Janssen Research & Development *

Statistical Analysis Plan

A Phase 3, Multicenter, Randomized, Placebo- and Active Comparator-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of Subcutaneously Administered Guselkumab for the Treatment of Chronic Plaque Psoriasis in Pediatric Subjects (≥6 To <18 Years of Age)

Protocol CNTO1959PSO3011; Phase 3

CNTO 1959 (Guselkumab)

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

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ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
CDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
CRF	case report form
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DBL	database lock
DC	Discontinuation
ECG	Electrocardiogram
FDLQI	Family Dermatology Life Quality Index
eCRF	electronic case report form
eC-SSRS	Electronic Columbia-Suicide Severity Rating Scale
FDA	Food and Drug Administration
IGA	Investigator's Global Assessment
IgG1λ	immunoglobulin G1 lambda
IWRS	interactive web response system
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NAbs	neutralizing antibodies
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamic
PFS	prefilled syringe
PFS-U	Pre-filled syringe with an UltraSafe PLUS™ Passive Needle Guard or Pre-filled syringe with an UltraSafe Passive® Needle Guard
CCI	CCI
PK	pharmacokinetic(s)
PQCs	product quality complaints
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SIAQ	Self-Injection Assessment Questionnaire

Summary of Amendment 1

This amendment is to change one of the coprimary endpoints for the US-Food and Drug Administration (FDA) specific co-primary endpoints based on feedback received from the FDA. The co-primary endpoints will remain unchanged for other regions. Specifically, the US-FDA specific coprimary endpoints will be the proportion of subjects who achieve a PASI 90 response and the proportion of subjects who achieve an IGA score of cleared (0) or minimal (1) at Week 16. One of the original co-primary endpoints: the proportion of subjects who achieve a PASI 75 response will become the first major secondary endpoint.

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the analyses of efficacy, safety, pharmacokinetics (PK), and immunogenicity of guselkumab as a treatment for pediatric patients with chronic plaque psoriasis in study CNTO1959PSO3011.

Guselkumab (CNTO 1959) is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody that binds to the p19 protein subunit of human interleukin (IL)-23 with high specificity and affinity. The binding of guselkumab to the IL-23p19 subunit blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23-specific intracellular signaling and subsequent activation and cytokine production. Guselkumab has been studied in Phase 1, Phase 2, and ongoing Phase 3 studies for the treatment of moderate to severe plaque psoriasis in adults. Guselkumab has been approved for the treatment of adults with moderate to severe plaque psoriasis in the United States, Europe, Canada and some other countries.

1.1. Trial Objectives

Primary Objectives

The primary objective of this study is to evaluate the efficacy and safety of guselkumab in pediatric participants aged ≥6 through <18 years with chronic plaque psoriasis.

Secondary Objectives

The secondary objectives of this study are:

- To evaluate the pharmacokinetics (PK) and immunogenicity of guselkumab in pediatric participants aged ≥6 through <18 years with chronic plaque psoriasis.
- To evaluate the effect of guselkumab on the dermatologic health-related quality of life in pediatric participants aged ≥6 through <18 years with chronic plaque psoriasis.
- To evaluate maintenance of response in participants who have active treatment withdrawn.
- To evaluate the efficacy and safety of retreatment with guselkumab.
- To generate clinical usability data and use experience with the CCI in pediatric participants with chronic plaque psoriasis and a body weight <70 kg.

1.2. Trial Design

This is a Phase 3, multicenter, randomized, placebo- and active comparator-controlled study evaluating the efficacy, safety, and PK of subcutaneously administered guselkumab for the treatment of chronic plaque psoriasis in pediatric participants ≥6 to <18 years of age. The participant population will be comprised of boys and girls who have had a diagnosis of chronic plaque-type psoriasis, defined as having an Investigator's Global Assessment (IGA) ≥3, a Psoriasis Area and Severity Index (PASI) ≥12, a ≥10% body surface area (BSA) involvement, and at least one of the following: very thick lesions, clinically relevant facial, genital, or hand/ foot

involvement, PASI ≥20, >20% BSA involvement, or IGA=4. Participants must also be a candidate for phototherapy or systemic treatment of plaque psoriasis and have plaque psoriasis considered by the investigator as inadequately controlled with phototherapy and/or topical therapy after an adequate dose and duration of therapy.

The main study will be conducted in 2 parts. In Part 1, the efficacy, safety, and PK of guselkumab will be evaluated in pediatric participants during a 16-week randomized, placebo- and active comparator-controlled period followed by an uncontrolled period of withdrawal and retreatment or initiation of treatment with guselkumab through Week 52.

Part 1 of the study will be divided into Part 1a (≥12 to <18 years of age [ie, adolescents]) and Part 1b (≥6 to <12 years of age) and enroll a minimum of 90 participants. Part 1a will enroll at least 60 participants randomized in a 2:1:1 ratio to guselkumab (n=30), placebo (n=15), and etanercept (n=15). Part 1b will enroll at least 30 participants randomized in a 1:1:1 ratio to guselkumab (n=10), placebo (n=10), and etanercept (n=10). Enrollment of participants ≥6 to <12 years of age in Part 1b will commence only after:

1) All participants ≥12 to <18 years of age in Part 1a will have completed Week 16, and all available safety data have been reviewed by an independent Data Monitoring Committee (DMC), with no important safety concerns identified.
2) All available guselkumab PK data for the ≥12 to <18-year-old participants through Week 16 have been evaluated to determine if the body weight-based dose used in Part 1a has provided systemic exposure comparable to adults, or whether a revised body weight-based dose should be instituted in Part 1b.

Participants randomized to guselkumab (up to CCI or placebo will receive a weight-based dose of study intervention at Weeks 0, 4, and 12. Participants randomized to etanercept will receive a weight-based etanercept dose up to 50 mg SC weekly through Week 15. Participants randomized to etanercept will be given the option to self-administer or have their caregiver administer at home or have the study intervention administered at the study site.

At Week 16:

- Participants initially randomized to guselkumab will be treated as follows:
  - PASI 90 responders at Week 16 will not receive any additional doses of guselkumab until they lose ≥50% of their Week 16 PASI response, at which time they will be retreated with guselkumab followed by a dose 4 weeks later, and then guselkumab q8w thereafter through Week 52.
  - PASI 90 nonresponders at Week 16 will receive a placebo injection at Week 16 to maintain the blind and continue treatment with guselkumab q8w from Week 20 through Week 52.
- Participants initially randomized to placebo will be treated as follows:
  - PASI 90 responders at Week 16 will not receive any additional doses of study intervention until they lose ≥50% of their Week 16 PASI response, at which time they will initiate

treatment with guselkumab SC followed by a dose 4 weeks later, and q8w thereafter through Week 52.

  - PASI 90 nonresponders will initiate treatment with guselkumab at Weeks 16 and 20, and q8w thereafter through Week 52.

- Participants initially randomized to etanercept will receive their last administration of etanercept at Week 15. Irrespective of PASI response at Week 16, participants or their legally acceptable representative will be given the option, in consultation with the investigator, to initiate treatment with guselkumab at Week 20 followed by a dose 4 weeks later, and then q8w thereafter through Week 48, **or** discontinue from study agent administration. This option allows for participants receiving etanercept who have not attained an adequate level of efficacy or have poor tolerance for weekly injections to switch to guselkumab.

Part 2 of the main study will be an open-label, single-arm study to collect additional efficacy, safety, and PK data for pediatric participants with a continuous weight-based dose regimen of guselkumab at Weeks 0, 4, and q8w thereafter through Week 52. Participants ≥12 to <18 years of age will begin enrollment in Part 2 after the reviews of safety and PK data through Week 16 for all participants ≥12 to <18 years of age in Part 1a have been completed, and an appropriate body weight-based dose that matches adult exposure has been confirmed, or a revised body weight-based dose has been determined. Enrollment of participants ≥6 to <12 years of age into Part 2 will not occur until all participants in Part 1b have completed 16 weeks of treatment and all efficacy data through Week 16 from Part 1 have been evaluated by the sponsor, and all available safety data have been reviewed by an independent DMC. Part 2 will enroll enough additional participants to achieve a total of at least 100 participants exposed to guselkumab (ie, at least 10 participants in Part 2, with the total number dependent on the number of participants randomized in Part 1 who are exposed to guselkumab).

In Part 2 of the main study, participants will be given the option to self-administer or have their caregiver administer study injections at the study site using the appropriate presentation (either a prefilled syringe (PFS) assembled with the UltraSafe Plus™ Passive Needle Guard (PFS-U) device, designed to deliver a single, fixed dose of [redacted] or a PFS assembled with the [redacted] which delivers [redacted] Depending on body weight, participants using the [redacted] may need to administer up to 2 injections using 2 devices. Participants must be at least 12 years of age to self-administer study injections. Participants or their caregivers will be trained on proper use of the device(s) and deemed capable, as determined by a health care provider (HCP). Otherwise injections will continue to be performed by a HCP.

All participants who complete either Part 1 or Part 2 of the main study through Week 52 will be offered the opportunity to participate in an open-label LTE. Participants will be required to return to the study site every 8 weeks for safety and efficacy assessments in addition to study intervention administration. The LTE will continue until approval for guselkumab in pediatric psoriasis is obtained or the development of the guselkumab pediatric plaque psoriasis indication is discontinued.

Efficacy assessments (IGA, PASI, BSA, Children's Dermatology Life Quality Index [CDLQI], and Family Dermatology Life Quality Index [FDLQI]) will be performed according to the Schedules of Activities. Serum samples for PK and immunogenicity analyses will be collected at the timepoints shown in the Schedules of Activities.

In Part 1 of the study, participants with a PASI score increase of ≥50% from their baseline PASI score at Week 8 or Week 12 will be allowed to use a topical steroid as rescue treatment, with the exception of ultra-high potency topical steroids (eg, clobetasol propionate, halobetasol propionate) which are not allowed at any time. It is recommended that participants use no more than 60 grams of topical steroids per week. In addition, participants should be managed using the lowest possible potency and frequency of rescue topical steroid. Participants must discontinue the use of rescue topical steroids by Week 20.

Safety and tolerability will be assessed by monitoring adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests, vital signs, physical examinations, growth, development and sexual maturity, concomitant medication review, injection pain (Faces Pain Scale, linear Injection Pain Visual Analog Scale), collection of Columbia-Suicide Severity Rating Scale (C-SSRS) data, measurement of serum immunoglobulins, observations for allergic reactions, immunogenicity, and assessments for early detection of TB. An independent DMC will be commissioned for this study to review safety data.

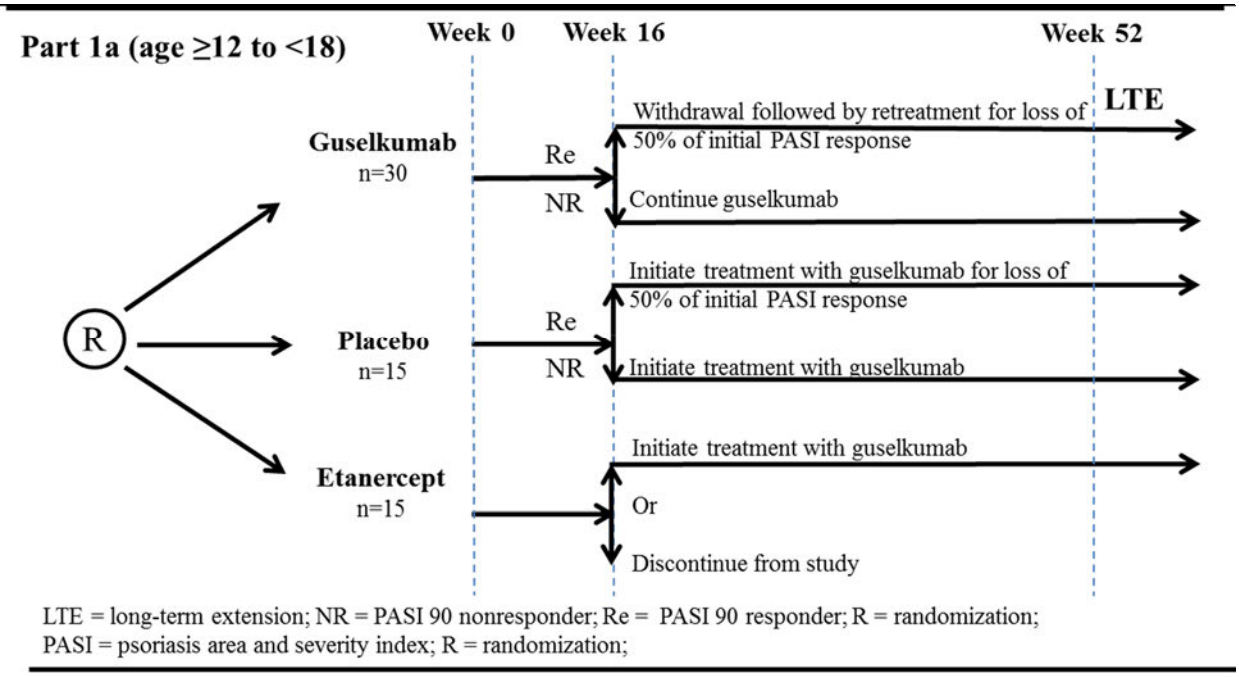
An interim analysis of the PK data will occur when all participants in Part 1a of the study complete their Week 16 visit. All available guselkumab PK data for participants ≥12 to <18 years of age through Week 16 will be evaluated via modeling and simulation, to determine if the body weight-based dose used in Part 1a provided exposure comparable with the exposure observed in adults, or whether a revised body weight-based dose should be instituted in Part 1b and Part 2 of the study.

There are 3 database locks (DBL) planned for this study at Week 16, Week 52 (end of the main study), and at the end of the study. The Week 16 DBL will occur after all participants in Part 1 of the study complete their Week 16 visit and will include only data from Part 1 of the study. The sponsor will be unblinded for Part 1 after the Week 16 DBL for Part 1 has occurred. The Week 52 DBL will occur after all participants in both Part 1 and Part 2 of the study complete their Week 52 visit. The investigators, participants, and site monitors will be unblinded after the Week 52 DBL has occurred. Additional database locks may be performed if deemed necessary.

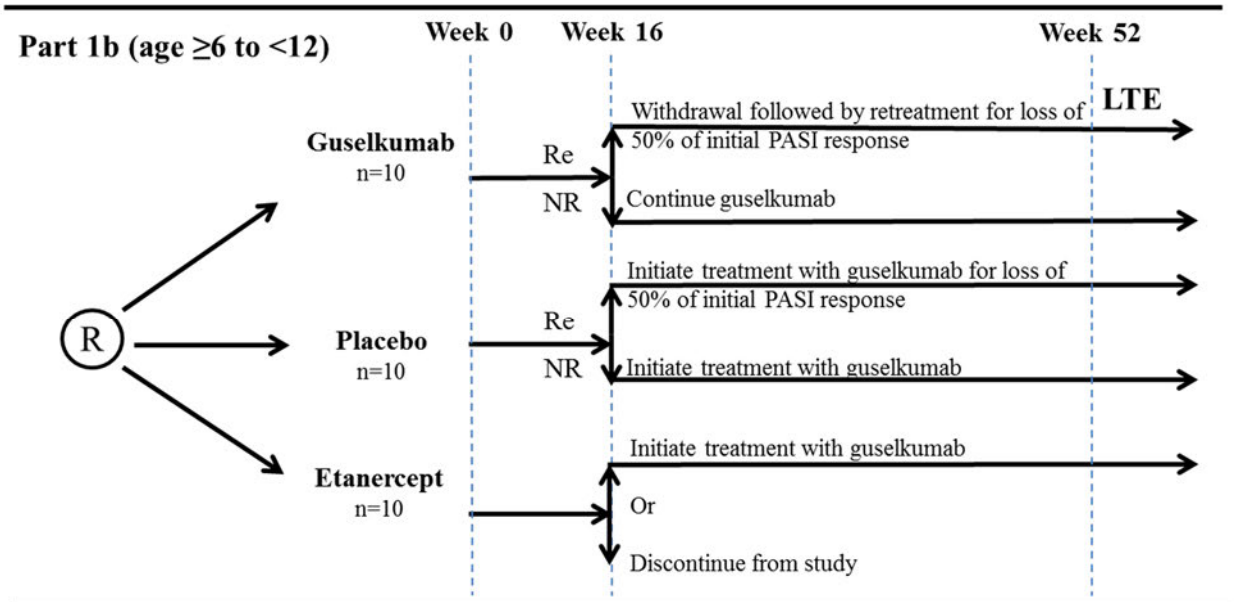
The end of the main study is defined as the timepoint when the last participant completes the Week 52 visit. The end of the complete study is defined as the timepoint when the last participant completes the last follow-up visit after guselkumab receives regulatory approval for use in pediatric patients or the sponsor discontinues development of guselkumab for the treatment of plaque psoriasis in pediatric patients.

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

Figure 1: Schematic Overview of the Study



LTE = long-term extension; NR = PASI 90 nonresponder; Re = PASI 90 responder; R = randomization; PASI = psoriasis area and severity index; R = randomization;



E = enrollment; LTE = long-term extension; NR = PASI 90 nonresponder; Re = PASI 90 responder; PASI = Psoriasis Area and Severity Index; R = randomization;
[a]The number of participants to be enrolled is dependent on the number of participants in Part 1 who are treated with guselkumab and will range from at least 10 participants to a sufficient number to ensure at least 100 participants are exposed to guselkumab.

1.3. Statistical Hypotheses for Trial Objectives

Primary Hypotheses:

The primary hypotheses are that guselkumab treatment is superior to placebo as assessed by the proportion of participants achieving an IGA score of cleared (0) or minimal (1) and the proportion of participants achieving a PASI 75 response at Week 16.

The major secondary hypotheses are that guselkumab treatment is:

- superior to placebo as assessed by the proportion of participants achieving a PASI 90 response at Week 16.
- superior to placebo as assessed by the proportion of participants achieving an IGA score of cleared (0) at Week 16.
- superior to placebo as assessed by the proportion of participants achieving a PASI 100 response at Week 16.
- superior to placebo in improving the dermatologic health-related quality of life in pediatric participants as assessed by the change from baseline in Children's Dermatology Life Quality Index (CDLQI) at Week 16.

1.4. Sample Size Justification

The assumptions for the sample size calculations for Part 1 of the study are based on the historical response rates from the adults and/or pediatric studies for placebo, guselkumab and the active comparator, etanercept. A power of at least 99% is targeted for the guselkumab versus placebo comparisons for the co-primary endpoints while a power of at least 81% is targeted for the etanercept versus placebo comparisons. Hereby, it is to be acknowledged that etanercept has already been established as an efficacious therapeutic agent for the treatment of pediatric plaque psoriasis. The etanercept active comparator arm is thus included as a "benchmark" (ie, assessment of the efficacy of etanercept compared to placebo is intended to help internally validate the overall results of the pediatric psoriasis study). No formal efficacy comparisons between etanercept and guselkumab will be performed because the relatively small number of participants does not provide sufficient power to detect a difference between these two active treatment groups.

Assumptions for Placebo Response Rates

Across completed adult studies in moderate to severe plaque psoriasis, the placebo response rates for the endpoint of PGA/IGA (0 or 1) have varied between 3.9% and 8.5%, and PASI 75 rates have varied between 3.1% and 8.1% for clinical studies of ENBREL, STELARA, guselkumab, and HUMIRA. In the completed pediatric plaque psoriasis studies (ENBREL, STELARA), the placebo response rates were slightly higher. The PGA responder (0 or 1) rates were 13% and 5.4%, while the PASI 75 rates were 11% and 10.8%, respectively. Note that PGA is a similar measure to IGA which will be used in this study. Therefore, based on consideration of all the available data, an assumption of a 13% placebo response rate for both IGA 0/1 and PASI 75 was utilized for the proposed guselkumab pediatric study.

Assumptions for Guselkumab Response Rates

The IGA responder (0 or 1) rates in the active treatment arm of the adult guselkumab Phase 3 studies (CNTO1959PSO3001 and CNTO1959PSO3002) were 85.1% and 84.1%, respectively, and the PASI 75 rates were 91.2% and 86.3%, respectively. For the proposed pediatric study, a range of the response rates from 65% to 85% for both IGA 0/1 and PASI 75 in the guselkumab treatment group were utilized.

Power for Guselkumab and Placebo Comparisons

At baseline in Part 1, approximately 40 participants (30 in Part 1a and 10 in Part 1b) will be randomized to guselkumab, and approximately 25 participants (15 in Part 1a and 10 in Part 1b) will be randomized to placebo.

As shown in Table 1, with the conservative assumptions of response rates of 65% in the guselkumab treatment group and 13% in the placebo group, the proposed 40 participants in the guselkumab group and 25 in the placebo group provide at least 99% power to detect a significant difference in the proportion of IGA responders (0 or 1) and PASI 75 responders at Week 16 separately between the guselkumab and placebo treatment groups at a 2-sided significance level of 0.05. These sample sizes are also chosen to ensure sufficient power for major secondary endpoints.

Table 1: Power to Detect a Treatment Effect for Guselkumab Based on Different Assumptions of Response Rates

Endpoint IGA Score of 0 or 1/PASI 75 at Week 16		Power
Placebo (n=25)	Guselkumab (n=40)	
13%	65%	>99%
13%	70%	>99%
13%	75%	>99%
13%	85%	>99%

IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index

Assumptions for Etanercept Response Rates

The PGA responder (0 or 1) rate in the etanercept group of the etanercept pediatric plaque psoriasis study was 53% and the PASI 75 rate was 57%. Therefore, a range of response rates from 53% to 60% for both IGA 0/1 and PASI 75 in the etanercept active comparator treatment group is utilized for the proposed pediatric study.

Power for Etanercept and Placebo Comparisons

With approximately 25 participants (15 in Part 1a and 10 in Part 1b) randomized to receive etanercept, and approximately 25 participants (15 in Part 1a and 10 in Part 1b) in the placebo group, there will be at least 81% power to detect a significant difference in the proportion of IGA responders (0 or 1) and PASI 75 responders at Week 16 separately between etanercept and placebo treatment groups at a 2-sided significance level of 0.05 (Table 2).

Table 2: Power to Detect a Treatment Effect for Etanercept Based on Different Assumptions of Response Rates

Endpoint IGA Score of 0 or 1/PASI 75 at Week 16		Power
Placebo (n=25)	Etanercept (n=25)	
13%	53%	81%
13%	55%	85%
13%	60%	92%

IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index

In Part 2, at least 10 participants will be enrolled, and will depend on the number of participants in Part 1 who are exposed to guselkumab, to ensure a total of at least 100 participants from Part 1 and Part 2 will be exposed to guselkumab in this study.

1.5. Randomization and Blinding

1.5.1. Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants in Part 1a (≥12 to <18 years of age) will be randomized in a 2:1:1 ratio to guselkumab, placebo, or etanercept and participants in Part 1b (≥6 to <12 years of age) will be randomized separately in a 1:1:1 ratio to 1 of same 3 treatment groups using computer-generated randomization schedules, prepared before the study initiation by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by pooled region (North America/Australia/Brazil [referred to as NA] and Europe[EU]). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study intervention kit(s) for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

Randomization will not be used in Part 2 of this study. All participants in Part 2 will receive open-label guselkumab.

1.5.2. Blinding

For Part 1 of the main study, the investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (eg, study drug serum concentrations, antibodies to study drug, 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 investigators should not be unblinded until the Week 52 database lock is completed. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the participant. In such cases, the investigator may in an emergency determine the identity of the treatment using the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented by the IWRS, in the appropriate section of the CRF, and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

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

One interim PK analysis is planned for this study after all participants ≥12 to <18 years of age in Part 1a have completed Week 16. This evaluation will be conducted by sponsor personnel who are otherwise not participating in the conduct of this study. Efficacy data will not be analyzed in this interim analysis.

The DMC and Statistical Support Group (SSG: an external independent team supporting analytical and operational aspects of the DMC as described in the DMC Charter) will be unblinded. The contents of the unblinded data to which the DMC and SSG have access should not be divulged, in any way, to members of the study team or to any members of the Sponsor Committee unless specifically requested by the Sponsor Committee Chairperson. The Sponsor Committee Chairperson will only request unblinded data to assess safety if absolutely needed and those individuals unblinded to the data will be documented in advance and not directly involved in study conduct. More detailed information is included in the DMC Charter.

The Sponsor will be unblinded after the last participant in Part 1 has completed their Week 16 visit and the Week 16 DBL has occurred. The investigators, participants, and sponsor site monitors will be unblinded after the last participants in Part 1 and Part 2 have completed the Week 52 visit, and the Week 52 DBL has occurred.

Blinding procedures are not applicable for participants in Part 1 who are randomized to open-label etanercept, with the exception of the blinded efficacy evaluator, and all participants in Part 2 of the main study who will receive open-label guselkumab and will not be blinded in this study.

2. GENERAL ANALYSIS DEFINITIONS

This analysis plan provides the general analysis definitions and describes the planned subject information, efficacy, safety, pharmacokinetics, and antibody analyses for the three planned DBLs at Week 16, Week 52 and end of the study.

2.1. Imputation Rules for Partial or Missing AE Dates

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the study agent start
  - The day of study agent start, if the month/year of the onset of AE is the same as month/year of the study agent start date and month/year of the AE resolution date is different
  - The day of study agent start or day of AE resolution date, whichever is the earliest, if month/year of the onset of AE and month/year of the study agent start date and month/year of the AE resolution date are same
- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the study agent start date
  - Month and day of the study agent start date, if this date is in the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the study agent start date,
  - The AE resolution date.

Completely missing onset dates will not be imputed.

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

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

Completely missing resolution dates will not be imputed.

2.2. Visit Windows

Nominal visits will be used for all by-visit analyses in the study unless otherwise specified, regardless of the scheduled visit window. The study visits scheduled should occur at the times delineated in the Time and Events Schedule of the protocol. All visits from Week 0 through Week 52 should occur within ±7 days of the scheduled visit. If a study visit occurs outside this window, the sponsor should be consulted about how the subject should resume his/her normal dosing schedule relative to the baseline visit (Week 0). The other follow-up study visit should occur within ±14 days of the scheduled visit.

2.3. Pooling Algorithm for Analysis Centers

Study centers will be pooled by region (NA, EU) as a stratification factor for the efficacy analyses if appropriate.

2.4. Analysis Sets

2.4.1. Efficacy Analysis Sets

2.4.1.1. Full Analysis Set

Full Analysis Set for Part 1

The efficacy analysis set for Part 1 of the study will be based upon the Full Analysis Set (FAS) which includes all randomized subjects in Part 1a and Part 1b. In the efficacy analyses, subjects will be analyzed according to their assigned treatment group regardless of their actual treatment received.

Depending on the endpoints, selected secondary efficacy analyses will be performed on subsets of all randomized subjects:

- PASI 90 responders withdrawn from study agent at Week 16
- PASI 90 responders withdrawn from study agent at Week 16 and later retreated with guselkumab
- PASI 90 non-responders at Week 16 who continued guselkumab treatment
- Etanercept subjects who crossed over to receive treatment of guselkumab

Full Analysis Set for Part 2

The efficacy analyses for Part 2 of the study will be based upon the Full Analysis Set which includes all subjects enrolled in Part 2.

Full Analysis Set for LTE

The efficacy analyses for Long Term Extension will be based upon the Full Analysis Set which includes all subjects who entered into the LTE period.

2.4.1.2. Per Protocol Analysis Set

The efficacy analysis for the co-primary endpoints will also be performed based on the per protocol analysis set. The per protocol population includes subjects in full analysis set except those

- who did not meet the inclusion criterion 2 in the protocol as listed below:

  Have a diagnosis of chronic plaque-type psoriasis for at least 6 months (with or without PsA), prior to first administration of study intervention, defined as having at screening and baseline:

  - IGA ≥3 **and**
  - PASI ≥12 **and**
  - ≥10% BSA involvement **and**

  at **least one** of the following:

- very thick lesions **or**
- clinically relevant facial, genital, or hand/ foot involvement **or**
- PASI≥20 **or**
- >20% BSA involvement **or**
- IGA=4

- who violated the exclusion diagnosis criteria 1 or 2:
  - Currently have nonplaque forms of psoriasis (eg, erythrodermic, guttate, or pustular).
  - Have current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium).

- who violated the concomitant or previous psoriasis medical therapies-related exclusion criteria (9, 11-19) as listed below:
  - Has previously received guselkumab or etanercept.
  - Has received any anti-TNFα biologic therapy (with the exception of etanercept, see exclusion 9) within the previous 3 months before the first administration of study intervention.
  - Has received any therapeutic agent directly targeted to IL-12/23, IL-17, or IL-23 within 6 months of the first administration of study intervention (including but not limited to ustekinumab, tildrakizumab, secukinumab, ixekizumab, risankizumab, or brodalumab).
  - Has received natalizumab, efalizumab, or agents that deplete B or T cells (eg, rituximab, alemtuzumab, abatacept, anakinra, or visilizumab) within 12 months of screening, or, if after receiving these agents, evidence is available at screening of persistent depletion of the targeted lymphocyte population.
  - Has received any systemic immunosuppressants (eg, methotrexate [MTX], azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, and tacrolimus) within 4 weeks of the first administration of study intervention.
  - Has received phototherapy or any systemic medications/treatments that could affect psoriasis or IGA evaluations (including, but not limited to, oral or injectable corticosteroids, retinoids, 1,25-dihydroxy vitamin D3 and analogues, psoralens, sulfasalazine, hydroxyurea, fumaric acid derivatives, herbal treatments, or traditional Taiwanese, Korean, or Chinese medicines) within 4 weeks of the first administration of study intervention.

- Has used topical medications/treatments that could affect psoriasis or IGA evaluations (including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, pimecrolimus, tacrolimus, or topical traditional Taiwanese, Korean, or Chinese medicines) within 2 weeks of the first administration of study intervention.
- Is currently receiving lithium, antimalarials, or intramuscular (IM) gold, or has received lithium, antimalarials, or IM gold within 4 weeks of the first administration of study intervention.
- Has received an experimental antibody or biologic therapy within the previous 6 months, or received any other experimental therapy or new investigational agent (topical or systemic) within 30 days or 5 half-lives (whichever is longer) of any study intervention administration or is currently enrolled in another study using an investigational agent or procedure.

- who did not complete the specified exposure to study agent as outline below
  - Subject randomized to guselkumab at Week 0 but did not receive all scheduled guselkumab administrations (ie, Week 0, Week 4, and Week 12), or received one or more extra guselkumab administrations.
  - Subject randomized to etanercept at Week 0 but missed two or more scheduled etanercept administrations (weekly dose through Week 15), or received one or more extra etanercept administrations.

Subjects who discontinued the study agent due to unsatisfactory therapeutic effect or an adverse event (AE) of worsening of psoriasis, or subjects who started prohibited medications and continued receiving study agents prior to Week 16 will be included in the per protocol analysis and the treatment failure rules specified in Section 5.1.3.3 will apply. Subjects who used rescue medication will also be included in the per protocol analysis and the rescue treatment rules specified in section 5.1.3.5 will apply.

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

2.4.2. Safety Analysis Set

Safety analyses for both Part 1 and Part 2 will be performed on the safety analysis set, which is defined as all treated subjects who received at least 1 injection of study agent (partial or complete). For the safety analyses in Part 1, subjects will be analyzed according to the actual treatment received during the study irrespective of the treatment assigned at randomization.

Safety analyses for LTE will be performed on the safety analysis set including all subjects who entered into LTE and received at least 1 injection at or after Week 52.

2.4.3. Pharmacokinetics Analysis Set

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

2.4.4. Immunogenicity Analysis Set

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

In both PK and immunogenicity analyses, subjects will be analyzed according to the actual treatment received.

2.5. Definition of Subgroups

To evaluate the consistency of efficacy based on demographic characteristics, baseline disease characteristics, and psoriasis medication history, subgroup analyses will be performed for the co-primary endpoints. The subgroups include, but are not limited to, the following:

Baseline demographics:

- Sex (male, female)
- Race
- Region (North America/Australia/Brazil, Europe)
- Baseline Age (≥ 6 to <12 years, ≥ 12 to <18 years)
- Baseline weight (<70 kg, ≥70 kg)

Baseline disease characteristics:

- Age at diagnosis (years) (< 8, ≥ 8)
- Psoriasis disease duration (years) (< 3, ≥ 3)
- Baseline PASI (<20, ≥20)
- Baseline IGA (<4, =4)
- Baseline BSA (<20%, ≥20%)
- Psoriatic arthritis (Yes, No)
- Baseline CDLQI (< 10, ≥ 10)

Psoriasis medication history:

- Phototherapy (ultraviolet B light [UVB] or psoralen and ultraviolet A light therapy [PUVA])
  - Never used
  - Ever used
- Non-biologic systemics (PUVA, MTX, cyclosporine, acitretin, apremilast, or tofacitinib)
  - Never used
  - Ever Used

- Biologics (infliximab, alefecept, efalizumab, ustekinumab, briakinumab, secukinumab, ixekizumab, brodalumab, or adalimumab)
  - Never used
  - Ever Used
- Non-biologic systemics or biologics (as defined above)
  - Never used
  - Ever used

2.6. Study Day

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

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

2.7. Baseline

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

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

3.1. Interim Analysis

One interim analysis is planned for this study after all participants ≥12 to <18 years of age in Part 1a have completed Week 16. All available guselkumab PK data for participants ≥12 to <18 years of age through Week 16 will be evaluated via modeling and simulation, to determine if the body weight-based dose used in Part 1a provided exposure comparable to adults, or whether a revised body weight-based dose should be instituted in Part 1b. This evaluation will be conducted by sponsor personnel who are otherwise not participating in the conduct of this study. Efficacy data will not be analyzed in the interim analyses and no adjustment will be made for the significance level.

Details of the interim analyses are included in a separate interim analysis plan.

3.2. Data Monitoring Committee

The DMC will be an independent committee of 3 members and will include individuals with expertise in pediatric dermatology, and biostatistics. None of the members will be participating as investigators in the study. The major function of this committee will be to monitor the safety of the study intervention. The DMC will periodically review tabulated safety summaries and any additional safety data that the DMC may request during the conduct of the study. Prior to any DMC review, the DMC charter will define and document the content of the safety summaries, the DMC's role and responsibilities, and the general procedures (including communications).

Prior to enrollment of participants ≥6 to <12 years of age in Part 1b and enrollment of participants ≥12 to <18 years of age into Part 2, the DMC will review all available safety data once all participants enrolled in Part 1a of the study have completed their Week 16 visit or discontinued from the study, and provide a recommendation as to whether the sponsor can initiate enrollment of Part 1b and Part 2. Additionally, prior to enrollment of participants ≥6 to <12 years of age into Part 2, the DMC will review all available safety data once all participants in Part 1b have completed 16 weeks of treatment or discontinued from the study, and provide a recommendation as to whether enrollment of participants ≥6 to <12 years of age into Part 2 can be initiated.

Details of the DMC safety reviews are included in a separate DMC Charter and DMC SAP. The DMC SAP contains definitions of analysis sets, derived variables, scope and objects of the DMC, data-cutoff points, statistical methods and output to be produced for the safety reviews as required by the DMC Charter. Additionally, a dedicated DMC Data Presentation Specifications (DPS) document details output and programming specifications.

4. SUBJECT INFORMATION

Unless otherwise noted, the subject information analyses will be performed based on the full analysis sets for Part 1 and Part 2 of the study. The number of subjects in each part of the study and in each analysis set will be summarized by assigned treatment group and overall. In addition, the distribution of subjects by region, country, and site will be presented.

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

4.1. Demographics and Baseline Characteristics

4.1.1. Demographics

Table 3 presents a list of the demographic variables that will be summarized by treatment group, and overall for the full analysis set in Part 1 and Part 2 of the study.

Age will be calculated as (date of informed consent – date of birth + 1) / 365.25 in units of years.

BMI will be calculated as weight/height^2 with units of kg/m^2.

Table 3: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Weight (kg)	
Height (cm)	
BMI (kg/m^2)	
Categorical Variables:	

Age (≥ 6 to <12 years, ≥ 12 to <18 years)	Frequency distribution with the number and percentage of subjects in each category.
Weight (<70 kg, ≥70 kg)	
Sex (male, female)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	

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

In addition, the histogram plots for the distributions of age at baseline will be provided.

4.1.2. Baseline Characteristics

Psoriasis baseline disease characteristics (i.e., psoriasis disease duration [years], age at diagnosis [years], BSA [%], psoriatic arthritis, baseline IGA score, baseline PASI score [0-72], baseline FDLQI, and baseline CDLQI) will be summarized by treatment group for Part 1 and Part 2.

4.2. Disposition Information

Disposition information will be based upon the full analysis set. The number of subjects in the following disposition categories will be summarized for the periods through Week 16 and through Week 52 for Part 1, for the period through Week 52 for Part 2, and for the period of the LTE:

- Subjects randomized (Part 1 only)
- Subjects treated
- Subjects who completed the study
- Subjects who discontinued study agent and reasons for discontinuation
- Subjects who terminated study prematurely and reasons for termination

Listings of subjects will be provided for the following categories:

- Subjects who discontinued study agent
- Subjects who terminated study prematurely
- Subjects who were unblinded during the study period (Part 1 only)
- Subjects who were randomized but did not receive study agent (Part 1 only) and subjects who enrolled but did not receive study agent (Part 2 only)
- Subjects who met treatment failure criteria and reason
- Subjects who used rescue medication (Part 1 only)

4.3. Treatment Compliance

For Part 1, study agent compliance will be summarized descriptively for the full analysis set. The number of subjects by randomized treatment versus actual treatment will be presented in a summary table.

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

4.4. Extent of Exposure

The exposure data will be summarized through Week 16, through Week 52, and through LTE. The number of active study agent injections, and the cumulative dose of study agent will be summarized by treatment group for the safety analysis set.

In addition, the number of subjects who were withdrawn and retreated with guselkumab after Week 16, and the number of subjects who initiated guselkumab after Week 16 will be summarized for Part 1.

4.5. Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or results of the clinical trial. Subjects with major protocol deviations will be identified prior to database lock and the subjects with major protocol deviations will be summarized by category.

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

The above summaries will be presented through Week 16 and through Week 52 for Part 1 by randomized treatment group, through Week 52 for Part 2 of the study, and through the end of study for subjects who continued in the LTE period. Subjects with major protocol deviations will also be listed.

4.6. Prior and Concomitant Medications

Subjects' prior psoriasis medication history with topical agents, phototherapy, non-biologic systemic therapies, and biologic medications will be summarized by treatment group for the full analysis set for Part 1 and Part 2 of the study. See Section for lists of medications in each category. In addition, reasons for which subjects discontinued previous systemic therapies (contraindication, inadequate response, intolerance [ie, AEs], or other) will be summarized by treatment group.

The number of subjects who received concomitant treatment with a moisturizer for psoriasis will also be summarized through Week 16 for Part 1.

Subjects who received the following concomitant medications will be listed:

- Corticosteroids (intralesional, IV or oral) for indications other than psoriasis and/or psoriatic arthritis
- Intra-articular corticosteroids

5. EFFICACY

Unless otherwise stated, efficacy data summaries will be provided for the full analysis set for each part. The Fisher's exact test, stratified by age group and region, will be used to compare the proportion of subjects responding to treatment if appropriate. Continuous response parameters (i.e. change from baseline in CDLQI) will be compared using Mixed Model Repeat Measurement (MMRM) analysis with factors of treatment, region, age group, baseline, visit, baseline by visit and treatment by visit; or an analysis of covariance (ANCOVA) model, adjusting for baseline value, age group, and region. If the normality assumption is violated, non-parametric methods will be used as appropriate. All statistical testing will be performed at a 2-sided significance level of 0.05.

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

5.1. Analysis Specifications

5.1.1. Level of Significance

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

5.1.1.1. Multiplicity Adjustment for Testing Procedures

US-FDA specific primary and major secondary endpoints and analyses are defined in Section 5.4. Globally (i.e., regions other than the United States), the following primary and major secondary endpoints will be tested. There are 2 co-primary endpoints in this study:

- The proportion of subjects who achieve an IGA score of cleared (0) or minimal (1) at Week 16
- The proportion of subjects who achieve a PASI 75 response at Week 16

Both of the co-primary endpoint analyses will be compared between the guselkumab treatment group and the placebo group and tested at a 2-sided α-level of 0.05. If one of the comparisons is not significant at the 2-sided α-level of 0.05, the co-primary endpoints will be considered not significant.

In addition, there are 4 major secondary endpoints in this study to be compared between the guselkumab group and the placebo group:

- The proportion of subjects who achieve a PASI 90 response at Week 16.
- The proportion of subjects who achieve an IGA score of cleared (0) at Week 16.
- The proportion of subjects who achieve a PASI 100 response at Week 16.
- The change from baseline in CDLQI at Week 16

In order to control the overall Type 1 error rate, the co-primary analyses and major secondary analyses will be tested in a fixed sequence as ordered above. That is, the analyses of the major secondary endpoints will be performed only if both primary analyses are significant, and will be performed in the fixed sequence testing approach, as specified above. If a given comparison between the guselkumab treatment group and the placebo group is not significant at the 2-sided α-level of 0.05, the remaining treatment group comparisons in this sequence will be considered not significant and will be considered as supportive analyses.

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

5.1.2.1. Investigator's Global Assessment

The Investigator's Global Assessment (IGA) documents the investigator's assessment of the subject's psoriasis at a given time point. Overall lesions are graded for induration, erythema, and scaling. The patient's psoriasis is assessed as cleared (0), minimal (1), mild (2), moderate (3), or severe (4).

Efficacy endpoints related to the IGA score are defined below:

IGA cleared responder

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

IGA cleared or minimal responder

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

IGA mild or better responder

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

5.1.2.2. Psoriasis Area and Severity Index

The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. In the PASI system, the body is divided into 4 regions: the head, trunk, upper extremities, and lower extremities. Each of these areas is assessed separately for the percentage of the area involved, which translates to a numeric score that ranges from 0 (indicates no involvement) to 6 (90%-100% involvement), and for erythema, induration, and scaling, which are each rated on a scale of 0 to 4. The PASI produces a numeric score that can range from 0 (no psoriasis) to 72. A higher score indicates more severe disease.

Efficacy endpoints related to the PASI score are defined below:

PASI 50 Responder

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

PASI 75 Responder

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

PASI 90 Responder

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

PASI 100 Responder

Subjects with 100% improvement in PASI from baseline (PASI score=0) will be considered PASI 100 responders.

Loss of PASI 90 Response

Defined as <90% improvement in PASI from baseline after Week 16 in a participant who had achieved ≥90% improvement in PASI from baseline at Week 16.

Loss of 50% of PASI Improvement

Defined as a loss of ≥50% of the improvement in PASI at Week 16 after treatment is withdrawn.

5.1.2.3. Body Surface Area

The percentage of a participant's total body surface area affected by psoriasis will be assessed.

5.1.2.4. Children Dermatology Life Quality Index

The Children Dermatology Life Quality Index (CDLQI) 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 an adapted version of DLQI. The CDLQI, a 10-item questionnaire has a 4 item response option and a recall period of 1 week. The instrument is designed for use in children (ie, participants from 4 to 16 years of age), is self-explanatory and can be simply handed to the participant who is asked to fill it in with the help of the child's parent or caregiver. In addition to evaluating overall quality of life, the CDLQI can be used to assess 6 different aspects that may affect quality of life: symptoms and feelings, leisure, school or holidays, personal relationships, sleep, and treatment. The scoring of each question is as follows:

Very much	Scored 3
Quite a lot	Scored 2
Only a little	Scored 1
Not at all	Scored 0
Question unanswered	Scored 0
Question 7: Prevented school	Scored 3

The CDLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. A higher score indicates more severe disease. The 6 CDLQI components scores are calculated as follows:

Symptoms and feelings	Questions 1 and 2	Score maximum 6
Leisure	Questions 4, 5 and 6	Score maximum 9
School or holidays	Questions 7	Score maximum 3
Personal relationships	Questions 3 and 8	Score maximum 6
Sleep	Questions 9	Score maximum 3
Treatment	Questions 10	Score maximum 3

5.1.2.5. Family Dermatology Life Quality Index

The FDLQI is a dermatology-specific quality of life instrument for the family members of patients having any skin disease. It has 10 items asking the family members/partners about the impact of a patient's skin disease on different aspects of their quality of life (e.g. emotional, physical well-being, relationships, social life, leisure activities, burden of care, job/study, housework and expenditure). The frame of reference for items is over the last 1 month. Each item has a four-point response option, where Not at all/Not relevant = 0; A little = 1; Quite a lot = 2; and Very much = 3. The scores of individual items (0–3) are added to give a total scale score that ranges from 0 to 30; a higher score indicates greater impairment of quality of life. The FDLQI is designed to be used as an additional outcome measure in conjunction with the CDLQI or any other patient-completed questionnaire. This instrument should be completed by a participant's primary care-giver.

5.1.3. Data Handling Rules

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

5.1.3.1. Partial Component Score

PASI and IGA

For missing component scores in IGA and PASI data, the IGA and PASI total score will not be calculated and the value is missing. The data handling rules described in Section 5.1.3.3, 5.1.3.5, and 5.1.3.6 would apply.

CDLQI

For a partially answered questionnaire (eg, not all 10 answers in the CDLQI questionnaire were available) or incorrectly completed questionnaire in CDLQI, the following data handling rules would apply before applying the treatment failure rules and early escape rules:

- If one question is left unanswered, this question will be scored 0. The total score and each of the 6 component scores will then be calculated.
- If two or more questions are left unanswered, the total score and the affected component scores will be set to missing.

If both parts of question 7 are completed, the higher of the two scores should be used.

FDLQI

For a partially answered questionnaire in FDLQI, the following data handling rules would apply before applying the treatment failure rules and early escape rules:

- If one question is left unanswered, this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
- If two or more questions are left unanswered the questionnaire is not scored.
- If two or more response options are ticked, 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.

5.1.3.2. Treatment Failure Criteria

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

The particular protocol-prohibited medications/therapies include:

Topical Therapies:

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

Phototherapy or Systemic Therapies:

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

5.1.3.3. Treatment Failure Rules

A subject who meets one or more treatment failure criteria specified in Section 5.1.3.2 will be considered a treatment failure from that point onward. The baseline values will be used for all directly measured endpoints regardless of the actual measurements. Zero will be assigned to improvement and percent improvement, and non-responder status will be assigned to binary response variables.

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

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

5.1.3.4. Rescue Treatment

In Part 1 of the study, participants with a PASI score increase of ≥50% from their baseline PASI score at Week 8 or Week 12 will be allowed to use a topical steroid as rescue treatment up until Week 16, with the exception of ultra-high potency topical steroids (eg, clobetasol propionate, halobetasol propionate) which are not allowed at any time. It is recommended that participants use no more than 60 grams of topical steroids per week. In addition, participants should be managed using the lowest possible potency and frequency of rescue topical steroid. Participants must discontinue the use of rescue topical steroids by Week 20.

5.1.3.5. Rescue Treatment Rules

Subjects who use a low to high potency topical steroid starting at Week 8 or Week 12 as a result of being eligible for rescue treatment will be considered as nonresponders for binary endpoints and zero (no change from baseline) will be assigned to continuous outcomes from that point onward through Week 16. The analysis at and after Week 20 will use the observed data without imputation. Treatment failure rules will be applied if subjects continue to use or initiate treatment of a low to high potency topical steroid after Week 20.

5.1.3.6. Missing Data Imputation

After the treatment failures and rescue treatment rules are applied, the remaining missing data will be handled as follows for all of the efficacy analyses including the analyses at key visits (eg Week 16) and over time through Week 52:

- Non-responder imputation will be applied for binary efficacy endpoints.
- No imputation will be performed for missing post baseline continuous values. The statistical model (ie, MMRM) will adjust for missing data.

For the analyses related to the time to event endpoints during the withdrawal and retreatment period, missing PASI score after the Week 16 visit will not be imputed and the value will remain as missing after applying treatment failure rules.

For the efficacy analyses that evaluate the efficacy of retreatment or initiation of guselkumab, after the treatment failure rules are applied, no imputation will be performed for missing data following the retreatment or initiation of guselkumab.

For the efficacy analyses through LTE period, no treatment failures and no missing data imputation will be performed, and the analyses will be based on observed data.

5.2. Primary Efficacy Endpoints

5.2.1. Definition

There are 2 co-primary endpoints in this study: the proportion of subjects who achieve an IGA score of cleared (0) or minimal (1) at Week 16 and the proportion of subjects who achieve a PASI 75 response at Week 16. Refer to Section 5.1.2.1 and 5.1.2.2 for the definition of IGA and PASI responses.

5.2.2. Primary Estimand

The composite estimand assesses the treatment effects not only based on the variable measurements, but also based on intercurrent event defined in TF criteria and rescue treatment criteria. If a subject had to use rescue medication or meet TF criteria, the subject will be a non-responder for co-primary endpoints. This estimand acknowledges that subjects meeting the TF criteria or using rescue treatment have an unfavorable outcome.

Population: subjects with chronic plaque psoriasis who are randomized to guselkumab or placebo in Part 1 of the study.

Variable: the endpoint is defined as proportion of subjects who achieve an IGA score of cleared (0) or minimal (1) at Week 16 or the proportion of subjects who achieve a PASI 75 response at Week 16. Non-responder status is assigned after meet TF or rescue treatment criteria.

Intercurrent Events: the intercurrent event is captured through the variable definition.

Population-level summary: difference in response proportions between guselkumab group and placebo group.

5.2.3. Analysis Methods

These 2 co-primary endpoints will be compared between the guselkumab group and the placebo group. In these primary efficacy analyses, data from all randomized subjects will be analyzed according to their assigned treatment group (ie, full analysis set). The number and proportion of subjects who achieve an IGA score of cleared (0) or minimal (1) and a PASI 75 response at Week 16 will be summarized for each treatment group respectively. The differences in proportions between guselkumab and placebo treatment groups with exact 95% confidence intervals will also be presented.

To address the primary objective, a 2-sided (α=0.05) Fisher's exact test, stratified by age group ($\geq$ 6 to <12 years, $\geq$ 12 to <18 years) and pooled region (NA, EU), will be used for the co-primary endpoints. The study will be considered positive if the guselkumab group is significantly different from the placebo group for both co-primary endpoints. Both co-primary endpoints will be tested at a 2-sided α-level of 0.05. If one of the comparisons is not significant, the co-primary endpoints will be considered not significant.

In addition, the comparison between etanercept and placebo for the co-primary endpoints will be performed using Fisher's exact test, stratified by age and region, and nominal p-values will be reported.

5.2.4. Data Handling

Subjects who meet treatment failure criteria specified in Section 5.1.3.2 or rescue treatment criteria in Section 5.1.3.4 prior to Week 16 will be considered not to have achieved an IGA score of cleared (0) or minimal (1) or a PASI 75 response at Week 16. In addition, subjects with a missing IGA or PASI score at Week 16 or who do not return for evaluation at Week 16 will be considered not to have achieved the respective endpoint at Week 16.

5.2.5. Sensitivity Analysis

To assess the robustness of the co-primary endpoint analysis results, two sensitivity analyses will be conducted for the co-primary endpoints as specified below.

Sensitivity Analysis 1

For subjects who have missing IGA or PASI score at Week 16, the score will not be imputed. That is, the Fisher's exact test, stratified by age group and region, will be used for the co-primary endpoints will be performed using observed data after applying treatment failure rules (as defined in Section 5.1.3.2) and rescue treatment rules (as defined in Section 5.1.3.5).

Sensitivity Analysis 2

The second sensitivity analysis will be performed using multiple imputations by fully conditional specification (MI FCS), after applying treatment failure rules (as defined in Section 5.1.3.2) and rescue treatment rules (as defined in Section 5.1.3.5). The missing data of the IGA score of 0/1 and PASI 75 responses will be imputed with FCS logistic regression with treatment group, region, and age group in the model with 500 imputation and seed =36789. The proportion of IGA score of 0/1 and PASI 75 responses at Week 16 will be compared between the guselkumab and the placebo group combining the Mantel-Haenszel estimates stratified by region and age group obtained from the multiple imputation datasets using PROC MIANALYZE.

5.2.6. Subgroup Analysis

For each of the subgroups defined in Section 2.5, the proportion of subjects achieving an IGA score of 0/1 and a PASI 75 response at Week 16 by treatment group will be summarized. Differences in the proportion and the associated exact 95% confidence intervals (CI) for the differences will be provided.

In addition, the proportion of subjects achieving an IGA score of 0/1 and the proportion of PASI 75 responders at Week 16 by region, country and investigator site will be summarized.

5.2.7. Per Protocol Analyses

Per protocol analyses will be performed for the co-primary endpoints, similar to the primary analyses but based on the per protocol analysis set as defined in Section 2.4.1.2.

5.3. Major Secondary Endpoints

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

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

5.3.1. Definition

There are 4 major secondary endpoints in this study to be compared between the guselkumab group and the placebo group:

- The proportion of participants achieving a PASI 90 response at Week 16.
- The proportion of participants achieving an IGA score of cleared (0) at Week 16.
- The proportion of participants achieving a PASI 100 response at Week 16.
- The change from baseline in CDLQI at Week 16.

5.3.2. Major Secondary Estimands

5.3.2.1. Estimands for Binary Endpoints of IGA or PASI Responses

Population: subjects with chronic plaque psoriasis who are randomized to guselkumab or placebo in Part 1 of the study.

Variable: the endpoint is defined as the proportion of subjects who achieve a PASI 90 response at Week 16, the proportion of subjects who achieve an IGA score of cleared (0) at Week 16, or the proportion of subjects who achieve a PASI 100 response at Week 16. Non-responder status is assigned after a subject meets TF or rescue treatment criteria.

Intercurrent Events: the intercurrent event is captured through the variable definition.

Population-level summary: difference in response proportions between guselkumab group and placebo group.

5.3.2.2. Estimands for Continuous Endpoint of CDLQI

5.3.2.2.1. Composite Strategy

The composite strategy assesses the treatment effects not only based on the variable measurements, but also based on intercurrent events defined in TF and rescue treatment criteria.

Population: subjects with chronic plaque psoriasis who are randomized to guselkumab or placebo in Part 1 of the study.

Variable: the endpoint is defined as the change from baseline in CDLQI at Week 16. Zero change is assigned after a subject meet TF or rescue treatment criteria.

Intercurrent Events: the intercurrent event is captured through the variable definition.

Population-level summary: difference in LSmean between guselkumab group and placebo group.

5.3.2.2.2. Treatment Policy Strategy

The treatment policy strategy is to use all observed data collected for the endpoint, regardless of the occurrence of the intercurrent event (i.e. TF or rescue treatment).

Population: subjects with chronic plaque psoriasis who are randomized to guselkumab or placebo in Part 1 of the study.

Variable: the endpoint is defined as the change from baseline in CDLQI at Week 16.

Intercurrent Events: regardless of the intercurrent event of meeting TF or rescue treatment criteria.

Population-level summary: difference in LSmean between guselkumab group and placebo group.

5.3.3. Analysis Methods

For categorical response parameters (PASI 90, IGA score of 0, PASI 100 response) at Week 16, the Fisher's exact test, stratified by age group and region, will be used to compare the proportion of participants responding to treatment between the guselkumab and placebo group. The p-values and the differences in proportions with exact 95% confidence intervals will be presented.

The change from baseline in CDLQI at Week 16 will be analyzed using a Mixed Model for Repeated Measures (MMRM) model to test the difference between treatment groups and adjust for missing data. The independent variables for this model may include treatment group (guselkumab, placebo, and etanercept), region (NA, EU), age group (6 - <12 years, 12- <18 years), baseline CDLQI score, visit week, an interaction of baseline CDLQI score and visit, and an interaction of treatment and visit as appropriate. An unstructured (UN) variance-covariance matrix for repeated measures within a subject will be used. The treatment difference between guselkumab and the placebo group will be estimated by difference in LSmeans. The 95% CIs for difference in LSmean between the groups and p-values will be calculated.

In addition, the comparison between etanercept and placebo for the major secondary endpoints will be performed and nominal p-values will be reported.

5.3.4. Data Handling

Data handling rules specified in Section 5.2.4 will be applied to the major secondary analyses. After applying the treatment failure or rescue treatment rules, the remaining missing data will be imputed. Zero will be assigned to change from baseline in CDLQI score, and non-responder status will be assigned to PASI 90, IGA 0/1, and PASI100 response variables.

5.3.5. Sensitivity Analysis

To assess the robustness of the major secondary endpoint analysis results, sensitivity analyses will be conducted as specified in .Table 4

Table 4: Sensitivity Analyses for Major Secondary Endpoints

Endpoint	Estimand	Methods
The proportion of subjects who achieve a PASI 90 response at Week 16	Sensitivity analysis 1	Observed data after apply TF and rescue treatment rule
	Sensitivity analysis 2	Multiple imputation with FCS logistic regression (similar to the sensitivity analysis for the primary endpoint with the same seed and the number of imputations)

The proportion of subjects who achieve an IGA score of cleared (0) at Week 16	Sensitivity analysis 1	Observed data after apply TF and rescue treatment rule
	Sensitivity analysis 2	Multiple imputation with FCS logistic regression (similar to the sensitivity analysis for the primary endpoint with the same seed and the number of imputations)
The proportion of subjects who achieve a PASI 100 response at Week 16	Sensitivity analysis 1	Observed data after apply TF and rescue treatment rule
	Sensitivity analysis 2	Multiple imputation with FCS logistic regression (similar to the sensitivity analysis for the primary endpoint with the same seed and the number of imputations)
The change from baseline in CDLQI at Week 16	Sensitivity analysis 1	After apply TF and rescue treatment rule, multiple imputation with Markov Chain Monte Carlo (MCMC) algorithm will be used, which assumes that all the variables in the imputation model have a joint multivariate normal distribution
	Supplementary analysis	MMRM model will be used to test the difference between treatment groups based on observed data. No TF or rescue treatment rule apply.

5.4. US-FDA specific Primary and Major Secondary Efficacy Analyses

5.4.1. Multiplicity Adjustment for Testing Procedures

The US-FDA specific co-primary endpoints are:

- The proportion of subjects who achieve an IGA score of cleared (0) or minimal (1) at Week 16
- The proportion of subjects who achieve a PASI 90 response at Week 16

Both of the US-FDA specific co-primary endpoint analyses will be compared between the guselkumab treatment group and the placebo group and tested at a 2-sided α-level of 0.05. If one of the comparisons is not significant at the 2-sided α-level of 0.05, the co-primary endpoints will be considered not significant.

In addition, the following US-FDA specific major secondary endpoints will be compared between the guselkumab group and the placebo group:

- The proportion of subjects who achieve a PASI 75 response at Week 16.
- The proportion of subjects who achieve an IGA score of cleared (0) at Week 16.
- The proportion of subjects who achieve a PASI 100 response at Week 16.
- The change from baseline in CDLQI at Week 16

In order to control the overall Type 1 error rate, the US-FDA specific co-primary analyses and major secondary analyses will be tested in a fixed sequence as ordered above. That is, the analyses

of the major secondary endpoints will be performed only if both primary analyses are significant and will be performed in the fixed sequence testing approach, as specified above. If a given comparison between the guselkumab treatment group and the placebo group is not significant at the 2-sided α-level of 0.05, the remaining treatment group comparisons in this sequence will be considered not significant and will be considered as supportive analyses.

5.4.2. Analysis Methods

For US-FDA specific primary and major secondary endpoints, the proportion of participants responding to treatment will be compared between the guselkumab and placebo group in the same manner as the global primary and major secondary endpoints. Table 5 presents the differences between the US-FDA specific primary and major secondary endpoints to the global endpoints. The same endpoints are not listed.

Table 5: Differences between US-FDA specific primary and major secondary endpoints to global endpoints

	Global endpoints	**US-FDA specified endpoints**
Co-primary	PASI 75 response at Week 16 is one of the co-primary endpoints.	PASI 90 response at Week 16 is one of the co-primary endpoints.
Major secondary	PASI 90 response at Week 16 is the first major secondary endpoint.	PASI 75 response at Week 16 is the first major secondary endpoint.
Analysis methods	Fisher's exact test, stratified by age group and pooled region, will be used to compare the PASI 90 and PASI 75 response rates between treatment groups.	Same
Sensitivity analyses	1. Observed data after apply TF and rescue treatment rule. 2. Multiple imputation with FCS logistic regression.	Same

5.5. Other Efficacy Variables)

Other secondary efficacy endpoints include

- Investigator's Global Assessment (IGA)
- Psoriasis Area and Severity Index (PASI)
- Percent of body surface area with psoriasis skin involvement (BSA)
- Children's Dermatology Life Quality Index (CDLQI)
- Family Dermatology Life Quality Index (FDLQI)

5.5.1. Definition

Refer to Section 0 for the definitions of the other efficacy endpoints described in the following section.

5.5.2. Analysis Methods

5.5.2.1. Secondary Analyses for Participants Randomized in Part 1

For Part 1, the other secondary efficacy analyses described in this section below will be based on the full analysis set combining subjects from Part 1a and Part 1b. All statistical testing will be performed at the 2-sided 0.05 significance level. Nominal p-values will be presented. The Fisher's exact test, stratified by age and region, will be used to compare the proportion of participants responding to treatment. Continuous response parameters will be compared using an MMRM analysis with fixed factors of treatment, baseline value, age, region, visit, treatment by visit and baseline by visit interaction terms. Life table estimates will be provided for the time to event variables. Subjects who meet loss of response criteria (eg, loss of PASI 90 response, loss of 50% Week 16 PASI improvement) will be considered an 'Event'. Subjects who did not meet the criteria for loss of response at Week 52 will be censored.

In addition, for the analyses related to patient reported outcomes (CDLQI and FDLQI), only subjects with baseline measurements will be included.

The analyses of other secondary efficacy analyses outlined in the following sections in general will be carried out for 2 periods.

Analyses through Week 16 (placebo controlled period)

Efficacy analyses at Week 16 and over time through Week 16 will be summarized by randomized treatment group at Week 0

- **Placebo**: subjects randomized to placebo group at Week 0
- **Guselkumab**: subjects randomized to guselkumab treatment group at Week 0
- **Etanercept**: subjects randomized to etanercept treatment group at Week 0

Analyses from Week 16 to Week 52 (withdrawal and retreatment period)

- Efficacy of PASI 90 responders at Week 16
  - After withdrawal of guselkumab: To evaluate the loss of response after withdrawal of study agent, efficacy analyses will be performed for subjects who were randomized to guselkumab at Week 0, were PASI 90 responders at Week 16 and were withdrawn from study agent after Week 16. Non-responder status will be assigned after retreatment for binary endpoints. The measurement at the time of retreatment will be carried forward after retreatment for continuous endpoints.
  - After retreatment with guselkumab: To evaluate the efficacy of retreatment with guselkumab, efficacy data at and after retreatment (ie, at the time of retreatment, 4 weeks after retreatment, 8 weeks after retreatment) will be summarized for subjects who were randomized to guselkumab at Week 0, were withdrawn from study agent

at Week 16, experienced a loss of 50% of the Week 16 PASI improvement, and were retreated with guselkumab.

- For subjects who were randomized to placebo at Week 0, and were PASI 90 responders at Week 16, efficacy data will be listed after Week 16.

– Efficacy of PASI 90 non-responders at Week 16

- Efficacy analyses for those subjects who were PASI 90 non-responders at Week 16 will be performed for the following treatment groups.
  - **Placebo → Guselkumab**: Subjects who were randomized to placebo at Week 0, were PASI 90 non-responders at Week 16 and crossed over to guselkumab at Week 16.
  - **Guselkumab**: Subjects who were randomized to guselkumab at Week 0, were PASI 90 non-responders at Week 16 and continued to receive guselkumab at Week 16.

– Efficacy of etanercept cross over subjects

- **Etanercept → Guselkumab**: To evaluate the efficacy of guselkumab in subjects previously treated with etanercept, efficacy analyses will be performed from Week 20 through Week 52 for subjects who were randomized to etanercept at Week 0, and crossed over to guselkumab at Week 20.

5.5.2.1.1. Analyses Related to IGA

5.5.2.1.1.1. Through Week 16

- The proportion of IGA responses (IGA score of cleared [0]; an IGA score of cleared [0] or minimal [1]; and an IGA score of mild or better [≤2]) will be summarized over time through Week 16 by treatment group. Line plots will be provided displaying the proportions and exact 95% CIs of subjects achieving an IGA score of 0; and an IGA score of 0/1 through Week 16.
- The proportion of IGA responses (IGA score of cleared [0]; an IGA score of cleared [0] or minimal [1]; and an IGA score of mild or better [≤2]) will be summarized over time through Week 16 by treatment group using observed data after applying treatment failure rules and rescue treatment rules.

5.5.2.1.1.2. From Week 16 through Week 52

PASI 90 responders at Week 16 (after withdrawal of guselkumab)

- To evaluate the efficacy of the maintenance therapy, the proportion of IGA responses (IGA score of cleared [0]; an IGA score of cleared [0] or minimal [1]; and an IGA score of mild or better [≤2]) will be summarized over time through Week 52 for subjects randomized to the guselkumab group who were PASI 90 responders at Week 16. Non-responder status will be assigned after retreatment of guselkumab.

PASI 90 responders at Week 16 (after retreatment of guselkumab)

- IGA scores at the time of retreatment of guselkumab and the proportion of retreated participants who achieve an IGA score of cleared (0), an IGA score of cleared (0) or minimal (1), and an IGA score of mild or better (≤2) over time (eg, 4 weeks after retreatment, 8 weeks after retreatment, 12 weeks after retreatment) following the retreatment of guselkumab will be summarized for subjects randomized to the guselkumab group who were PASI 90 responders at Week 16.

PASI 90 non-responders at Week 16

- The proportion of IGA responses (IGA score of cleared [0]; an IGA score of cleared [0] or minimal [1]; and an IGA score of mild or better [≤2]) will be summarized over time through Week 52 by treatment group.

5.5.2.1.2. Analyses Related to PASI

5.5.2.1.2.1. Through Week 16

- The proportion of participants who achieve a PASI 50 response at Week 16 will be compared between the guselkumab group and the placebo group using Fisher's exact test stratified by region and age. The differences in proportions with exact 95% confidence intervals will be presented.
- The percent improvement from baseline in PASI at Week 16 will be compared between the guselkumab group and the placebo group using a using Wilcoxon rank-sum test.
- The percent improvement from baseline in PASI will be summarized over time through Week 16 by treatment group.
- The proportion of PASI responses (PASI 50, 75, 90, and 100) will be summarized over time through Week 16 by treatment group. Line plots will be provided displaying proportions and exact 95% CIs of PASI 100 responders and PASI 90 responders through Week 16.
- The proportion of PASI responses (PASI 50, 75, 90, and 100) will be summarized over time through Week 16 by treatment group using observed data after applying treatment failure rules and rescue treatment rules.
- The proportion of subjects who achieve 100% improvement, ≥90%, ≥75%, or ≥50% improvement from baseline in PASI component (induration, erythema, and scaling) and region component (head, trunk, upper extremities, and lower extremities) will be summarized at Week 16 by treatment group.

5.5.2.1.2.2. From Week 16 through Week 52

PASI 90 responders at Week 16 (after withdrawal of guselkumab)

- The time to loss of PASI 90 response after withdrawal will be summarized for participants randomized to the guselkumab group who were PASI 90 responders at Week 16. The percent of subjects who maintained a PASI 90 response from Week 20 through Week 52 will be estimated from life-table methodology and a survival curve (probability that participants maintain PASI 90 response after withdrawn) will be presented.

- The duration of PASI 90 response will be summarized using life-table methodology for participants randomized to the guselkumab group who were PASI 90 responders at Week 16. The estimated number of weeks at which 90%, 75%, 50% and 25% of subjects maintained a PASI 90 response will be provided.
- The time to loss of 50% of the Week 16 PASI improvement (ie, time to retreatment) after withdrawal will be summarized for participants randomized to guselkumab group. The percent of subjects who experienced loss of 50% of Week 16 PASI improvement from Week 20 through Week 52 will be estimated from life-table methodology and cumulative incidence of loss of 50% of Week 16 PASI improvement curve will be presented.
- The time to loss of 50% of Week 16 PASI improvement will be summarized using life-table methodology for participants randomized to the guselkumab group who were PASI 90 responders at Week 16. The estimated number of weeks at which 90%, 75%, 50% and 25% of subjects experienced loss of 50% of Week 16 PASI improvement will be provided.
- The proportion of PASI responses (PASI 50, 75, 90, and 100) will be summarized over time through Week 52 for subjects randomized to the guselkumab group who were PASI 90 responders at Week 16. Non-responder status will be assigned after retreatment of guselkumab.
- The percent improvement from baseline in PASI will be summarized over time through Week 52 for subjects randomized to the guselkumab group who were PASI 90 responders at Week 16. PASI score at the time of retreatment will be carried forward after retreatment of guselkumab through Week 52.

PASI 90 responders at Week 16 (after retreatment of guselkumab)

- PASI score and PASI percent improvement at the time of retreatment with guselkumab will be summarized for subjects randomized to the guselkumab group who experienced loss of 50% of Week 16 PASI improvement.
- The PASI responses (PASI 50, 75, 90 and 100) with respect to baseline will be summarized over time (eg, 4 weeks after retreatment, 8 weeks after retreatment, 12 weeks after retreatment) following retreatment with guselkumab.

PASI 90 non-responders at Week 16

- The proportion of PASI responses (PASI 50, 75, 90, and 100) will be summarized over time through Week 52 by treatment group.

5.5.2.1.3. Analyses Related to CDLQI, FDLQI, and BSA

5.5.2.1.3.1. Through Week 16

- The proportion of subjects achieving a CDLQI of 0 or 1 will be summarized at Week 8 and Week 16 among randomized participants with a baseline CDLQI>1. The proportion of subjects with CDLQI of 0 or 1 at Week 16 will be compared between the guselkumab group and the placebo group using Fisher's exact test stratified by pooled region and age group.
- The change from baseline in CDLQI total score will be summarized at Week8 and Week 16.

- The change from baseline in each CDLQI component score will be summarized at Week 16.
- The proportion of subjects achieving a FDLQI of 0 or 1 will be summarized at Week 8 and Week 16 among randomized subjects with a baseline FDLQI>1. The proportion of subjects with FDLQI of 0 or 1 at Week 16 will be compared between the guselkumab group and the placebo group using Fisher's exact test stratified by region and age group.
- The change from baseline in FDLQI total score will be summarized at Week 8 and Week 16. The change from baseline in FDLQI at Week 16 will be compared between the guselkumab group and the placebo group using a Mixed Model for Repeated Measures (MMRM) model to test the difference between treatment groups and adjust for missing data.
- The change from baseline in each FDLQI component score will be summarized at Week 16.
- The change from baseline in BSA at Week 16 will be compared between the guselkumab group and the placebo group using a MMRM model.
- BSA involved and change from baseline in BSA will be summarized over time through Week 16.

In addition, relevant comparisons for secondary analyses at Week 16 will also be conducted between the etanercept group and the placebo group.

5.5.2.1.3.2. From Week 16 through Week 52

PASI 90 responders at Week 16 (after withdrawal of guselkumab)

- CDLQI score will be summarized at Week 16 and Week 28 for subjects randomized to the guselkumab group who were PASI 90 responder at Week 16, and were withdrawn from study agent at Week 16. Subjects who were retreated with guselkumab prior to Week 28 will be excluded.
- FDLQI score will be summarized at Week 16 and Week 28 for subjects randomized to the guselkumab group who were PASI 90 responder at Week 16, and were withdrawn from study agent at Week 16. Subjects who were retreated with guselkumab prior to Week 28 will be excluded.
- BSA involved and change from baseline in BSA will be summarized From Week 16 through Week 52 for subjects randomized to the guselkumab group who were PASI 90 responders at Week 16. BSA score at the time of retreatment will be carried forward after retreatment of guselkumab through Week 52.

PASI 90 responders at Week 16 (after retreatment guselkumab)

- The average duration of retreatment with guselkumab, CDLQI score at the time of retreatment, and CDLQI score at Week 52 will be summarized for subjects randomized to the guselkumab group who were PASI 90 responder at Week 16 and retreated prior to Week 52.
- FDLQI score at the time of retreatment, and FDLQI score at Week 52 will be summarized for subjects randomized to the guselkumab group who were PASI 90 responder at Week 16 and retreated prior to Week 52.

- BSA involved and change from baseline in BSA will be summarized at the time of retreatment and over time (eg, 4 weeks after retreatment, 8 weeks after retreatment, 12 weeks after retreatment) following retreatment with guselkumab.

PASI 90 non-responders at Week 16

- The proportion of participants achieving a CDLQI of 0 or 1 will be summarized over time through Week 52 among randomized subjects who were PASI 90 non-responder at Week 16 and with a baseline CDLQI>1.
- The change from baseline in CDLQI total score will be summarized over time through Week 52.
- The change from baseline in each CDLQI component score will be summarized at Week 52.
- The proportion of participants achieving a FDLQI of 0 or 1 will be summarized over time through Week 52 among randomized subjects who were PASI 90 non-responder at Week 16 and with a baseline FDLQI>1.
- The change from baseline in FDLQI total score will be summarized over time through Week 52.
- BSA involved and change from baseline in BSA will be summarized over time through Week 52.

5.5.2.2. Secondary Analyses for Participants Enrolled in Part 2

Efficacy analyses will be summarized for full analysis set in Part 2

- The proportion of PASI responses (PASI 50, 75, 90, and 100) will be summarized over time through Week 52.
- The proportions of subjects achieving an IGA score of cleared (0); an IGA score of cleared (0) or minimal (1); and an IGA score of mild or better (≤2) will be summarized over time through Week 52.
- The percent improvement from baseline in PASI will be summarized over through Week 52.
- BSA involved and change from baseline in BSA will be summarized over time through Week 52.
- The proportion of participants achieving an CDLQI of 0 or 1 will be summarized over time through Week 52 among participants with a baseline CDLQI>1.
- The change from baseline in CDLQI score will be summarized over time through Week 52.
-
- The proportion of participants achieving an FDLQI of 0 or 1 will be summarized over time through Week 52 among participants with a baseline FDLQI>1.
- The change from baseline in FDLQI score will be summarized over time through Week 52.

5.5.2.3. Efficacy Analyses for Long Term Extension

Efficacy in the LTE period (from Week 52 through the end of the study) will be summarized for all subjects who entered LTE.

- The proportion of PASI responses (PASI 50, 75, 90, and 100) will be summarized over time through the end of the study.
- The proportions of subjects achieving an IGA score of cleared (0); an IGA score of cleared (0) or minimal (1); and an IGA score of mild or better (≤2) will be summarized over time through the end of the study.
- The percent improvement from baseline in PASI will be summarized over time through the end of the study.
- BSA involved and change from baseline in BSA will be summarized over time through the end of the study.

In addition, PASI responses, IGA responses, percent improvement in PASI, and change in BSA will be summarized at Week 60 and Week 84 after retreatment among guselkumab subjects who were withdrawn from guselkumab at Week 16 and were subsequently retreated upon loss of response or at Week 52 if a loss of response was not observed at or prior to Week 52.

5.5.3. Data Handling

For the efficacy analyses in Part 1, data handling rules specified in Section 5.1.3 will be applied to all IGA, PASI, CDLQI, FDLQI, and BSA related analyses.

For the efficacy analyses in Part 2, data handling rules specified in Section 5.1.3 except rescue treatment rules will be applied to all efficacy analyses.

For the efficacy analyses in LTE, the data will be summarized based on observed.

6. USABILITY ASSESSMENTS

In Part 2 of the main study, pediatric participants ≥12 years of age and caregivers of pediatric participants of any age will be given the option to administer study agent. The usability of the CCI will be assessed for subjects with weight <70 kg enrolled and treated in Part 2.

6.1. Definition

CCI [redacted]

CCI

CCI

6.2. Analysis Methods

The following analyses for usability will be performed for all subjects enrolled and treated in Part 2 based on observed data without missing data imputation or other data handling rules.

- The Observer Injection Checklist will be summarized. A listing of Observer Injection Checklist results at Week 0 will be provided for subjects who did not correctly administer the injections.
- The CCI [redacted] and responses will be listed.
- A listing of product quality complaints (PQCs) associated with CCI [redacted] device will be provided for the safety analysis set in Part 1 and Part 2.

7. SAFETY

Safety will be assessed by summarizing the incidence and type of AEs and examining changes in laboratory parameters (hematology and chemistry), vital signs, and suicidal ideation and behavior.

In the safety analyses for Part 1, subjects who were randomized and received at least 1 (partial or complete) dose of study agent administration will be included and analyzed according to the treatment they actually received, regardless of the treatment assigned at randomization. No formal statistical comparison is planned.

For Part 2, the safety analyses will be performed for all subjects enrolled in Part 2 and treated.

For LTE, the safety analyses will be performed for all subjects entered in LTE and treated at or after Week 52.

Depending on the safety data categories, the cumulative safety data will be analyzed through different study periods which include but are not limited to through Week 16, through Week 52, and through the LTE as appropriate. Unless otherwise specified, tabular summaries of safety events for key study periods are in general presented as follows:

Summaries through Week 16 (placebo-controlled period in Part 1):

Safety data through Week 16 will be summarized by treatment groups:

- Placebo
- Guselkumab
- Etanercept

This allows between-group comparisons of safety between the guselkumab group, etanercept group and the placebo group based on similar follow-up period in each group.

Summaries through Week 52 in Part 1

Safety data through Week 52 will be summarized by treatment group defined as follows:

1. **Placebo → Guselkumab:** all subjects who were randomized to placebo at Week 0, started treatment with placebo only, and later crossed over to receive treatment with guselkumab. Only the safety events/measurements from these subjects that occurred on or after their first administration of guselkumab will be included in this group.

2. **Guselkumab:** all subjects who were randomized to guselkumab at Week 0 and were treated with guselkumab. All the safety events/measurements from these subjects that occurred beginning at Week 0 will be included in this group.
3. **Etanercept → Guselkumab:** all subjects who were randomized to etanercept at Week 0, started treatment with etanercept only, and later crossed over to receive treatment with guselkumab. Only the safety events/measurements from these subjects that occurred on or after their first administration of guselkumab will be included in this group.
4. **Combined Guselkumab:** all subjects as described above in the Placebo → Guselkumab, the Etanercept → Guselkumab and the Guselkumab groups.

In addition, the summaries of selected AE rates per hundred subject-years of follow-up through Week 52 will be provided.

Selected safety analyses will also be performed after retreatment with guselkumab among subjects who were randomized to guselkumab at Week 0, were PASI 90 responders at Week 16, were withdrawn from and then retreated with guselkumab.

Summaries through Week 52 in Part 2

Safety data through Week 52 will be summarized for all subjects who were enrolled in Part 2 and received at least 1 study agent administration of guselkumab. All the safety events/measurements from these subjects that occurred beginning at Week 0 will be included in this group.

Summaries through the LTE

Safety data through the LTE will be summarized for all subjects who participated in the LTE and were treated with guselkumab. All the safety events/measurements from Week 52 through the end of the study will be included in this group.

7.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version xx). Any AE occurring at or after the initial administration of study agent through the end of the trial is considered to be treatment emergent. If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study agent based on partial onset date or resolution date. All reported treatment-emergent adverse events will be summarized by MedDRA system organ class, preferred term, and actual treatment group. The numbers of subjects reporting at least 1 event of the following treatment emergent AE categories will be summarized.

- AEs
- Serious AEs (SAEs)
- AEs leading to discontinuation of study agent

- AEs by severity
- AEs by relationship to study agent
- Infections
- Serious infections
- Infections treated with oral or parenteral antimicrobial treatment
- Injection-site reactions

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

- Had SAEs
- Had AEs leading to discontinuation of study agent
- AEs of psoriasis
- AEs of severe intensity
- Serum sickness-like reactions and anaphylactic reactions

These summary tables will provide the count and percentage of subjects with 1 or more of the specified AEs by treatment group. The AEs and infections will also be summarized by age group through Week 16 and through Week 52 for Part 1. To adjust for the different duration of follow-up among treatment groups, number of events per hundred subject-years of follow-up through Week 52 will also be provided for all AEs.

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

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

Psoriasis rebound will be assessed during the withdrawal period for subjects withdrawn from guselkumab at Week 16. Psoriasis rebound is defined as an event of new erythrodermic or pustular psoriasis, or a PASI of ≥ 125% of the baseline PASI (ie, a worsening of PASI by 25% or greater from baseline) that occurred during the withdrawal period from the time subjects are withdrawn from guselkumab at Week 16.

In addition, safety will be assessed for subjects who are withdrawn from guselkumab at Week 16 and subsequently retreated upon loss of response. These analyses will include safety categories of AE, infection, and injection site reaction within 16 weeks after retreatment.

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

7.2. Clinical Laboratory Tests

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

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

Descriptive statistics for selected clinical laboratory analyte and for change from baseline at each scheduled post-baseline visit through Week 16 will be provided by treatment group for Part 1. Box plots of laboratory measurements and change from baseline through Week 52 will be provided for selected laboratory analytes.

Applicable laboratory results will be graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE version 4.03). The proportion of subjects with post-baseline values by maximum toxicity grade for clinical laboratory tests will be summarized by treatment group.

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

7.3. Vital Signs, Weight, Height

Body weight, height and vital signs variables including respiratory rate, blood pressure (systolic and diastolic), and temperature will be measured at visits as per the time and events schedule in the protocol. Descriptive statistics of the observed value and change from baseline of the vital signs through Week 16 will be summarized by treatment group for Part 1. Box plots of vital signs and change from baseline through Week 52 will be provided.

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

7.4. Other Safety Parameters

7.4.1. Suicidal Ideation and Behavior

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be used as a screening tool to prospectively evaluate suicidal ideation and behavior in children and adolescents ≥6 to <18 years of age. The C-SSRS is an investigator-administered questionnaire that defines 5 subtypes of suicidal ideation and four possible suicidal behaviors, as well as non-suicidal self-injurious behavior (NSSIB) and completed suicide. There are 4 versions of the C-SSRS will be used in this study; a baseline version for children ≥6 to <12 years of age, a Baseline/Screening version for adolescents ≥12 years of age, a Children's Since Last Visit version will be completed at all other visits, and a Since Last Visit version for adolescents. The 'Baseline' and 'Baseline/Screening

version of the C-SSRS will be conducted at Screening followed by the Since Last Visit version of the C-SSRS at all other visits through the end of the study.

The C-SSRS will be performed during each evaluation visit according to the assessment schedule and should be performed after the CDLQI and before any other study procedure. Participants will be interviewed by the investigator or study site personnel in a private, quiet place.

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

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

Suicidal Ideation (1-5)

1 = Wish to be Dead

2 = Non-specific Active Suicidal Thoughts

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

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

5 = Active Suicidal Ideation with Specific Plan and Intent

Suicidal Behavior (6-10)

6 = Preparatory Acts or Behavior

7 = Aborted Attempt

8 = Interrupted Attempt

9 = Actual Attempt (non-fatal)

10 = Completed Suicide

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

Subjects with any suicidal ideation, suicidal behavior, or self-injurious behavior will be listed.

7.4.2. Injection Pain

Pain experienced with each placebo or guselkumab injection will be assessed at each study visit at which an injection is administered. Injection pain will be assessed using the Faces Pain Scale-Revised (FPS-R) for children ≥6 to <12 years of age, and the linear Injection Pain Visual Analog Scale (VAS) for adolescents ≥12 to <18 years of age.

The FPS-S evaluates how much pain subjects experienced with the injection. The score ranges from 0 to 10, with score of 0 shows "no pain" and score of 10 shows very much pain. The VAS evaluates injection pain by placing a vertical mark on the line (100 mm in length from 0 of no injection pain to 100 of very much pain). A trained observer will measure the distance in millimeters (0-100) from the left of the scale to the participant's mark.

Descriptive statistics of FPS-R and VAS including mean, SD, median, minimal, and maximal will be summarized by visit and study intervention received.

7.4.3. Head Circumference

Descriptive statistics of head circumference and change from baseline will be summarized at Week 0 and Week 52 for participants ≥6 to <12 years of age.

7.4.4. Tanner Staging

Count and percentage of tanner scale (range from stage 1 to stage 5) will be summarized by gender and age group.

8. PHARMACOKINETICS/PHARMACODYNAMICS

8.1. Pharmacokinetics

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

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

All concentrations below the lowest quantifiable sample concentration of the assay (BQL) or missing data will be labeled as such in the concentration data listings or Statistical Analysis System (SAS) dataset. The BQL concentrations will be treated as zero in the summary statistics.

For the analysis of serum guselkumab concentrations, descriptive statistics, including arithmetic mean, SD, median, interquartile range, minimum, and maximum will be calculated, where appropriate, at each scheduled sampling time point by treatment group. The PK concentration data may be displayed graphically. The following analyses will be performed by treatment group if appropriate:

- In Part 1, serum guselkumab concentrations will be summarized for the following periods.
    - From Week 0 through Week 16 for all subjects randomized and treated with guselkumab by age (6 to <12, 12 to <18 years), baseline weight (<70, ≥70 kg), and overall;
    - From Week 0 through Week 44 by visit for subjects treated with guselkumab .
        - Subjects randomized to placebo → guselkumab and guselkumab (who are PASI 90 non-responders at Week 16)
        - Subjects randomized to etanercept → guselkumab (who initiated treatment with guselkumab at Week 20)

        - Subjects randomized to guselkumab (who are PASI 90 responders at Week 16): From Week 0 through the time of retreatment with guselkumab. Serum guselkumab concentration will be excluded after retreatment.
    - Summary of serum guselkumab concentrations at the time of retreatment with guselkumab for subjects randomized to guselkumab who were PASI 90 responders and withdrawn from guselkumab at Week 16.
- In Part 2, serum guselkumab concentrations from Week 0 through Week 44 will be summarized by age (6 to <12, 12 to <18 years), baseline weight (<70, ≥70 kg), and overall for all subjects treated with guselkumab
- If needed, serum guselkumab concentrations from Week 0 through Week 16 will be summarized for all subjects treated with guselkumab (Part 1 and Part 2 combined).

All summaries for serum guselkumab concentration will exclude data collected after subjects (1) did not receive a scheduled guselkumab administration within ± 14 days of the protocol scheduled dosing date; (2) discontinued study agent administration; (3) received a partial, incorrect, or an additional guselkumab administration (ie, subjects received more than 1 guselkumab injection within the scheduled guselkumab injection window); or (4) received an increased or decreased dose due to body weight change (eg, from the initial category of <70 kg to the category of ≥70 kg or vice versa) for the concentration summaries by baseline weight. Of note, serum guselkumab concentrations prior to the first of such events will be included in the summaries. All subjects and samples excluded from the analysis will be clearly documented.

In addition, invalid concentration data will be excluded from analysis. A concentration will be considered invalid (1) if a sample prior to guselkumab injection was actually taken after guselkumab administration (based on date/time); or (2) a concentration value fell outside the predefined statistical range of mean ± 10*SD of the concentration values obtained at the same protocol specified sampling timepoint (refer to SOP-07948-GXP, Version 2.1).

If there were multiple samples collected prior to an injection, the closest sample before the injection will be used. If a sampling time or an injection time was missing, the date will be used. If sampling date was the same as the injection date, the sample will be included in the statistical summary.

A population PK analysis using a nonlinear mixed-effects modeling approach will be used to characterize the disposition characteristics of guselkumab in the current study. Data may be combined with those of other selected studies to support a relevant structural model. The CL/F and V/F values will be estimated. The influence of important variables (such as body weight and age) on the population PK parameter estimates will be evaluated. Details will be given in a population PK analysis plan and results of the population PK analysis will be presented in a separate technical report.

8.2. Immune Response

Blood samples will be collected for the detection of antibodies to guselkumab at the specified visits as shown in the Schedule of Activities (SoA) in the protocol.

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

The following analyses will be performed by treatment group as appropriate:

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

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

The effect of antibodies to guselkumab on PK, efficacy, and safety may be explored, if data permit.

8.3. Pharmacokinetic/Pharmacodynamic Relationships

The relationships between serum ustekinumab concentration and efficacy may be analyzed graphically. A suitable pharmacokinetic/pharmacodynamic (PK/PD) model will be developed to describe the exposure-response relationship. Data may be combined with those of other selected studies to support a relevant structural PK/PD model. The results of the population PK/PD analysis may be presented in a separate technical report.

REFERENCES

1. Maurer, W., Hothorn, L. A., Lehnacher, W. Multiple comparisons in drug clinical trials and preclinical assays: a prior ordered hypotheses. Biometrie in der Chemisch-in-Pharmazeutischen Industrie. 1995, 3-18