) throughout the 24-week follow-up period in subjects with psoriasis. Improvements in PASI scores were observed in all dose groups. The maximum clinical response was observed between Weeks 8 and 16 in all dose groups. At Week 12, a PASI 75 response was achieved by 50.0%, 60.0%, 60.0%, and 100.0% of subjects in the 10 mg, 30 mg, 100 mg, and 300 mg dose groups, respectively whereas 0% in the placebo group. In all dose groups except the 100-mg group, evidence of dose-response relationship was observed for the 10 mg, 30 mg and 300 mg dose groups in which the PASI 75 response was maintained through Week 24. PGA scores were generally consistent with results of the PASI analysis.

The safety results from this study show that CNTO 1959 or placebo administered either via IV infusion or SC injection in healthy subjects or by SC injection in subjects with moderate to severe psoriasis was generally safe and well tolerated. There was no dose-dependent response in the incidence of adverse events (AEs) and all AEs were considered to be mild to moderate in severity by the investigator. In healthy subjects, the most common AEs were headache (9 [25.0%] of 36 subjects treated with CNTO 1959 and 3 [27.3%] of 11 subjects treated with placebo), and upper respiratory tract infection (5 [13.9%] of 36 subjects treated with CNTO 1959 and 1 [9.1%] of 11 subjects treated with placebo). In subjects with psoriasis, the most common AEs were upper respiratory tract infection and vomiting (each in 2 [10.0%] of 20 subjects treated with CNTO 1959) which were not observed in subjects who received placebo (n = 4). One subject with psoriasis who received CNTO 1959 10 mg experienced a serious adverse event (SAE) of traumatic brain injury secondary to motor vehicle accident, which was considered unrelated to study drug by the investigator. No trends or dose related changes in vital signs, physical examinations, ECGs, or laboratory values were observed. No subjects terminated study participation due to AEs.

Thus, the Phase 1 data demonstrate that CNTO 1959 may be efficacious in the treatment of subjects with moderate to severe psoriasis with a good emerging safety profile. These results support further investigation of CNTO 1959 in Phase 2 studies.

## **1.2. Overall Rationale for the Study**

Palmoplantar pustulosis is a chronic and intensely inflammatory skin disease with pustules, erythema and scaling localized to the palms and soles. Palmoplantar pustulosis is an inflammatory hyperkeratosis that appears most commonly in middle-aged men and women, particularly those who are smokers. As clinical features of palmoplantar pustulosis, multiple vesicles occur on the thenar and antithenar regions of the palms and arches of feet, and these become pustular<sup>9</sup>. Erythema develops at the periphery of the lesions and fuses into plaques. Itching may be present. Punctate depressions and thickening occur frequently in the nails. Pustules recur in 2- to 4-week cycles and progress chronically. They may appear on the knees, lower extremities and scalp. In 10% of palmoplantar pustulosis cases, sternocostoclavicular ossification accompanied by chest pain develops as a complication<sup>10</sup>. This disease shares some common features with other pustular forms of psoriasis and is often classified as a localized form of pustular psoriasis. Quality of Life (QOL) decreased because the presence of painful lesions on the soles and the palms can significantly impair the patient's ability to walk and use their hands<sup>12</sup>. Commonly-used treatment options are limited to topical treatments such as corticosteroids, or active vitamin D<sub>3</sub> ointments, and phototherapy (ultraviolet [UV] radiation therapy). These therapies are modestly effective and can take up to 5-7 years before there is a significant clearance of lesions. T helper 17 (Th17) cells and IL-23 may play a role in promoting the inflammation observed in palmoplantar pustulosis<sup>2, 3, 7</sup>. The lesions of patients with palmoplantar pustulosis show an infiltration of neutrophils and Th17 cells as well as increased expression of IL-8, IL-17, IL-22, and IL-23. In addition, dendritic cells and keratinocytes demonstrate increased production of IL-23, a key cytokine which plays a role in the stabilization and proliferation of Th17 cells<sup>1, 3, 5</sup>. IL-23 also stimulates Th17 cells within the dermis to produce IL-17A, IL-17F, and IL-22, which, in turn, stimulates IL-8 production from keratinocytes. IL-8 promotes infiltration of neutrophils to the skin, promoting pustule formation<sup>5</sup>. These observations suggest that blockade of IL-23-mediated inflammation by CNTO 1959 (anti-IL-23 mAb) could provide therapeutic benefit to patients with palmoplantar pustulosis.

## **2. OBJECTIVES AND HYPOTHESIS**

### **2.1. Objectives**

#### **Primary Objectives**

The primary objectives of this study are:

- To evaluate the efficacy of CNTO 1959 in the treatment of subjects with palmoplantar pustulosis at Week 16
- To assess the safety and tolerability of CNTO 1959 in subjects with palmoplantar pustulosis

## Major Secondary Objectives

The major secondary objectives of this study are:

- To assess the pharmacokinetics and immunogenicity of CNTO 1959 following SC administration in subjects with palmoplantar pustulosis
- To assess the impact of treatment with CNTO 1959 on the health related QOL measurement in subjects with palmoplantar pustulosis at Week 16
- To assess possible time point with maximum clinical response of CNTO 1959 after two dose injection.

## Exploratory Objectives

The exploratory objectives of this study are:

- To explore biomarkers following CNTO 1959 administration in subjects with palmoplantar pustulosis
- To explore the impact of treatment with CNTO 1959 on pustulotic arthro-osteitis (PAO) in the subset of subjects with PAO at screening
- To explore possible overall process of clinical response of CNTO 1959 over time.

### 2.2. Hypothesis

The primary hypothesis of this study is that CNTO 1959 treatment, 200 mg SC injection at Week 0 and Week 4, is superior to placebo in terms of the change from baseline of Palmoplantar Pustulosis Severity Index (PPSI) total score at Week 16.

## 3. STUDY DESIGN AND RATIONALE

### 3.1. Overview of Study Design

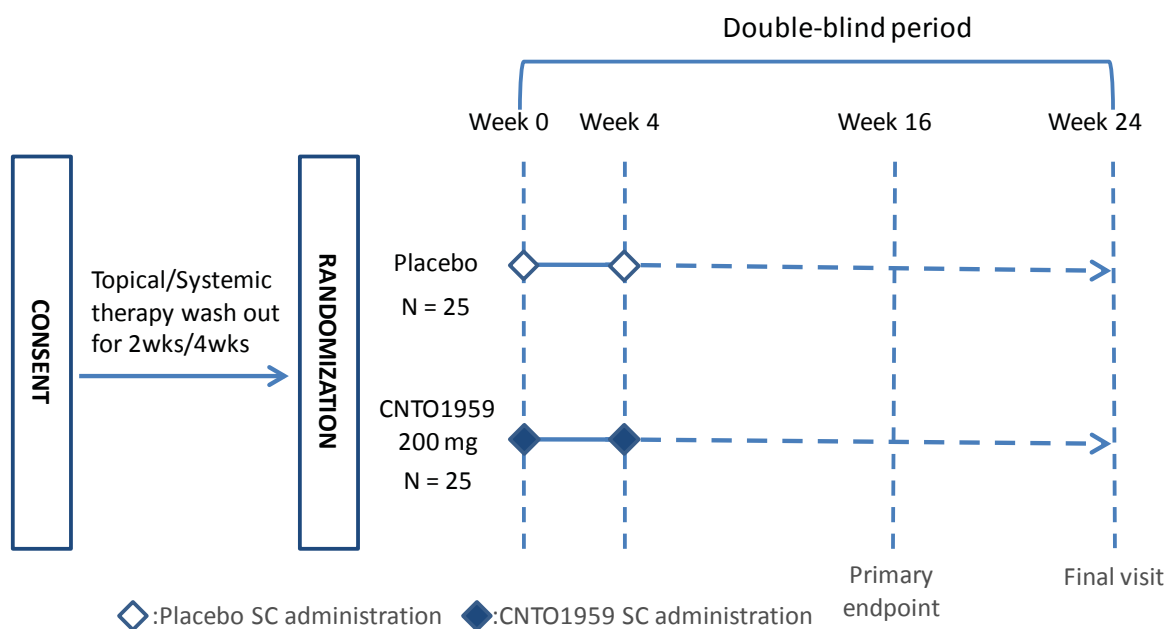
This is a Phase 2, randomized, double-blind, placebo-controlled, parallel group, multicenter study of CNTO 1959 in subjects with palmoplantar pustulosis. Approximately 50 subjects will be randomly assigned to 1 of 2 treatment groups (CNTO 1959 200 mg SC or placebo SC) in a 1:1 ratio and will receive study drug at Week 0 and Week 4. After randomization (Week 0), subjects will return to the study site for 9 evaluation visits (Weeks 1, 2, 4, 6, 8, 12, 16, 20 and 24). The overall study schema is provided in Figure 1.

The target population consists of moderate to severe subjects with palmoplantar pustulosis defined as those subjects who have pathognomonic skin manifestation of palmoplantar pustulosis on palms and/or soles. Subjects must have had an inadequate response to prior conventional treatment (eg, topical corticosteroids, active vitamin D<sub>3</sub>, etretinate or phototherapy) and must have active lesions at screening and baseline (PPSI score of 7 or greater). Subjects with extra-palmoplantar lesions and/or PAO can be included. See Section "SUBJECT SELECTION" for inclusion and exclusion criteria.

The total duration of subject participation will be approximately 30 weeks, which includes a screening period of about 6 weeks before dosing. Subjects will return to the study site on Weeks 1, 2, 4, 6, 8, 12, 16, 20 and 24. Completion of the Week 24 assessment constitutes the subject's completion of the study.

Assessments of efficacy, safety, pharmacokinetics, immunogenicity and pharmacodynamic biomarkers will be conducted in this study. Efficacy measurements include PPSI, PPPASI (Palmoplantar Pustulosis Area and Severity Index), PGA and the Dermatology Life Quality Index (DLQI). Safety assessments will include AEs, vital signs, laboratory parameters, and ECGs. Pharmacokinetics and immunogenicity measurements will be made over time. Biomarker measurements include the evaluation of relevant markers in serum and whole blood and skin biopsy biomarkers (only subjects who consent to participate in skin biopsy). One of the goals of the biomarker analyses is to evaluate the pharmacodynamics of CNTO 1959 and aid in evaluating the drug-clinical response relationship. However, studies of variation of DNA and/or RNA using obtained biomarkers sample (eg. identification of DNA and/or RNA sequences) will not be performed. The frequency/timing of all of the above measurements is provided in the Time and Events Schedule Table.

The data from this study will be cleaned and locked for analysis at the Week 16 and Week 24 database locks (DBLs). The purpose of Week 16 DBLs is to perform selected analyses to be used by the sponsor in planning for the CNTO 1959 next phase clinical program.



**Figure 1 Schematic Overview of the Study**

### **3.2. Study Design Rationale**

This is the first study of CNTO 1959 administrating in subjects with palmoplantar pustulosis. This is a Phase 2, randomized, placebo-controlled, parallel-group, multicenter study designed to assess the efficacy and safety of CNTO 1959 in adult subjects with palmoplantar pustulosis.

In a Phase 1 study conducted in the USA in both normal healthy volunteers and psoriatic subjects (CNTO1959PSO1001), CNTO 1959 demonstrated acceptable safety and pharmacokinetics in both populations. Currently, there are two ongoing overseas studies (a Phase 2 dose-ranging study in subjects with psoriasis [CNTO1959PSO2001] and a phase 2 study in subjects with active rheumatoid arthritis [CNTO1275ARA2001]). In Japan, a Phase 1 study in Japanese subjects with psoriasis (CNTO1959PSO1002) is now being conducted.

The overall design of this study including dose levels and regimens was selected based on the organized psoriasis clinical studies.

#### **Placebo control, Randomization and Blinding**

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. 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. Limited sponsor personnel will become unblinded to treatment assignment at the Week 16 database lock (DBL). To minimize potential bias in the study even after the Week 16 DBL, treatment assignment blinding will be maintained for study sites, site monitors, and subjects participating in the study after the Week 16 DBL until the final DBL.

#### **Dose Rationale**

Based upon the clinical experience of psoriasis studies, 200 mg SC dosing at Week 0 and Week 4 was selected for evaluation in this study. Results from the Phase 1 study (CNTO1959PSO1001), demonstrated a trend for a dose-response relationship for the 10 mg, 30 mg and 300 mg dose groups. The doses for the Phase 2 dose-ranging study (CNTO1959PSO2001) in subjects with psoriasis were selected on the basis of the clinical efficacy, safety and pharmacokinetic data from the CNTO1959PSO1001 study. This ongoing Phase 2 trial is evaluating doses ranging from 5 mg to 200 mg with 200 mg induction dosing at Week 0 and Week 4 as the maximum dose regimen. Based on the modeling analysis, the 200 mg dose is predicted to achieve high levels of efficacy in subjects with psoriasis. In addition, the safety results from the CNTO1959PSO1001 study show that SC CNTO 1959 in psoriasis subjects was generally safe and well tolerated up to a dose of 300 mg. There was no dose-dependent response in the incidence of AEs at dose levels ranging from 10 mg to 300 mg. Thus, CNTO 1959 200 mg is expected to be well tolerated and achieve a high degree of



clinical efficacy in psoriasis subjects. Induction dosing at Weeks 0 and 4 will be included to achieve a more rapid onset of clinical response.

Pathogenesis of palmoplantar pustulosis has not been confirmed, however, Th17 cells and IL-23 may play a role in promoting the inflammation observed in palmoplantar pustulosis as same as observed in psoriasis. CNTO1959PPP2001 is the first clinical study of CNTO 1959 in subjects with palmoplantar pustulosis. The goals of this study are to assess efficacy, safety, pharmacokinetics and pharmacodynamics of CNTO 1959 administered as SC injection in subjects with palmoplantar pustulosis. Taking this into consideration, CNTO 1959 200 mg SC administration at Week 0 and Week 4 was selected as the dose regimen in order to demonstrate Proof of Concept for CNTO 1959 in palmoplantar pustulosis in this study.

In addition, no safety concerns have been noted to date in the preliminary data from the ongoing study CNTO1959PSO1002 in Japanese subjects with psoriasis receiving a single SC dose of 10, 30, 100 or 300 mg.

### **Study period**

Subjects will be followed from the last administration of study drug at Week 4 through the last study visit at Week 24. Primary endpoints evaluation is set at Week 16 based on the psoriasis study experience. In the CNTO1959PSO1001 study, clinical response reached to almost maximum at 12 to 16 weeks after dosing. Based on the results of CNTO1959PSO1001, it was assumed that clinical response will be observed at 16 weeks after dosing in subjects with palmoplantar pustulosis as well. Follow-up will be continued for 24 weeks in order to explore clinical response of CNTO 1959 over time.

Two database locks (DBLs) are planned. The first DBL will occur when the primary endpoints are assessed at Week 16, and the second DBL will occur at the end of the study (Week 24). Subject safety will be monitored through the end of the study as delineated in the Time and Events Schedule.

### **Assessments**

Subject assessments and evaluations for safety, efficacy, pharmacokinetics, and biomarkers will be performed as delineated in the Time and Events Schedule.

### **Biomarker Collection**

Biomarker samples will be collected to evaluate the biological activity of CNTO 1959, help to explain interindividual 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 pharmacodynamics of CNTO 1959 and aid in evaluating the drug-clinical response relationship.

## 4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 42 days before administration of the study drug.

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

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

### 4.1. Inclusion Criteria

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

1. Subject must be a man or woman aged 20 years or older.
2. Subject has had a diagnosis of palmoplantar pustulosis at screening (subjects with concurrent extra-palmoplantar lesions [includes plaque-type psoriasis lesions] and/or PAO also can be included).
3. Subject has active lesions on the palms or soles at screening and baseline (Week 0).
4. Subject has inadequate response to the treatment with topical steroid and/or topical vitamin D<sub>3</sub> 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.
5. Subject has a PPSI total score of 7 or greater at screening and baseline (Week 0).
6. At screening, the results of the following laboratory tests performed at the central laboratory must be within the limits specified below.
  - a. Hemoglobin  $\geq 10$  g/dL (SI:  $\geq 100$  g/L)
  - b. White blood cells  $\geq 3.5 \times 10^3$  cells/ $\mu$ L (SI:  $\geq 3.5$  GI/L)
  - c. Neutrophils  $\geq 1.5 \times 10^3$  cells/ $\mu$ L (SI:  $\geq 1.5$  GI/L)
  - d. Platelets  $\geq 100 \times 10^3$  cells/ $\mu$ L (SI:  $\geq 100$  GI/L)
  - e. Serum creatinine  $\leq 1.5$  mg/dL (SI:  $\leq 133$   $\mu$ mol/L)
  - f. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase levels must be  $\leq 2 \times$  the upper limit of normal (ULN)

for the central laboratory conducting the test.

**NOTE:** the investigator may consider the subject eligible if the previously abnormal laboratory test result is within the above limits on a repeat testing in the central laboratory. Only one repeat test is allowed.

7. Before randomization, a woman must be either:
  - Not of childbearing potential: premenarcheal; postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle stimulating hormone (FSH) level >40 IU/mL; permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy,
  - Of childbearing potential and practicing a highly effective method of birth control, consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (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.
8. A woman of childbearing potential must have a negative serum  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) test at screening and urine pregnancy test at Week 0.
9. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 3 months after receiving the last dose of the study drug.
10. 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 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 3 months after receiving the last dose of study drug.

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11. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study.
  12. Subject are considered eligible according to the following tuberculosis (TB) screening criteria:
    - a. Have no history of latent or active TB prior to screening. An exception is made for subjects currently receiving treatment for latent TB with no evidence of active TB, or who have a history of latent TB and documentation of having completed appropriate treatment for latent TB within 3 years prior to the first administration of any study drug. It is the responsibility of the investigator to verify the adequacy of previous antituberculous treatment and provide appropriate documentation.
    - b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
    - c. Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB has been initiated at least 3 weeks prior to the first administration of any study drug.
    - d. Within 2 months prior to the first administration of study drug, have a negative Interferon Gamma Release Assay (IGRA) result, or have a newly identified positive IGRA result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated at least 3 weeks prior to 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.

**Exception text**

IGRA is 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.

- e. Have a chest radiograph (both posterior-anterior and lateral views, substitutable with chest CT), taken within 3 months prior to the first administration of study drug and read by a qualified radiologist or pulmonologist, with no evidence of current, active TB or old TB.

## 4.2. Exclusion Criteria

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

1. Subject has a history of or current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, neurologic, cerebral, or psychiatric disease.
2. Subject has unstable cardiovascular disease, defined as a recent clinical deterioration (eg, unstable angina, rapid atrial fibrillation) in the last 3 months or a cardiac hospitalization within the last 3 months prior to screening.
3. Subject 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 (eg, recurrent pyelonephritis), fungal infection (eg, mucocutaneous candidiasis), or open, draining, or infected skin wounds or ulcers.
4. Subject 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 2 months prior to screening.
5. Subject has or has had herpes zoster within the 2 months prior to screening.
6. Subject 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.
7. Criterion modified per amendment
  - 7.1 Subject has been hospitalized for asthma within the previous 3 months to screening, ever required intubation for treatment of asthma, currently requires oral corticosteroids for the treatment of asthma, or required more than one short-term ( $\leq$  2 weeks) course of oral corticosteroids for asthma within 6 months prior to screening.
8. Subject has a transplanted organ (with exception of a corneal transplant > 3 months prior to the first administration of any study drug).
9. Subject has a history of active granulomatous infection, including histoplasmosis or coccidioidomycosis, prior to screening. Refer to inclusion criteria for information regarding eligibility with a history of latent TB.
10. Subject has had a nontuberculous mycobacterial infection or opportunistic infection

- (eg, cytomegalovirus, pneumocystosis and aspergillosis) within 6 months prior to screening.
11. Subject has a chest radiograph (substitutable with chest CT) within 3 months prior to the first administration of study drug that shows an abnormality suggestive of a malignancy or current active infection, including TB.
  12. Subject has indeterminate initial and repeat IGRA results or a newly positive IGRA result and is unwilling or unable to undergo TB prophylaxis treatment.
  13. Subject is known to be infected with human immunodeficiency virus (HIV) or human T-lymphotropic virus-1 (HTLV-1). Tests positive for HIV infection or positive for HTLV-1 infection.
  14. Subject tests positive for hepatitis B virus (HBV) infection (see Attachment 7 for interpretation of Hepatitis B serologies) or has antibodies to hepatitis C virus (HCV) at screening.
  15. Subject has any known malignancy or has a history of malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ of the skin, or cervical carcinoma in situ that has been treated with no evidence of recurrence, or squamous cell carcinoma in situ of the skin that has been treated with no evidence of recurrence within 5 years prior to administration of any study drug).
  16. Subject has known allergies, hypersensitivity, or intolerance to placebo, CNTO 1959 or its excipients (refer to Investigator's Brochure).
  17. Subject has known intolerance or hypersensitivity to any biologic medication, or known allergies or clinically significant reactions to murine, chimeric, or human proteins, monoclonal antibodies, or antibody fragments.
  18. Subject has ever previously received CNTO 1959.
  19. Subject has received any anti-tumor necrosis factor alpha (TNF $\alpha$ ) biologic therapy within 3 months or 5 half-lives of the first administration of study drug, whichever is longer.
  20. Subject has received any therapeutic agent directly targeted to IL-6, IL-12, IL-17, or IL-23, (including but not limited to tocilizumab, ustekinumab, briakinumab [ABT-874], AIN457, and MK3222) within 6 months of the first administration of any study drug.
  21. Subject has received natalizumab, efalizumab, or agents that modulate B cells or T cells (eg, rituximab, alemtuzumab, abatacept, alefacept, or visilizumab) within 12

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months of the first administration of any study drug.

22. Subject has received any systemic immunosuppressants (eg, methotrexate [MTX], azathioprine, cyclosporine, mercaptopurine, mycophenolate mofetil, hydroxyurea, and tacrolimus) disease-modifying drugs (eg, sulfasalazine, intramuscular gold) or anakinra within 4 weeks of the first administration of any study drug.
23. Subject has received phototherapy or any systemic medications/treatments that could affect palmoplantar pustulosis or efficacy evaluation (including, but not limited to, oral or injectable corticosteroids, retinoids, psoralens, antibiotics, biotin drug, Chinese herbal preparations, and cyclosporine) within 4 weeks of the first administration of any study drug (See section. 8.2. Phototherapy and Systemic Therapy for Palmoplantar pustulosis).
24. Subject has received focal infection treatment (eg, tonsillectomy and dental therapy) within 6 months of the first administration of any study drug.
25. Subject has received systemic medications/treatments that could affect PAO or efficacy evaluation PAO except nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, bisphosphonates and MTX) within 4 weeks of the first administration of any study drug.
26. Subject has used topical medications/treatments to the palms and soles that could affect palmoplantar pustulosis or efficacy evaluation (including, but not limited to, corticosteroids, topical vitamin D<sub>3</sub> derivatives, tacrolimus, and antibiotics) within 2 weeks of the first administration of any study drug.
27. Subject is currently receiving lithium or antimalarials, or has received lithium or antimalarials within 4 weeks of the first administration of any study drug.
28. Subject has received, or is expected to receive, any live virus or bacterial vaccination within 3 months (or longer as indicated in the package insert of the relevant vaccine) prior to the first administration of any study drug.
29. Subject has had a Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening.
30. Subject has received an experimental antibody or biologic therapy within the previous 6 months, or received any other experimental therapy or new investigational agent within 30 days or 5 half-lives (whichever is longer) of any study drug administration or is currently enrolled in an investigational study.

31. Subject is a woman who is pregnant, breast-feeding, or planning to become pregnant or is a man who plans to father a child while enrolled in this study or within 3 months after receiving the last administration of any study drug.
32. Subject 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.
33. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.
34. Subject has current drug-induced palmoplantar pustulosis (eg, a new onset of palmoplantar pustulosis or an exacerbation of palmoplantar pustulosis from anti-TNF $\alpha$  drugs).
35. Subject is known to have had a substance abuse (drug or alcohol) problem within the previous 12 months.
36. Subject is unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.

**NOTE:** Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including additional 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, they should be excluded from participation in the study. This does not apply to the blood and serum samples collected on Day 1, because the results will not become available before dosing. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

### **4.3. Prohibitions and Restrictions**

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

1. A woman of childbearing potential who is heterosexually active must remain on a highly effective method of birth control (see inclusion criteria) during the study and for 3 months after receiving the last dose of any study drug.
2. A man who is sexually active with a woman of childbearing potential must use a double-barrier method of birth control (ie, male condom, female diaphragm or cervical cap, or condom) and all men must also not donate sperm during the study and for 3 months after receiving the last dose of study drug.



3. Subject must agree not to receive a live virus or bacterial vaccination during the study or up to 3 months after the last administration of any study drug.
4. Subject must agree not to receive a BCG vaccination during the study or up to 12 months after the last administration of any study drug.
5. Subject must comply with restrictions on prestudy and concomitant medications (see Section 8).
6. Subject must avoid prolonged sun exposure and avoid use of tanning booths or other UV light sources to the palms and soles during study.
7. Subject must agree to keep subjects on stable condition of smoking habit throughout the study.

## **5. TREATMENT ALLOCATION AND BLINDING**

### **Treatment Allocation**

#### **Procedures for Randomization**

Subjects will be randomly assigned to 1 of 2 treatment groups based on a randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by study site.

#### **Blinding**

With the exception of the unblinded pharmacy staff, the study site personnel, investigators, and the randomized subjects will be blinded to which drug (CNTO 1959 or placebo) throughout the study.

The sponsor medical monitor, site manager and other sponsor personnel will remain blinded throughout the study (subject treatment assignment and dosing regimen). After the Week 16 DBL, the data will be unblinded for analysis while subjects are still participating in the study. Identification of sponsor personnel who will have access to the unblinded subject data will be documented prior to unblinding.

#### **Maintenance of the Blind**

The unblinded pharmacy staff (Pharmacists or medically licensed individuals) responsible for the preparation of study drugs at each site will be unblinded to treatment assignment throughout the study and will prepare, dispense, and account for all study drugs. These individuals should have no other contact with the subject during the study other than study drug administration, should not communicate their knowledge of treatment assignment to any other study personnel. An

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independent, unblinded drug monitor will monitor any study drug preparation and accountability data.

Randomization codes will be disclosed fully only if the study is completed and the clinical database is locked. However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those subjects included in the interim analysis.

### **Emergency Unblinding**

The investigator will not be provided with randomization codes. The codes will be maintained within the centralized randomization service for this study, 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, treatment allocation) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of DBL and unblinding.

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

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, IRB/IEC 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**

The study drugs are NOT to be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing.

Subjects will be randomized to 1 of the following 2 treatment groups in a 1:1 ratio:

Group 1: Placebo SC at Week 0 and Week 4.

Group 2: CNTO 1959 200 mg SC at Week 0 and Week 4.

All subjects randomized will receive 2 injections of 1 mL each as SC injections at each administration (two 1 ml SC injection containing placebo or CNTO 1959). Details regarding administration method are provided in Drug Administration manual.

Before all injections at the study site, the appropriate personnel, medication (eg, epinephrine, inhaled beta-2-agonists and antihistamines), and other requirements to treat severe allergic reactions must be available. A physician must be available on site during all SC injections of study drug administered at the study site.

## **7. TREATMENT COMPLIANCE**

As study drug is administered at the study site, treatment compliance will be controlled by site personnel.

For study drug administrations, information regarding treatments that are administered outside of the scheduled windows will be collected. Information regarding missed administrations will be available. Subject worksheets will be reviewed and compared with the data entries on the eCRFs to ensure accuracy. Compliance with the treatment schedule is strongly encouraged. It is understood that treatment may be interrupted for many reasons.

The Week 4 injection should occur within  $\pm 3$  days of the scheduled visit.

## **8. PRESTUDY AND CONCOMITANT THERAPY**

### **8.1. Prestudy Therapy**

For the prestudy therapies, subjects must comply with restrictions provided in the "SUBJECT POPULATION" section in which the inclusion and exclusion criteria are listed. These therapies are not permitted throughout the study except as described in Section 8.2 Concomitant Therapy.

### **8.2. Concomitant Therapy**

Concurrent use of medications/treatments for palmoplantar pustulosis is not permitted during the study except as noted below.

***Topical therapy for palmoplantar pustulosis***

Concurrent use of topical medications/treatments for palmoplantar lesions (eg, corticosteroids, keratolytics, vitamin D<sub>3</sub> derivatives, topical tacrolimus, and antibiotics), and intralesional corticosteroids is not permitted for at least 2 weeks prior to the first administration of study drug and throughout the study.

The following therapies are permitted in the indicated time frames:

Topical moisturizers are permitted from screening period to throughout the study; however, subjects should not use these topical agents prior to the medical examinations on the day of a study visit.

***Phototherapy and Systemic Therapy for Palmoplantar pustulosis***

Focal infection treatments to the tonsils and/or dental are not permitted for at least 6 months prior to the first administration of study drug and throughout the study.

Concurrent use of phototherapy and systemic therapy for palmoplantar pustulosis (eg, PUVA, narrow band UVB, systemic retinoids\*, biotin drug, Chinese herbal preparations, antibiotics\*\* and cyclosporine) is not permitted for at least 4 weeks prior to the first administration of study drug and throughout the study.

\* Agents containing vitamin A and indicated for treatment of keratoderma or Keratosis

\*\* Only macrolides, tetracyclines, and lincomycins

***Therapy for palmoplantar pustulosis related arthro-osteitis***

Subjects with pustulotic arthro-osteitis (PAO) at screening who receive an NSAID 1 week before the start of study medication may continue to use the NSAID as long as the dosage is not changed. Dose can be reduced. However it cannot be re-escalated once it was reduced. Any other medications/treatments for PAO (eg, bisphosphonates, MTX, Chinese herbal preparations and antibiotics) are not permitted for at least 4 weeks prior to the first study drug administration and during the study treatment.

***Concomitant Medications for Conditions other than Palmoplantar pustulosis***

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

The use of NSAIDs for indications other than PAO should be limited to situations where, in the opinion of the treating physician, there are no adequate alternatives for at least 1 week prior to the first administration of study drug and throughout the study. However, systemic

immunosuppressants and disease-modifying agents, including, but not limited to, methotrexate, sulfasalazine, or intramuscular gold must be discontinued at least 4 weeks prior to administration of study drug as described in the “SUBJECT POPULATION” section and are prohibited during the study.

The biologic therapies described in the “SUBJECT POPULATION” section (anti-TNF $\alpha$ , agents targeting to IL-6, IL-12, IL-17, or IL-23, and agents modulating B cells or T cells) are prohibited during the study.

Corticosteroids should be used only as follows:

- **Topical and Intralesional Corticosteroids:** Topical or intralesional corticosteroids for the treatment of palmoplantar pustulosis are not allowed within 2 weeks prior to the first administration of study drug and during the study. Using topical or intralesional corticosteroids (except for strongest potency) for body area other than palms and soles is allowed. Every effort should be made to keep subjects on stable usage.
- **Systemic Corticosteroids (oral or IV only; intramuscular steroids are prohibited) :** Systemic corticosteroids use for the treatment of palmoplantar pustulosis are not allowed within 4 weeks prior to the first administration of study drug and during the study. Systemic corticosteroids for indications other than palmoplantar pustulosis should be limited to situations where, in the opinion of the treating physician, there are no adequate alternatives. They should be used on a short-term basis (in principle,  $\leq 2$  weeks). Longer-term use of systemic corticosteroids should be discussed with the medical monitor or designee and may require discontinuation from treatment.
- **Intra-articular and Epidural Corticosteroids:** Intra-articular and epidural corticosteroids are not allowed within 4 weeks prior to the first administration of study drug and during the study.
- **Other use of corticosteroids, such as inhaled, otic, ocular, nasal, or other routes of mucosal delivery of corticosteroids are allowed during the study.**

When a subject applies topical medication, which is prohibited to use for palmoplantar pustulosis concomitantly in this protocol, to body area other than palms and soles, the subject should avoid applying with bare hand (eg, with use of hand glove).

If the administration of any concomitant therapy is necessary, it must be reported in the appropriate section of the eCRF. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

### ***Prophylactic antituberculosis therapy for latent TB***

As a result of the TB screening, if a subject is judged to require prophylactic treatment, the subject has to receive prophylactic antituberculosis agent (isoniazid [INH], in principle) for at least 6 months beginning at least 3 weeks prior to the first study agent administration. The standard dose of INH is 300 mg/day (if subject is low body weight, 5 mg/kg/day will be administered). Study drug

should not be administered in case of discontinuing INH administration due to adverse reactions, etc. within 3 weeks before first dosing. After the study agent administration, if INH treatment cannot be continued due to adverse reactions, etc., such a case will be dealt with after consultation with the specialist.

## **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, clinical laboratory and safety 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 1, 2, 4, 6, and 8 visits should occur within  $\pm 3$  days of the scheduled visit date. All the other study visits should occur within  $\pm 7$  days of the scheduled visit date.

The total blood sampling volume for the study is approximately 275 mL (142 mL [for T-SPOT.TB test] or 139 mL [for QuantiFERON-TB Gold test]) for assessments of safety and efficacy, 85 mL for PK and immunogenicity, and 48 mL for biomarkers).

#### **9.1.2. Screening Period**

All subjects will have a screening visit that will occur within 6 weeks before their randomization visit (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.

With the exception of subjects with a history of appropriately treated latent TB within 3 years of the first administration of study drug, subjects must undergo testing for TB (see Attachment 6), 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 (both posterior-anterior and lateral views, substitutable with chest CT) results and responses to tuberculin skin or other TB testing.

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 6).

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 will undergo screening for HBV (see Attachment 7) and antibodies to HCV.

### **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. Double-blind Period**

#### **Week 0/Day of Randomization**

At Week 0, subjects who meet all inclusion criteria and do not meet any of the exclusion criteria will be randomized. All required tests and evaluations must be conducted before start of study drug administration.

#### **Post-randomization Visit (through Week 24)**

All visit procedures will be performed as specified in the Time and Events Schedule.

#### **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 is suggested for use during the evaluation:

“Have you had a new cough of > 14 days’ duration or a change in a chronic cough?”

“Have you had any of the following symptoms:

Persistent fever?

Unintentional weight loss?

Night sweats?”

“Have you had close contact with an individual with active TB?” (If there is uncertainty as to whether a contact should be considered “close,” a physician specializing in TB should be consulted.)

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

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

Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph (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 as outlined in Section 9.1.2. Subjects should be encouraged to return for all subsequent scheduled study visits according to the protocol.

#### **9.1.4. Safety follow-up after Early Termination**

If the subjects withdraw from the study within 12 weeks after last study drug administration, subjects will be followed for safety for up to 12 weeks after last study drug administration as per the Time and Events Schedule.

### **9.2. Efficacy**

#### **9.2.1. Evaluations**

Every effort should be made to ensure that the physician who performs the efficacy evaluations for a subject at baseline also performs all the evaluations for that subject at the subsequent visits. The assessments should be performed by the designated individual.



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**9.2.1.1. Palms and Sole Skin Lesion Evaluations****9.2.1.1.1. 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<sup>11</sup> (see Attachment 1). 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.

**9.2.1.1.2. Palmoplantar Pustulosis Area and Severity Index (PPPASI)**

The PPPASI assesses the severity of palmoplantar pustulosis lesions and their response to therapy with a score ranging from 0 to 72<sup>1</sup> (see Attachment 2).

**9.2.1.1.3. Physician's Global Assessment of palmoplantar pustulosis lesion (PGA)**

The PGA documents the Physician's Global Assessment of the subject's palmoplantar overall skin lesions status (see Attachment 3).

**9.2.1.1.4. Physician's Assessment of each skin lesion (PA–pustule, PA–vesicle, PA–nail)**

The PA documents the physician's assessment of the subject's pustule, vesicle and nail lesions status (see Attachment 4).

**9.2.1.1.5. Patient's Visual Analogue Scale assessment of Palmoplantar Pustulosis Severity (Patient's VAS-PPP severity)**

The Patient's Visual Analogue Scale assessment of Palmoplantar Pustulosis Severity will be recorded on a 10-cm VAS.

**9.2.1.2. Pustulotic Arthro-Osteitis Evaluations**

Pustulotic Arthro-Osteitis evaluations will be performed only for subjects with PAO at screening.

**9.2.1.2.1. Physician's Visual Analogue Scale Assessment of Pustulotic Arthro-Osteitis Activity (Physician's VAS-PAO activity)**

Physician's Visual Analogue Scale Assessment of Pustulotic Arthro-Osteitis Activity will be recorded on a 10-cm VAS.

**9.2.1.2.2. Patient's Visual Analogue Scale Assessment of Pustulotic Arthro-Osteitis Activity and Pain (Patient's VAS-PAO activity, Patient's VAS-PAO pain)**

Patient's Visual Analogue Scale Assessment of Pustulotic Arthro-Osteitis Activity and Pain will be recorded on the 10-cm VAS. The investigator will identify the main site where the patient will

evaluate pain. If there are multiple sites available for evaluation, up to 2 additional sites may be evaluated.

### **9.2.1.3. Quality of Life evaluations**

#### **9.2.1.3.1. Dermatology Life Quality Index (DLQI)**

The DLQI is a dermatology-specific QOL instrument designed to assess the impact of the disease on a subject's QOL. It is a 10-item questionnaire that in addition to evaluating overall QOL, can be used to assess 6 different aspects that may affect QOL: symptoms and feelings, daily activities, leisure, work or school performance, interpersonal relationships, and treatment.

#### **9.2.1.3.2. SF-36**

The QOL of the subject will be assessed using the 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.

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<sup>8</sup>.

#### **9.2.1.4. Other evaluations**

- Photography of palms and soles skin lesion will be taken to record as visual observation. If subject has a nail lesion, it should be taken. These photographs should be provided to the Sponsor.
- MRI image of 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.

### **9.2.2. Endpoints**

#### **Primary Endpoint**

The primary efficacy endpoint is the change from baseline in PPSI total score at Week 16.

#### **Major Secondary Endpoints**

The following are the major secondary endpoints:

- Change from baseline in PPSI total score over time
- Change in PPPASI total score over time from baseline to Week 16

- Proportion of subjects who achieve a PPPASI-50 over time from baseline to Week 16
- Proportion of subjects who achieve a PGA score of 1 over time from baseline to Week 16

### **Other Secondary Endpoints**

- Proportion of subjects who achieve a PPPASI-75 over time from baseline to Week 16
- Change in physician's assessment of 3 PA lesions over time from baseline to Week 16
- Change in Patient's VAS-PPP severity over time from baseline to Week 16
- Change in physician's VAS-PAO activity over time from baseline to Week 16
- Change in patient's VAS-PAO activity and pain over time from baseline to Week 16
- Change in DLQI over time from baseline to Week 16
- Change in SF-36 score over time from baseline to Week 16

## **9.3. Pharmacokinetics and Immunogenicity**

### **9.3.1. Evaluations**

Samples will be used to evaluate the pharmacokinetics, as well as the immunogenicity of CNTO 1959 (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 further characterization of immunogenicity or for the evaluation of relevant biomarkers. At visits where serum concentration and/or antibodies to CNTO 1959 will be evaluated, 1 blood draw of sufficient volume can be used. Venous blood samples will be collected and each serum sample will be divided into 3 aliquots (1 each for PK, antibodies to CNTO 1959, and a back-up).

A sample for pharmacokinetics and immunogenicity (only subjects who terminate after Week 12 of last study drug administration) assessment will be collected at the early termination visit if a subject terminates study participation.

### **9.3.2. Analytical Procedures**

#### **Pharmacokinetics**

Serum samples will be analyzed to determine concentrations of CNTO 1959 using a validated, specific, and sensitive dissociation-enhanced lanthanide fluorescent immunoassay (DELFI) method by or under the supervision of the sponsor.

#### **Immunogenicity**

The detection and characterization of antibodies to CNTO 1959 will be performed using a validated assay method by or under the supervision of the sponsor.

### **9.3.3. Pharmacokinetic Parameters**

If deemed necessary, a population pharmacokinetic approach using nonlinear mixed-effects model (NONMEM) will be used to characterize the pharmacokinetic parameters and exposure information of CNTO 1959.

### **9.3.4. Immunogenicity Assessments**

Antibodies to CNTO 1959 will be evaluated in serum samples collected from all subjects according to the Time and Events Schedule. Additionally, serum samples should also be collected at the last visit for subjects who are discontinued from treatment or withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to CNTO 1959 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to CNTO 1959 and/or further characterize the immunogenicity of CNTO 1959.

## **9.4. Biomarkers**

In order to better understand the pathological mechanisms involved in palmoplantar pustulosis and to identify a treatment response signature to CNTO 1959, following biomarkers will be evaluated according to the Time and Events Schedule.

Serum samples for biomarker analysis will be collected from all subjects. The concentrations of inflammatory biomarkers (protein) in serum samples will be measured (such as, but not limited to, IL 23p19, IL 17, IL 6, IL 8, IL 22, TNF $\alpha$ , and IL 12p40).

Whole blood samples will be collected from all subjects. Total ribonucleic acid (RNA) will be isolated from whole blood samples and used for comprehensive mRNA and microRNA expression level analyses.

Skin biopsy samples will be collected from subjects who consent separately to participate in biopsy assessment. Total ribonucleic acid (RNA) will be isolated from skin biopsy samples and used for comprehensive mRNA and microRNA expression level analyses.

Studies of variation of DNA and/or RNA using obtained biomarkers sample (eg. identification of DNA and/or RNA sequences) will not be performed.

## **9.5. Safety Evaluations**

The safety and tolerability of study drugs (placebo, CNTO 1959) will be monitored by physical examinations, detection of injection site and allergic reactions, ECGs, clinical laboratory tests, vital signs, concomitant medications and AEs according to the Time and Events Schedule. Serum and/or plasma samples collected for pharmacokinetic or pharmacodynamic analyses may additionally be used to evaluate biomarkers of safety that address concerns that arise during or after the study

period. However, studies of variation of DNA and/or RNA using obtained biomarkers sample (eg. identification of DNA and/or RNA sequences) will not be performed.

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 has determined follow-up to be unnecessary (see Section 12.3.1).

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 as specified in Section 12, Adverse Event Reporting.

### **Clinical Laboratory Tests**

Blood samples for serum chemistry and 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 adverse event section of the eCRF. The laboratory reports must be filed with the source documents.

The following tests will be performed:

#### ***Hematology Panel***

-hemoglobin	-white blood cell (WBC) count with differential <sup>a</sup>
-hematocrit	-Lymphocytes
-red blood cell (RBC) count	-Neutrophils
-platelet count	-Basophils
	-Eosinophils
	-Monocytes

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

#### ***Serum Chemistry Panel***

-Sodium	-Alkaline phosphatase
-Potassium	-Creatine <u>phosphokinase</u> (CPK) <sup>b</sup>
-Chloride	-Lactic dehydrogenase (LDH)
-Bicarbonate	-Troponin-I
-Blood urea nitrogen (BUN)	-Calcium

-Creatinine	-Phosphate, inorganic
-Glucose	-Albumin
-AST	-Total protein
-ALT	-C-reactive protein
-Total bilirubin	-Direct bilirubin <sup>c</sup>

- b. Assay isoenzymes if CPK >ULN.  
c. Assay direct bilirubin if total bilirubin >ULN.

### ***Lipid Panel***

-Total cholesterol	-Low density lipoprotein(LDL)-cholesterol
-Triglycerides	-High density lipoprotein(HDL)-cholesterol

### ***Urinalysis<sup>d</sup>***

-Specific gravity	-Protein
-pH	-Occult blood
-Glucose	-Ketones
-Bilirubin	

- d. Microscopic examination of RBC, WBC, casts, bacteria and such will be conducted if protein and/or occult blood are detected by urinalysis.

- Serum or urine Pregnancy Testing (Beta hCG) for women of childbearing potential<sup>\*\*</sup>
- Serology (HIV antigen/antibody, hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [anti-HBs], hepatitis B core antibody [anti-HBc total], Hepatitis B Viral DNA quantitative\* [HBV DNA], and HCV antibody, IGRA (T-SPOT.TB test or QuantiFERON-TB Gold test) , HTLV-1 Antibody, and Serum follicle stimulating hormone [FSH]<sup>\*\*</sup>)

### **Electrocardiogram (ECG)**

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

### **Vital Signs** (axillary temperature, pulse rate, blood pressure)

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\* See Attachment 7 for criteria of HBV DNA quantitative test required.

\*\* Female subject only.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

### **Physical Examination**

Physical examinations will be performed by the investigator.

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.

### **Height and Body Weight**

Measurement of height and body weight will be performed at the time-points specified in the Time and Events Schedule.

### **Allergic Reactions**

All subjects will be observed carefully for symptoms of allergic reactions for at least 30 minutes after the SC injection of study drug at the study site. If the reaction is not severe, subsequent injections at the appropriate treatment intervals may be undertaken with caution.

In the case of a severe allergic reaction (eg, anaphylaxis), the investigator will treat a subject with proper treatment at the investigator's discretion and will judge whether subject should discontinue the study treatment or not by their safety perspective. Subjects with severe reactions following an injection such as bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension with a decrease in systolic blood pressure greater than 40 mm Hg will not be permitted to receive any additional study treatment.

### **Injection Site Reactions**

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

## **9.6. Sample Collection and Handling**

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 Laboratory manual.

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## 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 24 of the double-blind period.

### 10.2. Discontinuation of Study Treatment

If the second study drug administration (Week 4) must be discontinued, this will not result in automatic withdrawal of the subject from the study. The subject should return for the remaining regularly scheduled study visits as long as the subject does not withdraw from the study.

A subject's study treatment should be discontinued if:

- The investigator or sponsor's medical monitor 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 has a chest radiograph (both posterior-anterior and lateral views, substitutable with chest CT) 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. 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 withdraws consent for administration of study drug.
- The subject is unable to adhere to the study visit schedule or comply with protocol requirements.



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- The subject develops a severe allergic reaction that occurs during or following a study drug administration, such as bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension.
  - 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 within 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.
  - The subject withdraws from the study.

### **10.3. Withdrawal From the Study**

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

- Lost to follow-up
- Death
- Withdrawal of consent
- The investigator or sponsor believes (eg, that for safety or tolerability reasons such as an adverse event) it is in the best interest of the subject to withdraw from the study.
- 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 completing the study, early termination assessments (see the Time and Events Schedule) should be obtained wherever possible. The subject should be encouraged to conduct the safety follow-up visits (see the Time and Events Schedule) for up to 12 weeks after his/her last study drug administration. 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.

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

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

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

### **Withdrawal From the Optional Research samples While Remaining in the Main Study**

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

## **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. The analyses will be performed 2 times. The first analysis will be performed for subject information, efficacy and adverse events for all subjects who have either completed the Week 16 visit or terminated study participation prior to Week 16. The second analysis will be performed for efficacy and safety items including adverse events for all subjects who have either completed their final visit (Week 24) or terminated study participation. No interim analysis based on the statistical inference is planned.

### **11.1. Subject Information**

Efficacy analyses will be performed with 2 analysis sets: full analysis set (FAS) and per-protocol set (PPS). The FAS is the population of all randomized subjects who received at least one dose of study drug and had any post-baseline efficacy assessment. The PPS is a subset of the full analysis set. The per-protocol analysis set excludes any subject with any of the major protocol deviations. The subjects meeting any major protocol deviation criteria will be determined prior to DBL and entered into the clinical database deviation dataset.

The safety analysis set is the population of all randomized subjects who received at least one dose of study drug.

For the FAS and the safety analysis set, descriptive statistics will be provided.

All randomized subjects who receive at least 1 dosing of CNTO 1959 and have serum CNTO 1959 concentration data will be included in the pharmacokinetic analysis set.

## 11.2. Sample Size Determination

In the phase 3 double blind controlled study for Maxacalcitol (topical vitamin D<sub>3</sub>) that is approved for a treatment of palmoplantar pustulosis in Japan, the mean change from baseline of skin observation total score for Maxacalcitol was -3.7 (standard deviation [SD] = 2.1, number of patients [N] = 94) and -1.9 (SD = 1.9, N=93) for placebo group, as results of the primary endpoint. Based on these results, 25 subjects per group (total of 50 subjects) are considered as appropriate for this study in consideration to uncertainty for the estimates with varying assumptions. The sample size of 25 subjects has an 84% power to detect a significant difference between the CNTO 1959 treatment group and the placebo group at a two-sided alpha level of 0.05, assuming a treatment difference in the change from baseline of PPSI total score at Week 16 of 1.8 with a SD of 2.1. Table 1 provides the power for detecting a treatment difference between the CNTO1959 treatment group and the placebo treatment group (for 25 subjects per group) under varying assumptions for the treatment difference of the change from baseline of PPSI total score.

**Table 1** Power to detect a treatment difference based on the change from baseline of PPSI total score

Mean Difference	Power
1.6	0.752
1.7	0.801
1.8	0.844
1.9	0.880
2.0	0.910

n = 25 for each group  
common SD = 2.1

## 11.3. Efficacy Analyses

### *Efficacy Definitions*

- Treatment Failure: Subjects who withdraw from the study due to lack of efficacy or an AE of worsening of palmoplantar pustulosis, or who initiated a protocol-prohibited medication/therapy during the study that could improve palmoplantar pustulosis are considered treatment failures.
- PPPASI 50 Responder: Subjects with  $\geq 50\%$  improvement in PPPASI from baseline will be considered PPPASI 50 responders.
- PPPASI 75 Responder: Subjects with  $\geq 75\%$  improvement in PPPASI from baseline will be considered PPPASI 75 responders.

### *Primary Endpoint*

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

The primary efficacy analysis will be performed using data from FAS. In this primary analysis, the change from baseline in PPSI total score at Week 16 will be analyzed using an analysis of covariance (ANCOVA) model with treatment as a factor and baseline score as a covariate. Treatment effect of CNTO1959 versus placebo will be estimated based on least-square (LS) means

of the difference. The p-value for the difference in treatment effect along with the 2-sided 95% CI will be presented. The last available post-baseline PPSI total score will be carried forward to impute the PPSI total score that are missing after discontinuation of treatment up to Week 16 of the double-blind treatment period. If a subject meets one of the criteria of a treatment failure, the subject will be designated a treatment failure for primary endpoint at all visits starting from the visit after the treatment failure and the last available post-baseline PPSI total score value will be assigned regardless of the actual observed data. To evaluate sensitivity of the results to the imputation method, the impact of missing data would be explored through various analysis methods.

### ***Major Secondary Endpoints***

Major secondary endpoints of this study are:

- The change from baseline in PPSI total score will also be summarized over time by treatment group using descriptive statistics. If the evaluation visit with larger difference between treatment groups than that of Week 16 is observed, same analysis will be performed for that visit as described for the primary analysis, to assess possible time point with maximum clinical response of CNTO 1959.
- The change from baseline in PPPASI at Week 16 will be analyzed using an ANCOVA model with treatment as a factor and baseline score as a covariate. Treatment effect of CNTO1959 versus placebo will be estimated based on least-square (LS) means of the difference. The p-value for the difference in treatment effect along with the 2-sided 95% CI will be presented. The change from baseline in PPPASI will also be summarized over time by treatment group using descriptive statistics.
- The proportion of subjects who achieve a PPPASI-50 at Week 16 and the proportion of subjects who achieve a PGA score of 1 or less at Week 16 will be compared between the CNTO 1959 treatment group and placebo group using Fisher's exact test. The proportion will also be summarized by treatment group using frequencies and percentages with 95% CI. Subjects who discontinued 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.

### ***Other Secondary Endpoints***

Other secondary endpoints are as follows;

- Proportion of subjects who achieve a PPPASI-75 over time from baseline to Week 16
- Change in physician's assessment of 3 PA lesions over time from baseline to Week 16
- Change in patient's VAS-PPP severity over time from baseline to Week 16
- Change in physician's VAS-PAO activity over time from baseline to Week 16
- Change in patient's VAS-PAO activity and pain over time from baseline to Week 16
- Change in DLQI over time from baseline to Week 16

- Change in SF-36 over time from baseline to Week 16

For other secondary endpoints, the continuous variables will be summarized by treatment group using descriptive statistics, which will include the number of subjects (N), mean, SD, median, minimum, and maximum and will be analyzed using an analysis of variance model based on appropriate rank scores or ANCOVA model. The categorical variables will be summarized by treatment group using frequencies and percentages. The binary variables will be compared using Fisher's exact test. These other secondary endpoints at other evaluation visits than Week 16 may be summarized as described above, if necessary.

#### **11.4. Pharmacokinetic Analyses**

Serum CNTO 1959 concentrations will be summarized with descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, maximum, 25% quantile and 75% quantile at each sampling time.

All serum concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the Clinical Study Report.

Mean or median serum CNTO 1959 concentration time profiles will be plotted after the first dose of study drug, and individual serum concentration time profiles may also be plotted.

Population PK analysis of serum concentration-time data of CNTO 1959 will be performed using NONMEM. Data may be combined with those of other clinical studies of CNTO 1959 to conduct the population PK analysis. Available baseline subject characteristics (demographics, laboratory variables, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

#### **11.5. Immunogenicity Analyses**

The incidence of antibodies to CNTO 1959 during the study will be summarized for all subjects who receive an administration 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). The serum antibody titer of confirmed positive samples will be reported.

#### **11.6. Biomarker Analyses**

Changes in the concentration of individual serum markers from baseline to the selected post treatment time points will be summarized in separate technical reports. Additional analyses may be performed following evaluation of the data. Biomarker analyses are considered exploratory and will be summarized in separate technical reports as well.

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### **11.7. Pharmacokinetic and Pharmacodynamic Analysis**

If deemed necessary, exploratory analysis may be conducted to evaluate the relationship between pharmacokinetics and pharmacodynamics of CNTO 1959. When exploratory analysis is conducted, the analysis plan and report will be developed as separate documents.

### **11.8. Safety Analyses**

#### **Adverse Events**

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. The following analyses will also be used to assess the safety of subjects in the study:

- The incidence of AEs
- The incidence of SAEs
- The incidence of infections
- The incidence of drug related AEs
- The incidence and type of injection site reactions

#### **Clinical Laboratory Tests**

Laboratory data will be summarized by type of laboratory test (eg, hematology, serum chemistry). Selected laboratory parameters will be summarized by treatment group. Markedly abnormal criteria (to be specified in the Statistical Analysis Plan) will be used to identify markedly abnormal laboratory results, which will be summarized by treatment group. A listing of subjects with any markedly abnormal laboratory results will also be provided.

The following parameters will be summarized using descriptive statistics and frequency table:

- Laboratory parameters and change from baseline in laboratory parameters (hematology and serum chemistry).
- Incidence of markedly abnormal laboratory parameters (hematology and serum chemistry).
- Lipid parameters and change from baseline in lipid parameters.
- High sensitivity C-reactive protein (hsCRP) and change from baseline in hsCRP.

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**Electrocardiogram (ECG)**

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

**Vital Signs**

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

**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 adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event 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 adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

**Serious Adverse Event**

A serious adverse event 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 adverse event 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 adverse event 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 adverse event 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.

#### **12.1.2. Attribution Definitions**

##### **Not Related**

An adverse event that is not related to the use of the drug.

##### **Doubtful**

An adverse event 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 adverse event 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.



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**Probable**

An adverse event 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 adverse event 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 a serious adverse event should be recorded on the serious adverse event page of the eCRF. Refer to Section 12.3.4 for information on Events of Special Interest.

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## **12.3. Procedures**

### **12.3.1. All Adverse Events**

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). Serious adverse events, including those spontaneously reported to the investigator within the last visit or 12 weeks after the last dose of study drug whichever is longer 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 adverse events 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 serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, 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 adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all serious adverse events that are unlisted (unexpected) and associated with the use of the study drug. The investigator (or sponsor where required) must report these

events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Subjects (or their designees, if appropriate) must be provided with a "wallet (study) card" indicating the following:

- Subject's name
- Study number
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number
- Statement, in the local language(s), that the subject is participating in a clinical study.

### **12.3.2. Serious Adverse Events**

All serious adverse events 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 serious adverse events 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 serious adverse event should be made by facsimile (fax).

All serious adverse events 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 a serious adverse event. 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 a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the 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 serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.

The cause of death of a subject in a study within the last visit or 12 weeks after the last dose of study drug whichever is longer, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

### **12.3.3. Pregnancy**

All initial reports of pregnancy 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, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further administration of study drug.

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. These events are to be considered serious only if they meet the definition of a serious adverse event.

## **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 serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event 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)**

The CNTO 1959 supplied for this study as a final lyophilized product is a white solid cake supplied in a 2 mL type 1 glass vial closed with a Teflon<sup>®</sup> coated stopper and aluminum seal with a blue plastic flip-off cap. The sterile product does not contain preservatives and is designed for single use only. The reconstituted CNTO 1959 drug product should be a clear solution and essentially free of visible particulate matter. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

The placebo supplied for this study is a liquid in vial. For further details regarding the composition of the placebo, refer to the study site investigational product procedures manual.

#### **14.2. Packaging**

One vial is packed in one box.

### **14.3. Labeling**

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

### **14.4. Preparation, Handling, and Storage**

CNTO 1959 and placebo must be stored at controlled temperatures ranging from 2°C to 8°C (36°F to 46°F) and protected from exposure to light. Protection from light is not required during dose preparation or administration of CNTO 1959 and placebo.

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

### **14.5. Drug Accountability**

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

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

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes. The immediate destruction of these drug supplies should be documented in the drug accountability records 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 Brochure
- Site investigational product procedures manual
- Laboratory manual
- Drug administration manual
- PRO questionnaires
- Electronic data capture (eDC) Manual
- Code break procedure

## **16. ETHICAL ASPECTS**

### **16.1. Study-Specific Design Considerations**

Rigorous scientific evidence is mandatory, and ethically required to demonstrate that a new treatment is effective, and that its efficacy substantially outweighs any safety risks or problems with tolerability before it can be marketed. Randomized, double-blind, placebo-controlled design was adopted for this study in order to demonstrate effectiveness of CNTO 1959. Subjects have to stop their usual treatments and to be limited using concomitant therapy and must adhere to other prohibitions and restrictions in accordance with the study procedure. However, subjects will be withdrawn from the study in case the investigator or sponsor believes (eg, for safety or tolerability reasons such as an adverse event), it is in the best interest of the subject to withdraw from the study or investigator deems the subject should initiate the protocol-prohibited medications treatment due to lack of efficacy or other reason. And subjects may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. After withdrawal from the study, alternative treatments are available for the subjects and they will not prejudice future treatment.

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 adverse events 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 subjects in this study based upon the standard of the Japan Red Cross (1 pint/400 mL of blood for donation).

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## **16.2. Regulatory Ethics Compliance**

### **16.2.1. Investigator Responsibilities**

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

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

### **16.2.2. Independent Ethics Committee or Institutional Review Board**

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

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

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), 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 update 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 adverse events 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 research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

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

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

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

### **17.3. Subject Identification, Enrollment, and Screening Logs**

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth.

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 informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; 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 study 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 scales and assessments designated by the sponsor will be recorded and will be considered 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**

eDC will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, 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.

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 a 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 clinical 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). 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.



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## **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 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.



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### **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, 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 clinical 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 exploratory 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 exploratory 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 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: 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.

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, which are each rated for the more severely affected location (palms or soles) on a scale of 0 to 4.

The severity of the disease is calculated as follows.

The scoring for the signs of the disease (erythema, pustules/vesicle and desquamation/scale) is:

0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe.

The PPSI formula is:  $PPSI \text{ total score} = (E + P + D)$

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

**References**

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

**Attachment 2: PPPASI (Palmoplantar Pustulosis Area and Severity Index)**

The PPPASI assesses the severity of palmoplantar pustulosis lesions and their response to therapy with a score ranging 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%, 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 scoring 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 palmoplantar pustulosis 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:

$$\text{PPPASI} = (E + P + D) \text{ Area} \times 0.2(\text{right palm}) + (E + P + D) \text{ Area} \times 0.2(\text{left palm}) + (E + P + D) \text{ Area} \times 0.3(\text{right sole}) + (E + P + D) \text{ Area} \times 0.3(\text{left sole})$$

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

**References**

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**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: PA (Physician's Assessment)**

The PA is used to determine the subject's pustule, vesicle and nail lesions, at a given time point.

< PA-Pustule, Vesicle and Nail lesions >

Each of Pustule, Vesicle and Nail will be graded based on the scales below.

0 = clear

1 = almost clear

2 = Mild

3 = Moderate

4 = Severe

5 = Very severe

**Attachment 5: Laboratory Assessments**

Serology / other screening	Urinalysis <sup>a</sup>	Hematology	Serum Chemistry	Lipid Panel
HIV Antigen/Antibody	Specific gravity	Hemoglobin	Albumin	Total cholesterol
Hepatitis B Surface Antigen	pH	Hematocrit	Alkaline phosphate	Triglycerides
Hepatitis B Surface Antibody	Protein	RBC count	ALT	Low density lipoprotein(LDL)-cholesterol
Hepatitis B Core Antibody	Glucose	WBC count with differential <sup>d</sup>	AST	High density lipoprotein(HDL)-cholesterol
Hepatitis C Antibody	Ketones	Lymphocytes	LDH	
Hepatitis B Viral DNA, Quantitative <sup>f</sup>	Bilirubin	Monocytes	Total bilirubin	
IGRA (T-SPOT.TB test or QuantiFERON-TB Gold)	Occult blood	Neutrophils	Direct bilirubin <sup>b</sup>	
HTLV-1 Antibody	Pregnancy Test <sup>c</sup>	Eosinophils	BUN	
Serum Beta hCG, Qualitative <sup>c</sup>		Basophils	Calcium	
Serum follicle stimulating hormone (FSH) <sup>c</sup>		Platelets	Troponin-I	
			CPK <sup>e</sup>	
			Creatinine	
			Glucose	
			Total protein	
			Phosphate, inorganic	
			Sodium	
			Bicarbonate	
			Potassium	
			Chloride	
			C-reactive protein	

a Microscopic examination of RBC, WBC, casts, bacteria and such will be conducted if protein and/or occult blood are detected by urinalysis.

b Assay if total bilirubin >ULN.

c Female subject only.

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

e Assay for isoenzymes if CPK >ULN.

f See Attachment 7 for criteria of HBV DNA quantitative test required.



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**Attachment 6: Interferon Gamma Release Assays (IGRAs)****QuantiFERON-TB Gold test**

The QuantiFERON-TB Gold test is one of the interferon- $\gamma$  (IFN- $\gamma$ ) 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- $\gamma$  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- $\gamma$  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- $\gamma$ -based tests to detect latent TB 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 in terms of the degree of exposure that contacts had to 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- $\gamma$ -based blood tests for active or latent *M. tuberculosis* infection has 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- $\gamma$  present in the plasma using spectrophotometry and computer software analysis.

The central laboratory will analyze and report test results for each subject, and sites will be informed of the results. Subjects who have an indeterminate result should have the test repeated. The QuantiFERON-TB Gold test can be performed at the study site or local laboratory in accordance with each laboratory's procedure.

If the qualitative result cannot be obtained from study sites or the local laboratory, it will be determined based on the criteria shown in the table below. 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.

Interpretation of QuantiFERON-TB Gold test result			
Mitogen minus (IU/mL)	TB Antigen minus (IU/mL)	Results	Interpretation
Any	$\geq 0.35$	Positive	<i>M. tuberculosis</i> infection likely
$\geq 0.5$	$\geq 0.1, < 0.35$	Incomplete	Determine comprehensively by taking into account the degree of risk of infection
	$< 0.1$	Negative	<i>M. tuberculosis</i> infection NOT likely

<b>Interpretation of QuantiFERON-TB Gold test result</b>			
Mitogen minus (IU/mL)	TB Antigen minus (IU/mL)	Results	Interpretation
<0.5	<0.35	Indeterminate	Do not perform determination because there is possibility of immunodeficiency

### **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- $\gamma$ .

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- $\gamma$  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- $\gamma$  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**

Collect a blood sample according to the instructions supplied with the collection device. The blood volume of standard is as follows:

- Adults and children 10 years old and over: one 6mL heparin tube or one 8mL CPT tubes or two 4mL CPT tubes

The tube contents must be inverted (8 – 10 times). Blood samples must be stored at room temperature (18-25°C), and shipped to the central laboratory on the same day.

The central laboratory will separate a layer of peripheral blood mononuclear cells (PBMCs) from a whole blood sample, and evaluate for tuberculosis infection with the use of the ELISPOT method.

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. The T-SPOT.TB test can be performed at the study site or local laboratory in accordance with each laboratory's procedure.

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 7: 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.

Eligibility based on Hepatitis B virus test results				
Action	Hepatitis B test result			
	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.

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**INVESTIGATOR AGREEMENT**

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

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

**Coordinating Investigator (where required):**

Name (typed or printed): \_\_\_\_\_

Institution and Address: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

(Day Month Year)

**Principal (Site) Investigator:**

Name (typed or printed): \_\_\_\_\_

Institution and Address: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Telephone Number: \_\_\_\_\_

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

(Day Month Year)

**Sponsor's Responsible Medical Officer:**Name (typed or printed): Volkmar Guenzler PukallInstitution: 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.

**LAST PAGE**

**Janssen Research & Development \***

**Statistical Analysis Plan**

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**Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Efficacy, Safety and Tolerability of CNTO 1959, a Human Anti-IL 23 Monoclonal Antibody, following Subcutaneous Administration in Subjects with Palmoplantar Pustulosis**

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**Protocol CNTO1959PPP2001; Phase 2**

**CNTO 1959**

**Status:** Approved 1.0  
**Date:** 31 July 2014  
**Prepared by:** Janssen Pharmaceutical K.K.  
**Document No.:** EDMS-ERI-88746737

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

**Confidentiality Statement**

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.



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**ABBREVIATIONS**

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BQL	Below quantification limit
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval
CRF	case report form
CRP	C-reactive protein
CSR	Clinical Study Report
DBL	database lock
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
FAS	full analysis set
eCRF	electronic case report form
LOCF	last observation carried forward
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCS	mental component summary scores
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NONMEM	nonlinear mixed-effects model
PA	Physician's Assessment
PAO	pustulotic arthro-osteitis
PASI	Psoriasis Area and Severity Index
PCS	physical component summary scores
PD	Pharmacodynamic
PGA	Physician's Global Assessment
PI	principal investigator
PK	pharmacokinetic(s)
PPP	Palmoplantar Pustulosis
PPPASI	Palmo-Plantar Pustulosis Area and Severity Index
PPS	per-protocol set
PPSI	Palmoplantar Pustulosis Severity Index
QOL	Quality of Life
QRS	QRS duration
QTc	corrected QT interval
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
VAS	Visual Analogue Scale
WBC	white blood cell

## 1. INTRODUCTION

### 1.1. Trial Objectives

#### Primary Objectives

The primary objectives of this study are:

- To evaluate the efficacy of CNTO 1959 in the treatment of subjects with palmoplantar pustulosis at Week 16
- To assess the safety and tolerability of CNTO 1959 in subjects with palmoplantar pustulosis

#### Major Secondary Objectives

The major secondary objectives of this study are:

- To assess the pharmacokinetics and immunogenicity of CNTO 1959 following SC administration in subjects with palmoplantar pustulosis
- To assess the impact of treatment with CNTO 1959 on the health related QOL measurement in subjects with palmoplantar pustulosis at Week 16
- To assess possible time point with maximum clinical response of CNTO 1959 after two dose injection.

#### Exploratory Objectives

The exploratory objectives of this study are:

- To explore biomarkers following CNTO 1959 administration in subjects with palmoplantar pustulosis
- To explore the impact of treatment with CNTO 1959 on pustulotic arthro-osteitis (PAO) in the subset of subjects with PAO at screening
- To explore possible overall process of clinical response of CNTO 1959 over time.

### 1.2. Trial Design

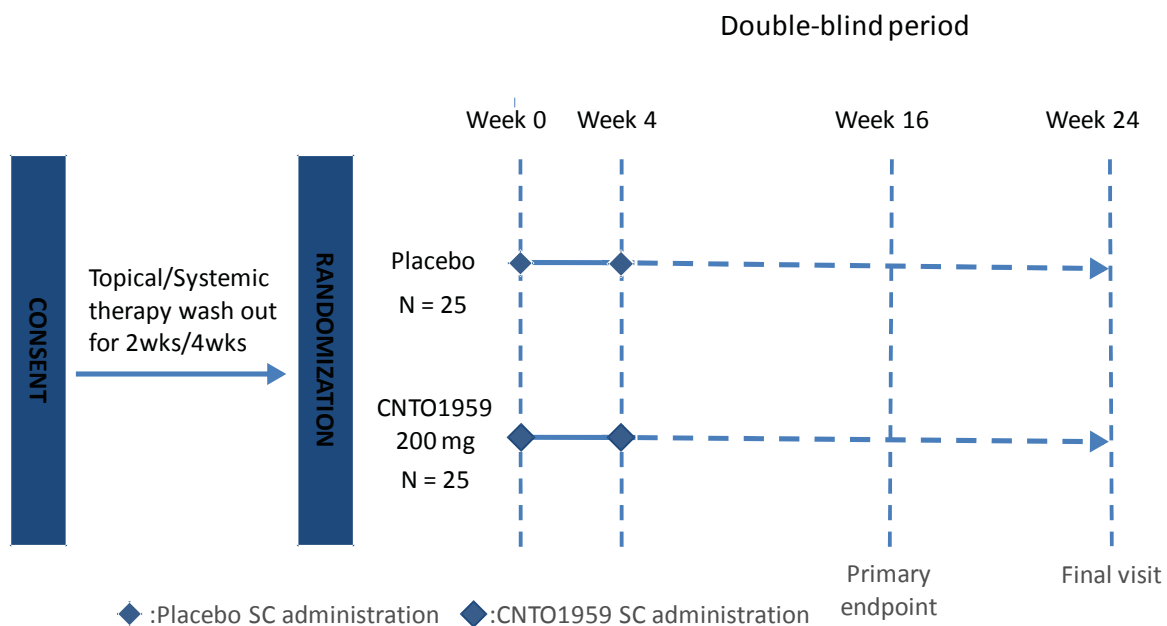
This is a Phase 2, randomized, double-blind, placebo-controlled, parallel group, multicenter study of CNTO 1959 in subjects with palmoplantar pustulosis. Approximately 50 subjects will be randomly assigned to 1 of 2 treatment groups (CNTO 1959 200 mg SC or placebo SC) in a 1:1 ratio and will receive study drug at Week 0 and Week 4. After randomization (Week 0), subjects will return to the study site for 9 evaluation visits (Weeks 1, 2, 4, 6, 8, 12, 16, 20 and 24). The overall study schema is provided in [Figure 1](#).

The target population consists of moderate to severe subjects with palmoplantar pustulosis defined as those subjects who have pathognomonic skin manifestation of palmoplantar pustulosis on palms and/or soles. Subjects must have had an inadequate response to prior conventional treatment (eg, topical corticosteroids, active vitamin D<sub>3</sub>, etretinate or phototherapy) and must

have active lesions at screening and baseline (PPSI score of 7 or greater). Subjects with extra-palmoplantar lesions and/or PAO can be included.

The total duration of subject participation will be approximately 30 weeks, which includes a screening period of about 6 weeks before dosing. Subjects will return to the study site on Weeks 1, 2, 4, 6, 8, 12, 16, 20 and 24. Completion of the Week 24 assessment constitutes the subject's completion of the study.

The data from this study will be cleaned and locked for analysis at the Week 16 and Week 24 database locks (DBLs). The purpose of Week 16 DBLs is to perform selected analyses to be used by the sponsor in planning for the CNTO 1959 next phase clinical program.



**Figure 1 Schematic Overview of the Study**

### 1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis of this study is that CNTO 1959 treatment, 200 mg SC injection at Week 0 and Week 4, is superior to placebo in terms of the change from baseline of Palmoplantar Pustulosis Severity Index (PPSI) total score at Week 16.

### 1.4. Sample Size Justification

In the phase 3 double blind controlled study for Maxacalcitol (topical vitamin D<sub>3</sub>) that is approved for a treatment of palmoplantar pustulosis in Japan, the mean change from baseline of skin observation total score for Maxacalcitol was -3.7 (standard deviation [SD] = 2.1, number of patients [N] = 94) and -1.9 (SD = 1.9, N=93) for placebo group, as results of the primary endpoint. Based on these results, 25 subjects per group (total of 50 subjects) are considered as

appropriate for this study in consideration to uncertainty for the estimates with varying assumptions. The sample size of 25 subjects has an 84% power to detect a significant difference between the CNTO 1959 treatment group and the placebo group at a two-sided alpha level of 0.05, assuming a treatment difference in the change from baseline of PPSI total score at Week 16 of 1.8 with a SD of 2.1. Table 1 provides the power for detecting a treatment difference between the CNTO1959 treatment group and the placebo treatment group (for 25 subjects per group) under varying assumptions for the treatment difference of the change from baseline of PPSI total score.

**Table 1 Power to detect a treatment difference based on the change from baseline of PPSI total score**

Mean Difference	Power
1.6	0.752
1.7	0.801
1.8	0.844
1.9	0.880
2.0	0.910

n = 25 for each group  
common SD = 2.1

## 1.5. Randomization and Blinding

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. Subjects will be randomly assigned to 1 of 2 treatment groups based on a randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by study site. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints. Limited sponsor personnel will become unblinded to treatment assignment at the Week 16 database lock (DBL). To minimize potential bias in the study even after the Week 16 DBL, treatment assignment blinding will be maintained for study sites, site monitors, and subjects participating in the study after the Week 16 DBL until the final DBL.

## 2. GENERAL ANALYSIS DEFINITIONS

This analysis plan provides the general analysis definitions and describes the planned subject information, efficacy and safety analyses.

### 2.1. Visit Windows

**Table 2: Visit Window**

Time Interval (label on output)	Time Interval (Day) <sup>a</sup>	Target Time Point
Week 0 (Baseline)	-42 to 1	1
Week 1	5 to 11	8
Week 2	12 to 18	15
Week 4	26 to 32	29
Week 6	40 to 46	43

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Week 8	54 to 60	57
Week 12	78 to 92	85
Week 16	106 to 120	113
Week 20	134 to 148	141
Week 24	162 to 176	169

---

<sup>a</sup> The first double-blind medication day is Day 1.

If two scheduled visits fall within the same interval, the one closest to the target day will be used for the descriptive statistics/tabulations per time point and graphics in order to have only one evaluation per subject per analysis time point. If distances of both visits to the target day are equal, the measurement with the latest date will be used. If also dates are equal, the measurement with the highest sequence number will be used. Listings and abnormality evaluation for safety will include all values at all visits.

## 2.2. Baseline Measurements

For each parameter, the baseline measurement is defined as the closest measurement taken prior to the initiation of the Week 0 administration unless otherwise specified.

## 2.3. Pooling Algorithm for Analysis Centers

Data from all sites will be pooled for all analysis.

## 2.4. Analysis Sets

There will be two database locks at Week 16 and Week 24 for this study.

Week 16 database lock will include all data through Week 16. In addition, the following data through Week 24 will also be included for those subjects who were supposed to have completed Week 24 visit (either terminated the study or completed through Week 24 visit) by the time the Week 16 database lock occurs. These additional data will be primarily used to assess the maintenance of clinical response through Week 24 in planning for the CNTO1959 Phase 3 clinical studies in PPP.

At the Week 16 database lock, the data will be unblinded for analysis while subjects are still being followed in the study. Identification of sponsor personnel who will have access to the unblinded subject-level data will be documented prior to unblinding. Investigators and study personnel, specified in separate list will remain blinded to subject-level data until the Week 24 database lock in order to maintain the integrity and blinding of the trial.

### 2.4.1. Efficacy Analysis Set(s)

#### 2.4.1.1. Primary Efficacy Analysis Set

Full analysis set (FAS) is the population of all randomized subjects who received at least one dose of study drug regardless of whether or not they received the assigned treatment and had any

post-baseline efficacy (PPSI) assessment. FAS will be the primary analysis population for efficacy analyses.

#### **2.4.1.2. Secondary Efficacy Analysis Set**

The PPS is a subset of the full analysis set. The per-protocol analysis set excludes any subject with any of the major protocol deviations. The subjects meeting any major protocol deviation criteria will be determined prior to DBL and entered into the clinical database deviation dataset.

Some major protocol deviations include the following:

- Prohibited concomitant treatment
- Inclusion/exclusion criteria not met
- Treatment deviation

Primary analysis including sensitivity analysis and major secondary analyses will be also performed using PPS.

#### **2.4.2. Safety Analysis Set**

The safety analysis set is the population of all randomized subjects who received at least one dose of study drug received during the study.

#### **2.4.3. Pharmacokinetics Analysis Set**

All randomized subjects who receive at least 1 dosing of CNTO 1959 and have serum CNTO 1959 concentration data will be included in the pharmacokinetic analysis set.

#### **2.4.4. Immunogenicity Analysis Set**

All randomized subjects who receive an administration 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).

#### **2.4.5. Pharmacodynamics Analysis Set**

All randomized subjects who receive at least 1 dosing of CNTO 1959 will be included in the pharmacodynamics analysis set.

### **2.5. Definition of Subgroups**

To evaluate the consistency of efficacy in the primary endpoint and PPPASI evaluation over demographic, baseline disease characteristics, and PPP medication history, subgroup analyses will be performed when the number of subjects in the subgroups permits.

#### **Baseline demographics:**

- Sex (male, female)

- Baseline age (< 65 years, ≥ 65 years)
- Baseline weight (≤ 70 kg, > 70 kg, ≤ 90 kg, > 90 kg)
- BMI (Normal (<25), Overweight (≥ 25))
- Smoking status
- Pustulotic Arthro-Osteitis (PAO) diagnosis at baseline (YES/NO)
- PPP related extra-palmoplantar lesions (YES/NO)
- plaque-type psoriasis (YES/NO)
- Tonsillectomy for focal infection (YES/NO)
- Dental therapies for focal infection (YES/NO)
- Nail lesion at baseline (0 (clear), >0)

### 3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

No interim analysis and data monitoring committee review are planned.

### 4. SUBJECT INFORMATION

For the summaries related to subject information, unless specified otherwise, subjects in safety population will be included. Most of the subject information data will be summarized in 3 columns (See data presentation specification) that include ‘Total’ column that combines placebo, and CNTO1959 treatment groups. Descriptive statistics, such as mean, median, standard deviation, IQ range, minimum and maximum for continuous variables, and counts and percentages for categorical variables will be used to summarize the data. In case of partial dates (complete month), it will be imputed with the first of the month. In case of partial dates and month, those will not be imputed and only year will be used.

#### 4.1. Demographics and Baseline Characteristics

The safety analysis set as well as full analysis set will be used for all tabulations. Subjects’ demographic data (eg, weight, age, height and sex) and baseline disease characteristics (eg, duration of disease, and baseline PPPASI score) will be summarized by treatment group.

#### Baseline Characteristics

Age (< 65 years, ≥ 65 years)\*, Sex, Weight (Baseline weight (≤ 70 kg, > 70 kg, ≤ 90 kg, > 90 kg)), Height, BMI (kg/m<sup>2</sup>), Smoking status

#### Disease Characteristics at Baseline

PPP disease duration (yrs)

Age at diagnosis (yrs)

PPSI score (0-12)\*: 7-9, 10-12



- 
- PPPASI score (0-72)\*: < 20, ≥ 20
- DLQI score (0-30)
- (5) PGA score: Cleared (0), Minimal (1), Mild (2), Moderate (3), Severe (4), Very Severe
- PA- (Pustule Lesions, Vesicle Lesions, Nail Lesions)
- VAS (Patient's VAS-PPP severity, Physician's VAS-PAO activity, Patient's VAS-PAO activity)
- PAO diagnosis at baseline
- For subjects who take MRI, sites (Anterior chest , Cervical spine, Thoracic spine, Lumbar spine, Sacroiliac joint, Other joints, Extra-articular long tubular bone/ flat bone, Other region)
- Evaluation site for PPSI: Palms, Soles
- Subjects with PPP related extra-palmoplantar
- Subjects with plaque-type psoriasis
- Subjects with any other type of lesions
- Tonsillectomy for focal infection (YES/NO)
- Dental therapies for focal infection (YES/NO)

\*Will be summarized by summary statistics and frequency table.

#### **4.2. Disposition Information**

Tabulations will be provided by treatment group for all ICed subjects with the following disposition information:

- Number of subjects screened (ICed), randomized, treated and not treated, completed all study agents, and discontinued all study agents, completed/ongoing the study
- Number of subjects in each analysis set (FAS, PPS, and Safety population)

In addition, summaries of subjects who terminated study participation and the reasons for discontinuation of study participation will be provided for the safety analysis set by treatment group.

#### **4.3. Treatment Compliance**

Number of the subjects receiving each scheduled treatments will be summarized. In addition, treatment compliance will be assessed by summarizing the protocol deviation (Section 4.5) of the

study agent administration related to incorrect study agent or dose received and administrations missed.

#### **4.4. Extent of Exposure**

The extent of exposure below will be evaluated for the safety analysis set.

Cumulative dose of CNTO 1959 received will be summarized. In addition, the average exposure (number of administrations) and average duration of follow-up (weeks) which starts from the date of first study agent administration will also be summarized by treatment group.

#### **4.5. Protocol Deviations**

Information of the major protocol deviations will be provided for all randomized subjects by treatment group.

#### **4.6. Prior and Concomitant Medications**

Subjects' PPP medication history and duration (category) will be summarized by treatment group. Concomitant medications other than PPP medication will also be summarized by treatment group. In addition, listings of subjects who received PPP medication / concomitant medication will be provided.

### **5. EFFICACY**

In general, data summaries will be provided for each treatment group (placebo and CNTO1959 treatment groups). Graphical data displays may also be used to summarize the data using FAS.

#### **5.1. Analysis Specifications**

##### **5.1.1. Level of Significance**

All statistical procedures will be performed 2-sided at a significance level of 0.05 and all confidence intervals will be two-sided. For major secondary endpoints, no adjustment for multiplicity will be conducted.

##### **5.1.2. Data Handling Rules**

###### **5.1.2.1. Treatment Failure Rules**

The treatment failure criteria are as follows:

- Subjects who terminated study early due to any of the following reasons:
  - Initiated a protocol-prohibited medication/therapy during the study that could improve palmoplantar pustulosis
  - Experienced treatment-emergent adverse event(defined in 6.1), pustular psoriasis, during the study

A subject who meets treatment failure criteria will be considered a treatment failure from the date of using the medications or the date of early termination onward. The last observation while on treatment (or baseline measurement if applicable) before starting the first prohibited or medication usage which may include the date of early withdrawn for subjects who are terminated early, whichever is earlier will be carried over for all continuous endpoints through the study regardless of the actual measurements, and non-responder statuses will be assigned to response variables. Failure rules will be applied before using the time window for all efficacy analysis through the study.

#### **5.1.2.2. Data Handling Rules for Efficacy Analyses**

After applying treatment failure rules, the last observation-carried-forward (LOCF) approach will be used for missing data for the efficacy analysis unless specified.

For longitudinal data for secondary efficacy analyses (i.e over time summaries), after the treatment failures are applied, no imputation will be performed for missing data (eg, lost to follow-up, missed study visit) and the values will remain as missing.

##### **5.1.2.2.1. Data Handling Rules for Dermatology Life Quality Index (DLQI)**

In addition to the data handling rules described in Section 5.1.2.2 the following data handling rules also apply to all the secondary analyses related to Dermatology Life Quality Index (DLQI). For a partially answered questionnaire (eg, not all 10 answers in the DLQI questionnaire were available):

- If one question's answer is not available, this question will be scored 0. The total score will then be calculated.
- If two or more questions' answers are unavailable, the questionnaire is not scored. Hence, the total score and each of the 6 component scores will be set to missing.
- If question 7 is answered 'yes' this is scored 3. If it is answered 'no', but the second half is left incomplete, the score will remain 0.
- If question 7 is answered 'no' or 'not relevant' but then either 'a lot' or 'a little' is ticked this is then scored 2 or 1.
- If two or more response options are ticked for one question, the response option with the highest score should be recorded.
- If there is a response between two tick boxes, the lower of the two score options should be recorded.

## **5.2. Primary Efficacy Endpoint(s)**

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

### **5.2.1. Definition**

Palmoplantar Pustulosis Severity Index (PPSI) assesses the severity of palmoplantar pustulosis

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lesions and their response to therapy. 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. The PPSI separately assessed for evaluation sites such as erythema, pustules/vesicle and desquamation/scale, which are each rated the most severe skin lesion on a scale of 0 to 4. PPSI total scores can range from 0 to 12, with higher scores indicating more severity.

### **5.2.2. Analysis Methods**

The change from baseline in PPSI total score at Week 16 will be analyzed using an analysis of covariance (ANCOVA) model with treatment as a factor and baseline PPSI total score as a covariate. Treatment effect of CNTO1959 versus placebo will be estimated based on least-square (LS) means of the difference. The p-value for the treatment difference along with the 2-sided 95% CI will be presented. If the normality assumption was significantly violated, a rank-based test will be performed for the primary analyses.

### **5.2.3. Sensitivity Analysis**

To test the robustness of the primary endpoint analysis result, for subjects with missing PPSI score at Week 16, after applied to treatment failure, the missing PPSI score at Week 16 will not be imputed (observed data will be used).

### **5.2.4. Subgroup Analysis**

Subgroup analyses defined in Section 2.6, will be performed using descriptive statistics for the change from baseline in PPSI total score and PPPASI total score at Week 16.

## **5.3. Major Secondary Endpoints**

The following are the major secondary endpoints:

- Change from baseline in PPSI total score through Week 24
- Change from baseline in PPPASI at Week 16 and through Week 24
- Proportion of subjects who achieve a PPPASI-50 at Week 16 and through Week 24
- Proportion of subjects who achieve a PGA score of 1 or less at Week 16 and through Week 24

### **5.3.1. Change from baseline in PPSI total score through Week 24**

#### **5.3.1.1. Analysis Methods**

The change from baseline in PPSI total score as well as the difference of mean change from baseline between CNTO1959 and placebo group will be summarized through Week 24 by treatment group using descriptive statistics. If the significant mean difference of change from baseline between CNTO1959 and placebo group is observed at Week 16, same analysis will be performed for the subsequent visit to explore the period of maximum clinical response of CNTO1959.

### **5.3.2. Change from baseline in PPPASI through at Week 16 and through Week 24**

#### **5.3.2.1. Definition**

Palmo-Plantar Pustulosis Area and Severity Index (PPPASI) assesses the severity of palmoplantar pustulosis lesions and their response to therapy with a score ranging from 0 to 72.

#### **5.3.2.2. Analysis Methods**

The change from baseline in PPPASI at Week 16 will be analyzed using an ANCOVA model with treatment as factors and baseline score as a covariate. The change from baseline in PPPASI will be analyzed in the same way as the primary endpoint (see section 5.2.2). The change from baseline in PPPASI total score through Week 24 will also be summarized by treatment group using descriptive statistics.

### **5.3.3. Proportion of subjects who achieve a PPPASI-50 at Week 16 and through Week 24**

#### **5.3.3.1. Definition**

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

#### **5.3.3.2. Analysis Methods**

The proportion of subjects who achieve a PPPASI-50 through Week 24 will also be summarized by treatment group using frequencies and percentages with 95% CI. PPPASI-50 responders at Week 16 will be compared between the CNTO 1959 treatment group and placebo group using Fisher's exact test.

### **5.3.4. Proportion of subjects who achieve a PGA score of 1 or less at Week 16 and through Week 24**

#### **5.3.4.1. Definition**

Physician's Global Assessment of palmoplantar pustulosis lesion (PGA) documents the Physician's Global Assessment of the subject's palmoplantar overall skin lesions status and can range from clear (0) to very severe (5) on a 6-point scale.

#### **5.3.4.2. Analysis Methods**

The proportion of subjects who achieve a PGA score of 1 or less through Week 24 will also be summarized by treatment group using frequencies and percentages with 95% CI. The proportion of subjects who achieve PGA score of 1 or less at Week 16 will be compared between the CNTO 1959 treatment group and placebo group using Fisher's exact test.

#### **5.4. Other Efficacy Variable(s)**

Other secondary endpoints as follows;

- Proportion of subjects who achieve a PPPASI-75 at Week 16 and through Week 24
- Proportion of subjects who achieve a PGA score of 2 or less through Week 24
- **Change from baseline in PA (each score) through Week 24**
- Change from baseline in Patient's VAS-PPP severity through Week 24
- Change from baseline in Physician's VAS-PAO activity through Week 24
- Change from baseline in Patient's VAS-PAO activity and pain through Week 24
- Change from baseline in DLQI through Week 24
- DLQI of Zero or one through Week 24
- Reduction in DLQI of five or more from baseline through Week 24
- Change from baseline in SF-36 through Week 24

##### **5.4.1. Proportion of subjects who achieve a PPPASI-75 at Week 16 and through Week 24**

###### **5.4.1.1. Definition**

PPPASI-75: Subjects with  $\geq 75\%$  improvement in PPPASI from baseline will be considered as PPPASI-75 responders.

###### **5.4.1.2. Analysis Methods**

The proportion of subjects who achieve a PPPASI-50 will be analyzed in the same way as those for PPPASI-50 (see section 5.3.3.2).

##### **5.4.2. Proportion of subjects who achieve a PGA score of 2 or less through Week 24**

###### **5.4.2.1. Analysis Methods**

The proportion of subjects who achieve PGA score of 2 or less will be analyzed in the same way as those for PGA score of 1 or less (see section 5.3.4.2).

**5.4.3. Change from baseline in PA (each score) through Week 24****5.4.3.1. Definition**

The Physician's Assessment (PA) documents the physician's assessment of the subject's pustule, vesicle and nail lesions status. Each of pustule, vesicle and nail will be graded from 0 to 5.

**5.4.3.2. Analysis Methods**

Cross tabulation of baseline and each PA score will be summarized by treatment through Week 24.

**5.4.4. Change from baseline in Patient's VAS-PPP severity through Week 24****5.4.4.1. Definition**

The Patient's Visual Analogue Scale assessment of Palmoplantar Pustulosis Severity (Patient's VAS-PPP) will be recorded on a 10-cm VAS.

**5.4.4.2. Analysis Methods**

The change from baseline in Patient's VAS-PPP as well as absolute value in Patient's VAS-PPP will also be summarized over time by treatment group using descriptive statistics.

**5.4.5. Change from baseline in Physician's VAS-PAO activity through Week 24****5.4.5.1. Definition**

Physician's Visual Analogue Scale Assessment of Pustulotic Arthro-Osteitis Activity (Physician's VAS-PAO activity) will be recorded on a 10-cm VAS for subjects with PAO at screening.

**5.4.5.2. Analysis Methods**

For subjects with PAO at screening, the change from baseline in Physician's VAS-PAO activity as well as absolute value will also be summarized through Week 24 by treatment group using descriptive statistics.

**5.4.6. Change from baseline in Patient's VAS-PAO activity and pain through Week 24****5.4.6.1. Definition**

Patient's Visual Analogue Scale Assessment of Pustulotic Arthro-Osteitis (Patient's VAS-PAO) Activity and Pain will be recorded on each 10-cm VAS. The investigator will specify the main site for the patient to evaluate of pain. If there are multiple site worth evaluating, additional 2 site could be evaluated.

#### **5.4.6.2. Analysis Methods**

Those for Patient's VAS-PAO will be analyzed in the same way as those for Physician's VAS-PAO activity (see section 5.4.5).

#### **5.4.7. Analyses related to DLQI**

##### **5.4.7.1. Definition**

The Dermatology Life Quality Index 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 questionnaire that in addition to evaluating overall quality of life, can be used to assess 6 different components that may affect quality of life: symptoms and feelings, daily activities, leisure, work or school performance, interpersonal relationships, and treatment. The DLQI total score is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. .

##### **5.4.7.2. Analysis Methods**

The change from baseline in DLQI will be summarized through Week 24 by treatment group using descriptive statistics. Proportion of subjects who have DLQI of Zero or one through Week 24 and reduce in DLQI of five or more from baseline through Week 24 will be summarized by treatment group using frequencies.

#### **5.4.8. Change from baseline in SF-36 at Week 16 and through Week 24**

##### **5.4.8.1. Definition**

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. The SF-36 also consists of 2 component summary scores: physical (PCS) and mental (MCS) component summary scores.

##### **5.4.8.2. Analysis Methods**

SF-36 at baseline and the change from baseline in SF-36 in each lower component scores and summary scores (PCS and MCS) will be summarized by treatment group through Week 24 using descriptive statistics.

## **6. SAFETY**

### **6.1. Adverse Events**

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the double-blind treatment period or adverse events that have worsened since baseline (ie, treatment-emergent adverse events) will be included in the analysis. However, for



the subjects withdraw from the study before 12 weeks after last study drug administration, all reported adverse events with onset or adverse events that have worsened since baseline for up to 12 weeks after last study drug administration will be included in the analysis.

For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

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

- The incidence of AEs
- The incidence of AEs  $\geq 5\%$  in any treatment group
- The incidence of SAEs
- The incidence of AEs by severe intensity
- The incidence of drug related AEs and SAEs
- The incidence of AEs leading to permanent discontinuation of study agent
- The incidence of infectious AEs
- The incidence of injection site reactions

## **6.2. Clinical Laboratory Tests**

Laboratory data will be summarized by type of laboratory test (eg, hematology, serum chemistry and urinalysis) and treatment group. Markedly abnormal criteria will be used to identify markedly abnormal laboratory results, which will be summarized by treatment group. Laboratory data will also be presented graphically in Box-plot by treatment group. A listing of subjects with any markedly abnormal laboratory results will also be provided.

- Laboratory parameters(hematology serum including MCV, MCH and MCHC as well as chemistry) and change from baseline in laboratory parameters will be summarized using descriptive statistics at each visit through Week 24
- Incidence of markedly abnormal laboratory parameters (hematology and serum chemistry) will be summarized using frequency table.

For the assessment of markedly abnormality, all pre/post-baseline data including one measured at unscheduled visit will be used.

- Qualitative parameters (urinalysis) selected lab parameters (RBC, Hemoglobin, Hematocrit, MCV, MCH, and MCHC) will be presented in cross tabulation of baseline and values at each time point, using normal range of central laboratory
- MCV, MCH and MCHC will be derived using the following formulae :  

$$\text{MCV [fl]} = (\text{Ht (\%)} \times 10) / \text{RBC (} 10^6 / \mu\text{L)}$$

$$\text{MCH [pg]} = (\text{Hb (g/dL)} \times 10) / \text{RBC}(10^6 / \mu\text{L}) \quad \text{MCHC [\%]} = (\text{Hb (g/dL)} \times 100) / \text{Ht (\%)}$$

<b>Table : Markedly Abnormal Criteria for Laboratory Parameters</b>	
<b>Hematology Test</b>	<b>Criteria for Markedly Abnormal Status</b>
RBC ( $\times 10^{12}/\text{L}$ )	< 3.0
Hemoglobin (g/L)	Decrease >20 & Value < 100.0
Hematocrit, fraction	Value < 0.27
Platelets ( $\times 10^9/\text{L}$ )	Percent decrease $\geq 50$ & Value < 75
WBC ( $\times 10^9/\text{L}$ )	Value <2.0 <b>OR</b> Value >20.0
Eosinophils, ( $\times 10^9/\text{L}$ )	Percent increase $\geq 100$ & Value > 0.8
Lymphocytes, ( $\times 10^9/\text{L}$ )	Percent decrease $\geq 33$ & Value <1.0
Neutrophils, ( $\times 10^9/\text{L}$ )	Percent decrease $\geq 33$ & Value <1.5
<b>Chemistry Test</b>	
BUN/Urea (mmol/L)	Percent increase $\geq 66$ & Value >14.28
Creatinine (umol/L)	Percent increase $\geq 66$ & Value > 132.6
Total Bilirubin (umol/L)	Percent increase $\geq 100$ & Value > 51.3
Alkaline phosphatase (U/L)	Percent increase $\geq 100$ & Value >250
ALT (U/L)	Percent increase $\geq 100$ & Value > 150
AST (U/L)	Percent increase $\geq 100$ & Value > 150
Sodium (mmol/L)	(Increase $\geq 10$ & Value >150) <b>OR</b> (Decrease $\geq 10$ & Value < 120)
Potassium (mmol/L)	(Increase $\geq 0.8$ & Value > 6.0) <b>OR</b> (Decrease $\geq 0.8$ & Value < 3.0)
Glucose (mmol/L)	(Percent increase $\geq 50\%$ & value > 8.88) <b>OR</b> (percent decrease $\geq 33\%$ & value < 3.05)
Chloride (mmol/L)	Value < 85 <b>OR</b> Value > 120
Calcium (mmol/L)	(Increase $\geq 0.5$ & Value > 2.87) <b>OR</b> (Decrease $\geq 0.37$ & Value < 1.87)
Bicarbonate (mmol/L)	(Value >35) <b>OR</b> ( Value < 15)
Albumin (g/L)	Decrease $\geq 10$ & Value < 30
Total protein (g/L)	Value < 45 <b>OR</b> Value > 100
Note: Increases and decreases above are relative to the baseline value.	

### 6.3. Vital Signs and Physical Examination Findings

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

## 6.4. Electrocardiogram

The observed value and change from baseline of ECG parameters will be summarized descriptively by visit and treatment group. The following proportions of subjects will be summarized:

Heart rate (low):  $\leq 50$  bpm AND  $\geq 15$  bpm decrease relative to the baseline value

Heart rate (high):  $\geq 120$  bpm AND  $\geq 50$  bpm increase relative to the baseline value

QRS interval:  $\geq 120$  msec OR  $\geq 25\%$  increase relative to the baseline value

Proportions of subjects with QTc  $>450$ ,  $>480$ ,  $>500$ .

Proportions of subjects with QTc changed by  $>30$  or  $>60$

All data will be listed.

## 7. PHARMACOKINETICS/PHARMACODYNAMICS AND IMMUNOGENICITY

### 7.1. Pharmacokinetics

Serum CNTO 1959 concentrations will be summarized with descriptive statistics, including arithmetic mean, SD, coefficient of variation (%CV), median, minimum, maximum, 25% quartile and 75% quartile at each sampling time point.

Serum CNTO 1959 concentrations will also be summarized by the baseline weight ( $\leq 70$  kg,  $> 70$  kg and  $\leq 90$  kg,  $> 90$  kg) with descriptive statistics, including arithmetic mean, SD, %CV, median, minimum, maximum, 25% quartile and 75% quartile at each sampling time.

The PK analysis will be based on subjects who received at least 1 administration of CNTO 1959 and had at least one evaluable serum sample. No imputation of missing concentration data will be performed, that is, data summaries will be based on the observed data. All serum concentrations below the lowest quantifiable sample concentration of the assay (BQL) or missing data will be labeled as such in the concentration data listings or Statistical Analysis Software™ (SAS) dataset. All subjects and samples excluded from the analysis will be clearly documented.

For descriptive statistics of serum concentration of CNTO 1959, following data handling rules will be applied;

- All BQL concentrations (i.e.  $<0.04$   $\mu\text{g/mL}$ ) will be treated as “0” (zero) in the summary statistics.
- Serum concentrations of CNTO 1959 data will be calculated based on the number of subjects with observed data, including BQL, at each sampling time.

- When more than half (>50%) of the serum concentrations of CNTO 1959 are BQL at each scheduled time point, mean, median, minimum and 25% quartile will be shown as 'BQL', and SD and %CV and 75% quartile will be shown as 'NC' (not calculated). Maximum observed value will be presented as maximum.
- When the number of serum concentrations data of CNTO 1959 at each scheduled time point is less than or equal to 2, only N and mean will be calculated, and SD, %CV, median, minimum, maximum, 25% quartile and 75% quartile will be shown as 'NC' regardless of the number of BQL.
- Only the data of samples within the visit time window (see [Table 2](#)) will be used to calculate.
- If adequate doses are not administered (including missing dose, received a partial, incorrect, or an additional CNTO 1959 administration) at Week 0 or Week 4, the observed data after the inadequate administration will be excluded from descriptive statistics. Of note, serum CNTO 1959 concentrations prior to the first of such events will be included in the summaries.
- Data of samples with no information about the sampling date and time and/or the drug administration (time and dosage) will be excluded from descriptive statistics.

Mean (SD) of serum CNTO 1959 concentration time profiles (in linear and semi-log scales) will be presented in figure. Actual sampling time at Week 0 pre-dose will be substituted with "0" in the figure.

Mean (SD) of serum CNTO 1959 concentrations will be shown in the figure (linear scale) by the baseline weight ( $\leq 70$  kg,  $> 70$  kg and  $\leq 90$  kg,  $> 90$  kg).

The number and proportion of subjects with BQL serum CNTO 1959 concentrations will be summarized by each sampling time point.

If feasible, a population PK analysis of serum concentration-time data of CNTO 1959 will be performed using nonlinear mixed-effects model (NONMEM) approach. 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.

## 7.2. Immunogenicity

The incidence of antibodies to CNTO 1959 during the study will be summarized for all subjects who receive at least 1 administration of CNTO 1959 and have appropriate serum samples for detection of antibodies to CNTO 1959 after administration (ie, subjects with at least 1 sample obtained after their first dose of CNTO 1959). No imputation of missing data will be performed, that is, data summaries will be based on the observed data. The incidence of positive antibodies to CNTO 1959 and antibody titers will be summarized. A list of subjects for antibodies to CNTO 1959 will be provided with titers.

Results from the analysis of antibodies to CNTO 1959 will be classified as positive or negative; as defined below:

Positive: Samples with detectable antibodies to CNTO 1959 will be classified as positive for antibodies to CNTO 1959. Subjects with at least 1 positive sample at any timepoint after exposure to CNTO 1959 will be classified as positive for antibodies to CNTO 1959. In the instance that a subject had a positive baseline sample, post-administration samples will be considered treatment emergent positives only when their titer was at least 2-fold higher than the baseline titer.

Negative: Samples without detectable antibodies to CNTO 1959 will be classified as negative for antibodies to CNTO 1959. Subjects will be designated negative for antibodies to CNTO 1959 when there was no positive sample at any timepoint after exposure to CNTO 1959.

### **7.3. Pharmacokinetic/Pharmacodynamic Relationships**

To explore the relationships between clinical response and systemic exposure to CNTO 1959, scatter plots of serum concentration of CNTO 1959 versus the change in PPSI total score and PPPASI score at Week 16 (LOCF) will be provided using data from individual subject.

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