Statistical Analysis Plan

A Phase 3b, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Guselkumab Versus Placebo for the Treatment of Low BSA Moderate Plaque Psoriasis With Special Site Involvement

Protocol CNTO1959PSO3017; Phase 3b

CNTO1959 (guselkumab)

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

TABLE OF CONTENTS

Contents

VERSION HISTORY

Table 1 – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	23 July 2024	Not Applicable	Initial release

1. INTRODUCTION

This statistical analysis plan contains definitions of analysis sets, derived variables, and statistical methods for the analysis of efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD), and Immunogenicity in the CNTO1959PSO3017 study. Guselkumab (CNTO 1959) is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that inhibits the biological activity of interleukin (IL)-23 for the treatment of psoriasis.

1.1. Objectives and Endpoints

Primary Objective

The primary objective of the study is to evaluate the clinical efficacy of guselkumab compared to placebo in participants with low BSA (2-15%) moderate plaque psoriasis (overall IGA 3) with the involvement of at least 1 special site of at least moderate severity. Qualifying sites include scalp with ss-IGA ≥3, face with f-IGA ≥3, intertriginous with i-IGA ≥3, or genital with sPGA-G ≥3.

Secondary Objectives

Secondary objectives of this study are to assess the efficacy of patient-reported outcomes, safety, tolerability, pharmacokinetics, pharmacodynamics, and pharmacogenomics for guselkumab in participants with low BSA moderate plaque psoriasis with special site involvement.

Table 2: The study objectives and endpoints are listed below.

OBJECTIVES AND ENDPOINTS	
Primary Objective	**Primary Endpoint**
The primary objective of the study is to evaluate the clinical efficacy of guselkumab compared to placebo, in participants with low BSA moderate plaque psoriasis with special site involvement.	The proportion of participants who achieve an Investigator's Global Assessment (IGA) score of cleared (0) or minimal (1) at Week 16
Secondary Objectives **Efficacy** To evaluate the efficacy of guselkumab compared with placebo in improving the signs and symptoms of psoriasis and patient-reported outcomes (PROs)	**Major Secondary Efficacy Endpoints** 1. Change from baseline in Body Surface Area (BSA) affected at Week 16 2. Change from baseline in total Psoriasis Area Severity Index (PASI) score at Week 16 3. The proportion of participants who achieve an IGA score of cleared (0) at Week 16 4. The proportion of participants who achieve a PASI 90 response at Week 16 5. The proportion of participants who achieve a PASI 100 response at Week 16 6. The proportion of participants who achieve a Scalp-Specific IGA (ss-IGA) score of absence of disease (0) or very mild disease (1) at Week 16, among randomized participants with an ss-IGA score ≥3 at baseline 7. The proportion of participants who achieve a static Physician's Global Assessment of Genitalia (sPGA-G) of clear (0) or minimal (1) at Week 16, among randomized participants with a sPGA-G score ≥3 at baseline 8. The proportion of participants who achieve a intertriginous (i)-IGA score of clear (0) or minimal (1) at Week 16, among randomized participants with an (i)-IGA score ≥3 at baseline 9. The proportion of participants who achieve a facial (f-)IGA of clear (0) or minimal (1) at Week 16, among randomized participants with an f-IGA score ≥3 at baseline 10. The change from baseline in Psoriasis Symptom and Sign Diary (PSSD) symptom score at Week 16 11. The proportion of participants who achieve ≥ 4-point reduction (improvement) in Psoriasis Symptom and Sign Diary (PSSD) itch score from baseline at Week 16, among participants with a PSSD itch score ≥ 4 at baseline 12. The proportion of participants with PSSD Individual Symptom Scale Score =0 at Week 16 among participants with PSSD >0 at baseline
Secondary Objectives **Safety** To evaluate the safety of guselkumab in participants with low BSA moderate plaque psoriasis with special site involvement	**Safety Endpoints** 1. The frequency and type of AEs and SAEs
Other Objectives To evaluate the efficacy of additional clinical and patient-	**Other Endpoints - Psoriasis Efficacy** **The following endpoints will compare the guselkumab with the placebo**

Table 2: The study objectives and endpoints are listed below.

OBJECTIVES AND ENDPOINTS	
Primary Objective	**Primary Endpoint**
reported outcomes	**group** 1. Change from baseline in BSA x IGA through Week 16 **The following endpoints relate to guselkumab group only** 2. Change from baseline in BSA x IGA over time through Week 48 3. The proportion of participants who achieve NPF target response (i.e., BSA≤1%) over time through Week 48 4. The proportion of participants who achieve NPF acceptable response (i.e., BSA ≤3% or BSA75) over time through Week 48 among those with baseline BSA >3% 5. The proportion of participants who achieve PASI 50/75/90/100 over time through Week 48 6. The proportion of participants who achieve IGA 0 over time through Week 48 7. The proportion of participants who achieve IGA 0/1 over time through Week 48 8. Time to achievement of NPF target response (i.e., BSA ≤1%) through Week 48 9. Time to achievement of NPF acceptable response (i.e, BSA≤3% or BSA75) through Week 48 10. The proportion of IGA 0/1 Week 16 responders who maintain IGA 0/1 response at Week 48 11. Change in BSA over time through Week 48 12. Change in PASI over time through Week 48 **<u>Other Endpoints – Special Site Efficacy</u>** **The following endpoints will compare the guselkumab with the placebo group** **Scalp** 13. Time to complete scalp psoriasis clearance (ss-IGA = 0) through Week 48, among randomized participants with scalp psoriasis at baseline 14. Proportion of participants with complete scalp psoriasis clearance (ss-IGA = 0) over time among randomized participants with scalp psoriasis at baseline over time through Week 16 15. Proportion of participants who achieve an ss-IGA score of absence of disease (0) or very mild disease (1) with at least 2-grade improvement from baseline at Week 16 among randomized participants with an ss-IGA score ≥2 at baseline **Genital** 16. Time to complete genital psoriasis clearance (sPGA-G = 0) through Week 48, among randomized participants with genital psoriasis at baseline 17. Proportion of participants with complete genital psoriasis clearance (sPGA-G = 0) among randomized participants with genital psoriasis at baseline over time through Week 16 18. Proportion of participants who achieve an sPGA-G score clear (0) or minimal (1) with at least 2-grade improvement from baseline at Week 16 among randomized participants with an sPGA-G score ≥2 at baseline

Table 2: The study objectives and endpoints are listed below.

OBJECTIVES AND ENDPOINTS	
Primary Objective	**Primary Endpoint**
	Intertriginous 19. Time to complete intertriginous psoriasis clearance (i-IGA = 0) through Week 48, among randomized participants with intertriginous psoriasis at baseline 20. Proportion of participants with complete intertriginous psoriasis clearance (i-IGA = 0) among randomized participants with intertriginous psoriasis at baseline over time through Week 16 21. Proportion of participants who achieve an i-IGA score of clear (0) or minimal (1) with at least 2-grade improvement from baseline at Week 16 among randomized participants with an i-IGA score ≥2 at baseline **Face** 22. Time to complete facial psoriasis clearance (f-IGA = 0) through Week 48, among randomized participants with facial psoriasis at baseline 23. Proportion of participants with complete facial psoriasis clearance (f-IGA = 0) among randomized participants with facial psoriasis at baseline over time through Week 16 24. Proportion of participants who achieve an f-IGA score of clear (0) or minimal (1) with at least 2-grade improvement from baseline at Week 16 among randomized participants with an f-IGA score ≥2 at baseline **These endpoints relate to guselkumab group only** 25. The proportion of participants achieving palmoplantar IGA (pp-IGA) of clear (0) or almost clear/minimal (1) with at least 2-point improvement over time through Week 48 among randomized participants with a pp-IGA score ≥2 at baseline 26. The proportion of participants achieving pp-IGA of clear (0) over time through Week 48 among randomized participants with palmoplantar psoriasis at baseline 27. The change from baseline in the Nail Psoriasis Severity Index (NAPSI) over time through Week 48 among randomized Participants with nail psoriasis at baseline 28. The percent improvement from baseline in NAPSI over time through Week 48 among randomized participants with nail psoriasis at baseline 29. The proportion of participants achieving NAPSI 50/75/90/100 response over time through Week 48, among randomized participants with nail psoriasis at baseline 30. The proportion of participants achieving NAPSI 0 over time through Week 48, among randomized participants with nail psoriasis at baseline **Other Endpoints - Patient-Reported Outcomes** **The following endpoints will be summarized for each of the guselkumab and placebo treatment groups** 31. The change from baseline in psoriatic arthritis impact of disease score (PsAID12) over time through Week 48 32. The proportion of participants with a score suggestive of PsA, i.e., ≥ 3 on the Psoriasis Epidemiology Screening Tool (PEST) over time through Week 48 among randomized participants with screening PEST score < 3

Table 2: The study objectives and endpoints are listed below.

OBJECTIVES AND ENDPOINTS	
Primary Objective	**Primary Endpoint**
	The following endpoints will compare the guselkumab group with the placebo group 33. The change from baseline in individual scale score of PSSD components at Week 16 34. The proportion of participants who achieve PSSD individual scale score of 0 at Week 16, among randomized participants with scale score ≥ 1 35. The proportion of participants who achieve a PSSD symptom score = 0 at Week 16, among randomized participants with PSSD symptom score ≥ 1 36. The proportions of participants who achieve a PSSD symptom score =0, a PSSD sign score =0, and the proportion of participants who achieve PSSD individual scale score of 0 for participants with a baseline symptom score, sign score, and each PSSD individual baseline scale score that is ≥1 over time through Week 16 37. The proportion of participants with Dermatology Life Quality Index (DLQI) 0/1 at Week 16 38. The change from baseline in patient-reported outcomes measurement information system-29 (PROMIS-29) score over time through Week 16 **These endpoints relate to the guselkumab group only:** 39. The change from baseline in PSSD symptom score over time through Week 48 40. The proportion of participants who achieve ≥4-point reduction (improvement) in PSSD itch score from baseline over time through Week 48 among participants with a PSSD itch score ≥4 at baseline 41. The proportion of participants with PSSD Individual Symptom Scale Score =0 over time through Week 48 among participants with PSSD Scale Score>0 at baseline 42. The change from baseline in individual scale score of PSSD components over time through Week 48 The proportion of participants who achieve a PSSD individual scale score of 0 over time through Week 48 among randomized participants with scale score ≥1 43. The proportion of participants who achieve a PSSD symptom score = 0 over time through Week 48 among randomized participants with PSSD symptom score ≥1 44. The proportions of participants who achieve a PSSD symptom score =0 and a PSSD sign score =0 and the proportion of participants who achieve a PSSD individual scale score of 0 for participants with a baseline symptom score, sign score, and each PSSD individual baseline scale score that is ≥1 over time through Week 48 45. The proportion of participants with Dermatology Life Quality Index (DLQI) 0/1 over time through Week 48 46. The proportion of participants with DLQI 0 over time through Week 48

Table 2: The study objectives and endpoints are listed below.

OBJECTIVES AND ENDPOINTS	
Primary Objective	**Primary Endpoint**
	47. The change from baseline in PROMIS-29 score over time through Week 48
Other Objectives	**Other Endpoints – Pharmacokinetics, Pharmacodynamics, Immunogenicity, Pharmacogenomics**
To evaluate pharmacokinetics and immunogenicity of guselkumab	1. Serum guselkumab concentrations 2. Antibodies to guselkumab
To evaluate pharmacodynamic (PD) effects of guselkumab	1. Change from baseline in cellular and molecular biomarkers in skin and blood
To evaluate pharmacogenomic of guselkumab	1. Genetic factors associated with clinical response and PD effects

1.2. Study Design

This is a Phase 3b, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of guselkumab versus placebo in participants with low BSA moderate plaque psoriasis with special site involvement.

Approximately 300 eligible participants will be randomized in a 2:1 ratio to receive either guselkumab CCI at Weeks 0 and 4 and then CCI or placebo (Figure 1). Randomization will be stratified by qualifying special sites (i.e., scalp, face, intertriginous, and genital) with approximately 25% of participants per each special site. If participants present with qualifying moderate psoriasis in multiple special sites, they will be allocated to the special site that is most severe, as determined by the participant. The study will aim to enroll no less than approximately 20% of participants from diverse racial-ethnic backgrounds (i.e., self-identify as non-white/non-Caucasian descent) to reflect the North American Census population.

There will be 2 treatment groups:

- A guselkumab group who will receive guselkumab CCI CCI at Weeks 0 and 4 and then CCI through Week 44. Placebo will be administered at Week 16 to maintain the blind.
- A placebo group who will receive placebo at Weeks 0, 4, and 12 after which they will cross over to receive guselkumab at Weeks 16, 20, 28, 36, and 44.

Further details on active and blinding study intervention administrations for both treatment groups are provided in Section 6.

There will be 2 database locks (DBLs) in this study, at Weeks 16 and 56. After all participants have completed the Week 16 visit (or discontinued from the study), a Week 16 DBL will be performed, and unblinded data will only be made available to select Sponsor and Contract Research Organization (CRO) team members involved with analysis of the data and preparation of analyses for the Week 16 DBL. All other Sponsor, site, and CRO personnel directly involved

with study conduct will remain blinded to treatment assignments until the Week 56 DBL and related analyses have been completed. A diagram of the study design is provided in Figure 1.

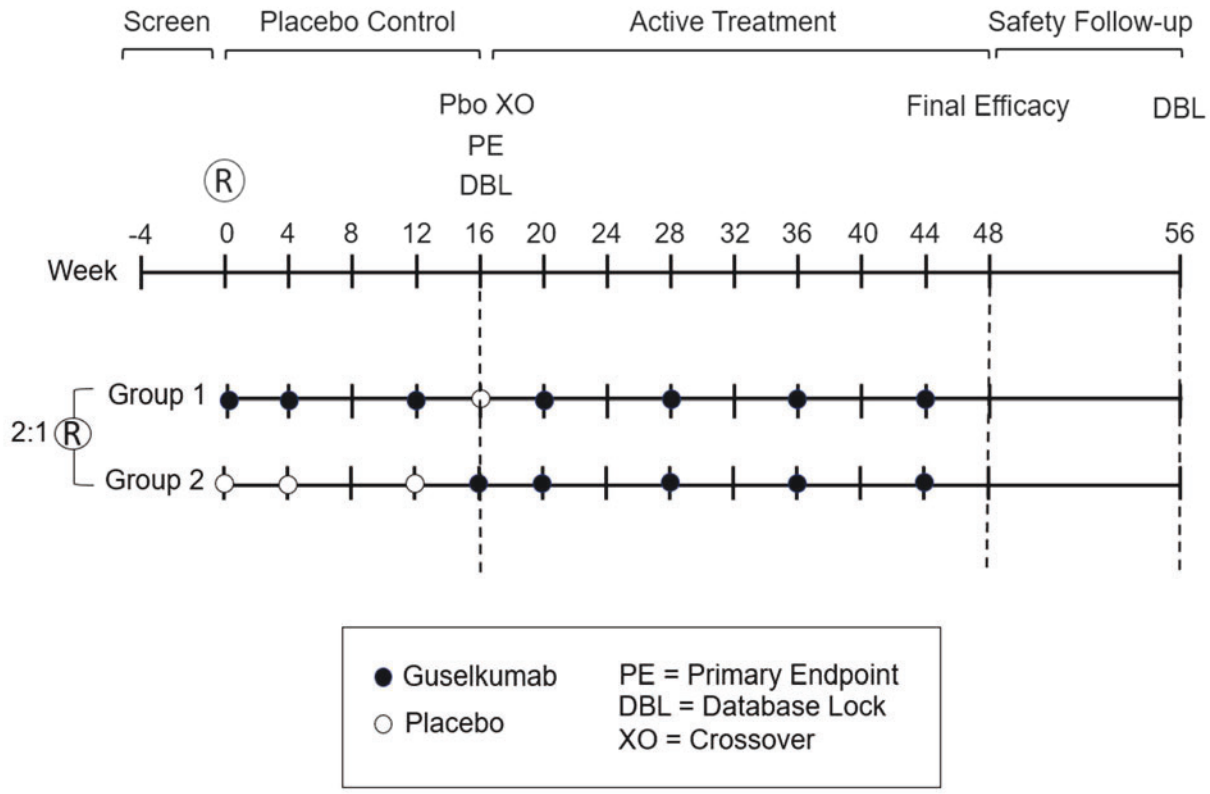
Week 0 through Week 16 (Placebo Controlled Period)

- Group I (n=200): guselkumab [redacted] at Weeks 0, 4, and 12. Placebo will be administered at Week 16 to maintain the blind.
- Group II (n=100): placebo at Weeks 0, 4, and 12 followed by guselkumab [redacted] at Weeks 16

From Week 0 through Week 44 (Placebo Controlled and Active Treatment Period)

- Group I (n=200): guselkumab group who will receive guselkumab [redacted] at Weeks 0 and 4 and then [redacted] through Week 44. Placebo will be administered at Week 16 to maintain the blind.
- Group II (n=100): placebo group who will receive placebo at Weeks 0, 4, and 12 after which they will cross over to receive guselkumab at Weeks 16, 20, 28, 36, and 44.

Figure 1: Schematic Overview of the Study



A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are

evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints. Comparisons are planned between guselkumab and placebo at Week 16.

2. STATISTICAL HYPOTHESES

It is hypothesized that guselkumab is superior to placebo in the treatment of low BSA moderate plaque psoriasis with special site involvement as assessed by the proportion of participants who achieve an IGA score of cleared (0) or minimal (1) at Week 16 (primary hypothesis)

3. SAMPLE SIZE DETERMINATION

Primary Endpoint

A sample size of approximately 300 participants (200 participants on guselkumab and 100 participants on placebo) will allow at least 90% power to detect treatment effect differences of 45% between guselkumab (60%) and placebo (15%) for the primary endpoint with a 2-sided alpha level of 0.05 (Table 3).

Table 3. Power Calculations for Primary Endpoints Based on Previous Studies

Primary endpoint	Placebo (N = 100)	Guselkumab (N = 200)	Delta	Power
Proportion of participants who achieve an IGA score of 0 or 1 with at least ≥ 2 grade improvement from baseline at Week 16	15%	55% **60%**	40% **45%**	>99% **>99%**

Major Secondary Endpoints

Table 4 provides the statistical power for special site related major secondary endpoints. The sample size is also chosen to ensure an adequate number of participants with low BSA moderate plaque psoriasis with each special site (scalp, face, intertriginous, and genital) involvement. The study will target to enroll approximately 25% of participants (i.e., 50 participants on guselkumab and 25 participants on placebo) for each special site. Fifty participants on guselkumab and 25 participants on placebo can achieve 90% power to detect a difference between the group proportions of 35% to 38% (Table 4).

Table 5 provides the statistical power for selected major secondary endpoints with 200 participants assigned to guselkumab and 100 assigned to placebo. This will provide at least 99% power to detect difference between gueslkmab and placebo for the selected major secondary endpoints assuming a 2-sided alpha level of 0.05.

Table 4: Treatment Difference (Delta) Detection for Each Special Site Involvement

Endpoint for each special site	Placebo (n=25)	Guselkumab (n=50)	Delta	Power
The proportion of participants who achieve a scalp-specific Investigator's Global Assessment (ss-IGA) score of absence of disease (0) or very mild disease (1) at Week 16 among randomized participants with an ss-IGA score ≥3 at baseline	15%	52%	37%	90%
The proportion of participants who achieve a static Physician's Global Assessment of Genitalia (sPGA-G) of clear (0) or minimal (1) at Week 16 among randomized participants with an sPGA-G score ≥3 at baseline	10%	45%	35%	90%
The proportion of participants who achieve a intertriginous IGA (i-IGA) score of clear (0) or minimal (1) at Week 16 among randomized participants with an i-IGA score ≥3 at baseline	10%	45%	35%	90%
The proportion of participants who achieve a facial IGA (f-IGA) of clear (0) or minimal (1) at Week 16 among randomized participants with an f-IGA score ≥3 at baseline	25%	63%	38%	90%

Table 5: Power Calculations for Selected Major Secondary Endpoints Based on Previous Studies

Major secondary endpoints	Placebo (n=100)	Guselkumab (n=200)	Delta	Power
Percentage change from baseline in PASI score at Week 16	0.6%	37.4 %	36.8%	>99%
The proportion of participants who achieve an IGA score of cleared (0) at Week 16	1.1%	47.7%	47.0%	>99%
The proportion of participants who achieve a PASI 90 response at Week 16	2.9%	73.3%	70.4%	>99%
The proportion of participants who achieve a PASI 100 response at Week 16	0.6%	37.40%	37%	>99%
The change from baseline in PSSD symptom score at Week 16	-3.0 (19.56)	-41.9 (24.61)	-38.9	>99%
The proportion of participants who achieve ≥ 4-point reduction (improvement) in Psoriasis Symptom and Sign Diary (PSSD) itch score from baseline at Week 16, among participants with a PSSD itch score ≥ 4 at baseline	5.7%	75.1%	69.4%	>99%
The proportion of participants with PSSD Individual Symptom Scale Score =0 at Week 16 among participants with PSSD >0 at baseline	0.8%	27.0%	26.2%	>99%

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

The analysis sets and the descriptions are defined below in Table 6.

Table 6: Analysis Sets

Analysis Sets	Description
Enrolled	All participants who signed the informed consent form (ICF). This analysis set will be used for summarizing the overall study completion/withdrawal information.

Table 6: Analysis Sets

Analysis Sets	Description
Full Analysis Set (FAS) -Efficacy Analysis Set	All participants who were randomized in the study. This analysis set will be used for the efficacy analyses.
Per Protocol Analysis Set (PPAS)	The per protocol analysis set includes a subset of participants in the Efficacy Analysis Set who were in compliance with the protocol. Specifically, the per-protocol population includes all randomized participants except those: 1. Who did meet inclusion criteria 3 or 4 • Overall IGA 3 (moderate) plaque psoriasis AND BSA 2-15% with at least 1 plaque outside of special sites AND Involvement of at least 1 special site with at least moderate severity. Qualifying sites include scalp with ss-IGA >=3, face with f-IGA >=3, intertriginous with i-IGA >=3 or genital with sPGA-g >=3 • Be inadequately controlled with or intolerant of at least 1 prior topical therapy (including but not limited to: corticosteroids, retinoids, vitamin D, or Vitamin D/steroid and retinoid/steroid combinations, tacrolimus, pimecrolimus, anthralin/dithranol, coal tar preparations, tapinarof, roflumilast, etc) 2. Who violated the exclusion diagnosis criteria in the protocol as listed below (1 or 2): • Has a non-plaque form of psoriasis (erythrodermic, guttate, or pustular) • Has current drug-induced psoriasis (e.g. a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium) 3. Who violated the exclusion criteria pertaining to prior psoriasis medication criteria (EC 5,6,7) in the protocol as listed below: • Ever received: Must be naïve to prior biologic (or biosimilars of) for the treatment of psoriasis, PsA, or any other indications that could impact the assessment of psoriasis. Prior biologics (or biosimilars of) may include, but not limited to, tumor necrosis factor (TNF)-inhibitors (e.g., adalimumab, etanercept, infliximab, or certolizumab or biosimilars), IL-17 inhibitors (e.g., secukinumab, ixekizumab, brodalumab, or bimekizumab), and IL-12/23 inhibitors (e.g., ustekinumab), or IL-23 inhibitor (e.g., guselkumab, risankizumab, or tildrakizumab). • Within 4 weeks: a) Any systemic immunosuppressants (e.g., methotrexate [MTX], azathioprine, cyclosporine, inhibitors of the JAK/TYK pathway, 6-thioguanine, mercaptopurine, mycophenolate mofetil, tacrolimus, acitretin, or anakinra). b) Any systemic medications that could affect psoriasis efficacy evaluations (including but not limited to oral or injectable corticosteroids, PDE4 pathway inhibitors [e.g., apremilast], retinoids [acitretin], 1, 25 dihydroxy vitamin D3 and analogs, psoralens, sulfasalazine, hydroxyurea, and fumaric acid derivatives etc.).c) Phototherapy or narrow band laser (e.g., Excimer or XTRAC). d) Lithium, antimalarials, or intramuscular (IM) gold. • Within 2 weeks: a) Any topical medications that could affect psoriasis efficacy evaluations (including but not limited to corticosteroids, retinoids, or vitamin D analog preparations, calcipotriene and betamethasone dipropionate

Table 6: Analysis Sets

Analysis Sets	Description
	ointment or foam, tacrolimus, pimecrolimus, anthralin/dithranol, coal tar preparations, PDE4 inhibitors, e.g., crisaborole, or other topicals used for the treatment of psoriasis, e.g., tapinarof, roflumilast, etc.). b) Any herbal or traditional medicines that could affect psoriasis efficacy evaluations (including but not limited to Chinese, Taiwanese, Korean, and other ethnic medicines). 4. Who did not complete the specified exposure to study agent as outlined below: • Participants randomized to placebo who received guselkumab prior to Week 16 • Participants randomized to guselkumab at Week 0 but did not receive all scheduled guselkumab administrations or received one or more placebo administrations prior to Week 16. Participants who discontinued the study agent due to unsatisfactory therapeutic effect or an adverse event (AE) of worsening of psoriasis, or participants who started prohibited medications and continued receiving study agents prior to the timepoint of per-protocol analysis will be included in the per-protocol analysis and ICE rules specified will apply. .
Scalp Special Site Analysis Set (SSSAS)	All participants who were randomized with ss-IGA score ≥3 at baseline. This analysis set will be used for the efficacy analyses for the scalp special site.
Genital Special Site Analysis Set (GSSAS)	All participants who were randomized with sPGA-G score ≥3 at baseline. This analysis set will be used for the efficacy analyses for the genital special site.
Intertriginous Special Site Analysis Set (ISSAS)	All participants who were randomized with an (i)-IGA score ≥3 at baseline. This analysis set will be used for the efficacy analyses for the intertriginous special site.
Facial Special Site Analysis Set (FSSAS)	All participants who were randomized with f-IGA score ≥3 at baseline. This analysis set will be used for the efficacy analyses for the face special site.
Safety Analysis Set (SAS)	All participants who received at least 1 (complete or partial) administration of study intervention (i.e., the treated population).
Immunogenicity Analysis Set (IAS)	All participants who received at least 1 (complete or partial) administration of guselkumab and who had at least 1 sample obtained after their first administration of guselkumab
PK Analysis Set (PKAS)	All participants who received at least 1 complete administration of guselkumab and had at least 1 valid blood sample drawn for PK analysis
PD Analysis Set (PDAS)	All participants who received at least 1 (complete or partial) administration of study intervention

5. STATISTICAL ANALYSES

5.1. General Considerations

In general, descriptive statistics will include counts and percentages for categorical variables, and mean, standard deviation (SD), median, interquartile (IQ) range, minimum, and maximum for continuous variables. Graphical data displays may also be used to summarize the data.

In this study, efficacy will be evaluated through Week 48. In addition, PK, immunogenicity, PD, biomarker, and safety measurement, and selected participant information data will be collected through Week 56.

Analyses and summaries (including overtime summaries) in general will be carried out during the following study periods when appropriate:

1. From Week 0 through Week 16 (Placebo Controlled Period)

2. From Week 0 through Week 48 (Placebo Controlled and Active Treatment Period)

3. From Week 0 through Week 56

Binary Response Efficacy Endpoints

For binary response efficacy endpoints, treatment comparisons will generally be performed using a Cochran-Mantel-Haenszel (CMH) test stratified by special site (scalp, face, intertriginous, and genital) involvement. The magnitude of the treatment difference will be estimated by the difference in response rates between the guselkumab and placebo groups with a 95% confidence interval (CI) calculated based on Wald statistics (Kim and Won, 2013).

For special site related binary response efficacy endpoints, treatment comparisons will generally be performed using a Chi-squared test. The magnitude of the treatment difference will be estimated by the difference in response rates between the guselkumab and placebo groups with a 95% confidence interval (CI) calculated.

In case of rare events the Fisher's exact test will be used for treatment comparisons as appropriate. The proportion difference between guselkumab group and placebo and the exact confidence interval will be calculated. In these analyses, participants with missing data will be imputed as not achieving the response.

Continuous Efficacy Endpoints

For continuous efficacy endpoints, treatment comparisons will be performed using a Mixed Effects Model for Repeated Measures (MMRM), which relies on the Missing at Random (MAR) assumption for the missing responses. Under the assumption of MAR, the missing data will be accounted for through correlation of repeated measures in the model.

The explanatory variables of the MMRM model will include treatment group, visit, baseline efficacy endpoint score, special site (scalp, face, intertriginous, and genital) an interaction term of visit with treatment group, and an interaction term of visit with baseline efficacy endpoint score. An unrestricted (UN) variance-covariance matrix for repeated measures within a participant will be used. If the model with unstructured covariance structure does not converge, alternative covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz (TOEPH) or autoregressive of order 1 (AR (1)).

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

The change from baseline is calculated as the post baseline value minus the baseline value.

Change from baseline= Post Baseline Value – Baseline Value

Percent Change from Baseline= ((Post Baseline Value-Baseline Value)/Baseline Value) *100

If a higher score indicates more severe disease in efficacy assessments, then a negative change indicates an improvement, and a positive change indicates worsening.

The treatment difference between a guselkumab group and the placebo group will be estimated by the difference in the LS means. The 95% CIs for the differences in LS means and p-values will be calculated.

Time to an Event Efficacy Endpoints

Survival analysis techniques such as life-table estimates will be calculated for time to event efficacy endpoints for the 2 treatment groups. The log-rank test stratified by special site (scalp, face, intertriginous, and genital) will be used to compare the time to event efficacy endpoints. For the special site related endpoints, stratification will not be used for the log rank test to compare the time to event efficacy endpoints.

5.1.1. Visit Windows

5.1.1.1. Visit Windows for Dosing and PK Analysis

All post-baseline visits from Baseline through Week 16 will have a visit window of ± 7 days counting from week 0 as Day 1. If a study visit occurs outside this window, the Sponsor should be consulted about how the participant should resume his or her normal dose schedule.

For PK analyses, if a participant has an administration outside the visit window at a visit, the concentration data collected at and after that visit will be excluded from the by-visit data analyses.

Information regarding study intervention administrations that are administered outside of the scheduled windows or missed will be recorded. Participant charts and worksheets may be reviewed and compared with the data entries on the eCRFs to ensure accuracy.

5.2. Participant Dispositions

The number of participants screened will be summarized overall.

Disposition will include tabulations, by randomized treatment group, of the number of participants who discontinued study agent administration, the primary reasons for discontinuation of study agent administration, the number of participants who discontinued study participation, and the primary reason for discontinuation of study participation.

Tabulations by randomized treatment group will also be provided for participants who met 1 or more ICE criteria as defined in Section 5.3.2.

Disposition data will be summarized through the study periods that include but are not limited to the following:

1. From Week 0 through Week 16 (Placebo Controlled Period)
2. From Week 0 through Week 48 (Placebo Controlled and Active Treatment Period)
3. From Week 16 through Week 48 (Active Treatment Period)

In addition, participants who were randomized but never treated and participants who were unblinded during the study will be presented in data listings.

5.3. Primary Endpoint(s) Analysis

The proportion of participants who achieve an Investigator's Global Assessment (IGA) score of cleared (0) or minimal (1) at Week 16. The primary endpoint analysis will be compared between the guselkumab treatment and the placebo treatment group and tested at a 2-sided α-level of 0.05.

Composite Strategy

The Composite Strategy assesses the treatment effects not only based on the variable measurements, but also based on intercurrent events (ICE) defined in Section 5.3.2.1.

If a participant met any of the ICEs in categories 1-2, then it will be handled with the composite strategy. Under the composite strategy, participants with the ICE prior to Week 16 will be treated as non-responders for the IGA cleared (0) or minimal (1) response for the primary analysis, regardless of the observed data.

Treatment Policy Strategy

If a participant met the ICE 3, then it will be handled with a treatment policy. Observed value will be used if available. For participants experiencing multiple ICEs, an ICE in categories 1-2 will supersede an ICE in category 3.

5.3.1. Definition of Endpoint(s)

5.3.1.1. Investigator's Global Assessment (IGA)

The Investigator's Global Assessment (IGA) documents the investigator's assessment of the Participant'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). Primary efficacy endpoints related to the IGA score is defined below:

IGA cleared or minimal responder

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

5.3.2. Estimand

5.3.2.1. Primary Estimand (Estimand 1)

The primary endpoint is the proportion of participants achieving an IGA score of 0/1 response at Week 16. This endpoint will be analyzed based on the estimands defined by the following 5 components:

- **Population:** Participants with low body surface area (BSA) moderate plaque psoriasis with special site involvement.
- **Treatment:**
  - Placebo
  - Guselkumab
- **Variable (Endpoints):** The proportion of participants who achieve an Investigator's Global Assessment (IGA) score of cleared (0) or minimal (1) at Week 16 . Participants who have intercurrent events (ICEs) 1-2 (defined below) prior to Week 16 will be considered as not achieved for IGA 0/1 response, regardless of the observed data.
- **Intercurrent Events (ICEs):** The following are the ICEs and corresponding strategies for this trial.
- 1. Initiated protocol prohibited medications/therapies for psoriasis, except for the following
  a) If the prohibited medication is a corticosteroid and was used for an indication other than psoriasis and for <=2 weeks (short term use)
  b) If the prohibited medication is a corticosteroid and the mode of delivery is inhaled, otic, ocular, nasal or other route of mucosal delivery.

  2. Discontinued study intervention due to lack of efficacy (e.g., lack of efficacy or an AE of worsening of psoriasis)

  3. Treatment discontinuation due to reasons other than ICE 2.

  ICE categories 1 to 2 will follow the composite strategy, where participants who meet them prior to Week 16 will be considered as nonresponders for IGA cleared (0) or minimal (1) response for the primary analysis, regardless of the observed data. The ICE category 3 will follow the treatment policy strategy, where participants who meet them prior to week 16, will use the observed values. For participants experiencing multiple ICEs, an ICE in categories 1 to 2 will supersede an ICE in category 3.
- **Population level summary:** Difference in proportion of participants who achieve an IGA score of cleared or minimal (IGA 0/1) between guselkumab and placebo at Week 16.

5.3.2.2. Supplementary Estimand (Estimand 2)

In this supplementary estimand, all intercurrent events are addressed by the **composite strategy**. The components of the supplementary estimand and variable (endpoint) are the same as those for the primary estimand.

Under Estimand 2, participants who have intercurrent events ICE 1-3 prior to the Week 16 will have non-response for the primary endpoint response, regardless of the observed data.

5.3.3. Analysis Methods

The primary endpoint will be analyzed at Week 16 DBL based on the primary estimand. If a participant experiences ICE of 1 or 2 prior to Week 16, will be treated as non-responders for, IGA score of cleared (0) or minimal (1) response, for the primary analysis. If a participant experiences ICE of 3 then observed value will be used if available.

This primary analysis will include all data collected up to and including Week 16 for all participants in the primary efficacy analysis set. In these primary efficacy analyses, data from all randomized participants will be analyzed according to their assigned treatment group. The primary endpoint at Week 16 will be summarized for each treatment group.

To address the primary objective, a 2-sided (α=0.05) CMH chi-squared test stratified by special site (scalp, face, intertriginous, genital) will be used for the primary endpoint.

Statistical analysis for both primary (Estimand 1) and supplementary estimand (Estimand 2) are the same.

The overall Type I error rate will be controlled at the significance level of 0.05. The study will be considered positive if the guselkumab group is significantly different from the placebo. Primary endpoint will be tested at a 2-sided α-level of 0.05.

If the comparison is positive for the primary endpoint, the testing will continue to the major secondary endpoint.

Participants with ICE categories of 1 or 2 before Week 16 will be considered as non-responders at Week 16. Participants with ICE category of 3 before Week 16, observed data will be utilized in the analysis. After accounting for the ICEs for the primary estimand, participants with the missing data of the primary endpoint at Week 16 will be considered as non-responders.

5.3.4. Subgroup Analyses

The consistency of treatment effect, the primary endpoint will be evaluated for the subgroups defined in Section 5.7.8, using the primary estimand **(Estimand 1**). For each subgroup analysis, the analysis set is the individual subgroup (Section 5.7.8) of the primary efficacy analysis set.

- For each of the subgroups, the difference between the guselkumab treatment group and placebo group in the proportion of participants achieving IGA score of cleared (0) or

minimal (1) at Week 16 and its 95% confidence interval (when the numbers of participants permit) will be calculated.

In addition, the primary endpoint at Week 16 by region, country and investigator site will be summarized.

5.3.5. Summary of Analyses Related to the Primary Endpoint

Table 7 below provides an overview of the analyses related to the primary endpoints, the estimands, the analysis sets, the data handling rules to be used, and the analysis methods and summary statistics.

Table 7: Summary of Analyses Related to the Primary Endpoint at Week 16

Analysis (Analysis Set)	Missing data	Analysis method/Summary statistics
Analyses based on **Primary Estimand (Estimand 1)**, where ICEs 1-2 are handled by the **composite strategy**, and ICE 3 is handled by the **treatment policy strategy**		
Full Analysis Set (FAS)	Missing data due to missed visits or missed data collection. Participants with missing data are considered to be non-responders' imputation (NRI)	• Summaries of the proportion of participants who achieved the endpoint • Treatment difference (guselkumab group-placebo group) and 95% CI • P-values based on CMH chi-squared test stratified by special site and represent the comparison with placebo.
Subgroup Analyses (Individual subgroup levels defined in Section 5.7.8, Full Analysis Set (FAS))	Missing data due to missed visits or missed data collection. Participants with missing data are considered to be non-responders' imputation (NRI)	• Summaries of the proportion of participants who achieved the endpoint by subgroup • Treatment difference (guselkumab group-placebo group) and 95% CI • P-values based on CMH chi-squared test stratified by special site and represent the comparison with placebo.
Analyses based on **Supplementary Estimand (Estimand 2)**, where all the intercurrent events are addressed by the **composite strategy** in which non-responder is used after the occurrence of an ICE.		
Supplementary Analysis 1 (Full Analysis Set (FAS))	Missing data due to missed visits or missed data collection. Participants with missing data are considered to be non-responders' imputation (NRI)	• Summaries of the proportion of participants who achieved the endpoint • Treatment difference (guselkumab group-placebo group) and 95% CI • P-values based on CMH chi-squared test stratified by special site and represent the comparison with placebo.

5.4. Secondary Endpoint(s) Analysis

5.4.1. Major Secondary Endpoint(s)

There are 12 major secondary endpoints for this study and listed below:

To evaluate the additional efficacy of guselkumab vs placebo

1. Change from baseline in BSA affected at Week 16
2. Change from baseline in total Psoriasis Area Severity Index (PASI) score at Week 16
3. The proportion of participants who achieve an IGA score of cleared (0) at Week 16
4. The proportion of participants who achieve a PASI 90 response at Week 16
5. The proportion of participants who achieve a PASI 100 response at Week 16
6. The proportion of participants who achieve a scalp-specific IGA (ss-IGA) score of absence of disease (0) or very mild disease (1) at Week 16 among randomized participants with an ss-IGA score ≥3 at baseline.
7. The proportion of participants who achieve a static Physician's Global Assessment of Genitalia (sPGA-G) score of clear (0) or minimal (1) at Week 16 among randomized participants with an sPGA-G score ≥3 at baseline
8. The proportion of participants who achieve an intertriginous IGA (i-IGA) score of clear (0) or minimal (1) at Week 16 among randomized participants with an i-IGA score ≥3 at baseline
9. The proportion of participants who achieve a facial IGA (f-IGA) score of clear (0) or minimal (1) at Week 16 among randomized participants with an f-IGA score ≥3 at baseline
10. The change from baseline in Psoriasis Symptom and Sign Diary (PSSD) total symptom score at Week 16
11. The proportion of participants who achieve ≥ 4-point reduction (improvement) from baseline in the Psoriasis Symptom and Sign Diary (PSSD) itch score at Week 16, among participants with baseline PSSD itch score ≥ 4 at baseline
12. The proportion of participants with PSSD individual symptom scale score= 0 at Week 16, among randomized participants with baseline PSSD>0 at baseline. (Note: In this endpoint "individual symptom scale score =0" is defined as "total symptom score =0"

5.4.1.1. Definition of Endpoint(s)

5.4.1.1.1. Body or Scalp Surface Area Affected by Psoriasis

The Body Surface Area (BSA) is a measurement of involved skin over the whole body. The overall BSA affected by psoriasis is estimated based on the participant's handprint (defined as the entire palmar surface of the hand including fingers). The surface area of the whole body is made up of approximately 100 "handprints" (as one "handprint" equates to approximately 1% of total body surface area).

The Scalp Surface Area (SSA) is a measurement of involved skin on the scalp. The adult SSA is around 520-705 cm^2, meaning that 1% SSA is about 5.2-7.1 cm^2. The thumbprint has an average surface area of about 5.5 $cm^2 \pm 1.3$ cm^2. Hence, the thumb (in particular, the thumb projection) can be used as a tool for accurate measurement of 1% SSA). The overall SSA affected by psoriasis can thus be estimated based on the participant's thumb.

5.4.1.1.2. Psoriasis Area and Severity Index (PASI)

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 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. Primary efficacy endpoint related to the PASI score is defined below:

PASI 90 Responder

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

PASI 100 Responder

Participants with a PASI score of 0 will be considered PASI 100 responders.

5.4.1.1.1. Investigator's Global Assessment (IGA) related endpoints

IGA cleared responder

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

5.4.1.1.2. Scalp-Specific Investigator's Global Assessment (ss-IGA)

The ss-IGA instrument is used to evaluate the disease severity of scalp psoriasis. The lesions are assessed in terms of the clinical signs of redness, thickness, and scaliness which are scored as: absence of disease (0), very mild disease (1), mild disease (2), moderate disease (3), or severe disease (4). The analysis for ss-IGA will be based on participants randomized at week 0 with baseline ss-IGA score ≥3. Efficacy endpoints related to the ss-IGA score is defined below:

ss-IGA absence of disease (0) or very mild disease (1) responder

Participants who achieve ss-IGA score of absence of disease (0) or mild disease (1) will be considered ss-IGA absence of disease (0) or very mild disease (1) responders.

ss-IGA absence of disease responder

Participants who achieve ss-IGA score of absence of disease (0) will be consider ss-IGA absence of disease responders.

5.4.1.1.3. Static Physician Global Assessment of Genitalia (sPGA-G)

The sPGA-G is used to evaluate the disease severity of genital psoriasis. Severity is determined by a combination of 3 plaque characteristics (erythema, elevation, and scale) based on the descriptions of each characteristic. The 6-point scale and associated severity categories are clear (0), minimal (1), mild (2), moderate (3), severe (4), and very severe (5).

sPGA-G clear (0) or minimal (1) responder

Participants who achieve sPGA-G score of clear (0) or minimal (1) will be considered sPGA-G clear or minimal responders.

5.4.1.1.4. Intertriginous Psoriasis Investigator's Global Assessment (i-IGA)

The IGA used for the full body assessment has been adapted with descriptions of disease features that are more consistent with intertriginous psoriasis presentation. The intertriginous areas affected to be scored include the axillary, sub-mammary, abdominal fold, inguinal, and intergluteal cleft/peri-anal region (distinct from genital/perineum involvement). The 5-point scale and associated severity categories are clear (0), minimal (1), mild (2), moderate (3), and severe (4). It should be noted that erythema may be the predominant feature and there may or may not be the presence of elevation or scaling. Therefore, scoring may be predominantly driven by the severity of erythema if it is the dominant presenting feature.

i-IGA clear (0) or minimal (1) responder

Participants who achieve i-IGA score of clear (0) or minimal (1) will be considered i-IGA clear or minimal responders.

5.4.1.1.5. Facial Psoriasis Investigator's Global Assessment (f-IGA)

The same IGA used for the full body assessment will be adapted for use, but only the face will be scored. The 5-point scale and associated severity categories are clear (0), minimal (1), mild (2), moderate (3), and severe (4). It should be noted that erythema, and to an extent, scaling, are the more prominent features of facial psoriasis and less often elevation. Therefore, scoring may be predominantly driven by the severity of erythema and scaling if these are the dominant presenting features.

f-IGA clear (0) or minimal (1) responder

Participants who achieve f-IGA score of clear (0) or minimal (1) will be considered f-IGA clear or minimal responders.

5.4.1.1.6. Psoriasis Symptom and Sign Diary (PSSD)

The PSSD includes PRO questionnaires designed to measure the severity of psoriasis symptoms and signs for the assessment of treatment benefits. The 7-day recall version asks the participant to answer the PRO questions thinking about the last 7 days. The PSSD is a self-administered PRO instrument and includes 11 items covering symptoms (itch, pain, stinging, burning and skin tightness) and patient observable signs (skin dryness, cracking, scaling, shedding or flaking, redness and bleeding) using 0 to 10 numerical rating scales for severity. Two subscores will be derived: the psoriasis symptom score and the psoriasis sign score. A higher score indicates more severe disease. For the entire study, from the screening visit through Week 48, participants will complete the 7-day recall version of the PSSD at study visits as indicated in the Schedule of Activities (See in the protocol).

The calculations of PSSD symptom, and sign scores are listed below:

Symptom Score (0-100)

a. Symptom score includes itch (Q1), pain (Q11), stinging (Q10), burning (Q9) and skin tightness (Q4).

b. Averaging items on the daily symptom scores when at least 3 items (≥ 50% of 5 items) on this scale are answered. Then, the average value is converted into 0-100 scoring such that Symptom score = average value x 10 with 0 representing the least severe and 100 the most severe.

Sign Score (0-100)

a. Sign score includes skin dryness (Q2), cracking (Q3), scaling (Q5), shedding or flaking (Q6), redness (Q7) and bleeding (Q8).

b. Averaging items on the sign scores when at least 3 items (≥50% of 6 items) on this scale are answered. Then, the average value is converted into 0-100 scoring such that Sign score = average value x 10 with 0 representing the least severe and 100 the most severe.

Seven daily symptom scores, and sign scores are averaged into a weekly score respectively (ie 7 days [from day -7 to -1] prior to a visit]. Four days out of 7 days (either consecutive or nonconsecutive) are necessary to derive a weekly score; otherwise, data are considered missing for that week.

Achieving ≥ 4-point reduction (improvement) in PSSD itch score

Participant achieving at least a 4-point improvement from baseline in PSSD itch score.

PSSD symptom score of 0 a PSSD symptom score of 0

Participant achieving a PSSD symptom score of 0.

5.4.1.2. Estimand(s)

The following describe the attributes of the estimands for the major secondary endpoints (corresponding to Estimands 3-14):

- Population: Participants with low body surface area (BSA) moderate plaque psoriasis with special site involvement.
- Treatment:

  - Placebo

  - Guselkumab

Table 8: Variables, Population-level Summary, and Intercurrent Event Strategy for each Major Secondary Endpoint (for Estimands 3-14)

Estimands	Variable (Endpoint)	Population-level summary	Intercurrent Event Strategy
3	The change from baseline in BSA affected at Week 16.	Difference in mean percentage change from baseline in BSA affected at Week 16 between guselkumab group and placebo group.	Percentage change from baseline in BSA affected at Week 16 will be set to have zero change after the occurrence of ICE 1 or 2. Observed value will be used for BSA affected after the occurrence of ICE 3. For participants experiencing multiple ICEs, an ICE in categories 1 or 2 will supersede an ICE in category 3.

Table 8: Variables, Population-level Summary, and Intercurrent Event Strategy for each Major Secondary Endpoint (for Estimands 3-14)

Estimands	Variable (Endpoint)	Population-level summary	Intercurrent Event Strategy
4	The change from baseline in PASI score at Week16.	Difference in mean percentage change from baseline in PASI score at Week 16 between guselkumab group and placebo group.	Percentage change from baseline in PASI score at Week 16 will be set to have zero change after the occurrence of ICE 1 or 2. Observed value will be used for PASI score after the occurrence of ICE 3. For participants experiencing multiple ICEs, an ICE in categories 1 or 2 will supersede an ICE in category 3.
5	The proportion of participants who achieve an IGA score of cleared (0) at Week 16.	Difference in proportion of participants who achieve an IGA score of cleared (0) at Week 16 between guselkumab group and placebo group.	A nonresponder status will be assigned to IGA score of cleared (0) after the occurrence of ICE 1 or 2. In addition, participants with missing IGA score of cleared (0) response at Week 16 or who do not return for evaluation at Week 16 will be considered to not have achieved IGA score of cleared (0) at Week 16. Observed value will be used for IGA score of cleared (0) response after the occurrence of ICE 3. For participants experiencing multiple ICEs, an ICE in categories 1 or 2 will supersede an ICE in category 3.
6	The proportion of participants who achieve a PASI 90 response at Week 16.	Difference in proportion of participants who achieve a PASI 90 response at Week 16 between guselkumab group and placebo group.	A nonresponder status will be assigned to PASI 90 response after the occurrence of ICE 1 or 2. In addition, participants with missing PASI 90 responses at Week 16 or who do not return for evaluation at Week 16 will be considered to not have achieved PASI 90 at Week 16. Observed value will be used for PASI 90 after the occurrence of ICE 3. For participants experiencing multiple ICEs, an ICE in categories 1 or 2 will supersede an ICE in category 3.
7	The proportion of participants who achieve a PASI 100 response at Week 16.	Difference in proportion of participants who achieve a PASI 100 response at Week 16 between guselkumab group and placebo group.	A nonresponder status will be assigned to PASI 100 response after the occurrence of ICE 1 or 2. In addition, participants with missing PASI 100 responses at Week 16 or who do not return for evaluation at Week 16 will be considered to not have achieved PASI 100 at Week 16. Observed value will be used for PASI 100 after the occurrence of ICE 3 . For participants experiencing multiple ICEs, an ICE in categories 1 or 2 will supersede an ICE in category 3 .

Table 8: Variables, Population-level Summary, and Intercurrent Event Strategy for each Major Secondary Endpoint (for Estimands 3-14)

Estimands	Variable (Endpoint)	Population-level summary	Intercurrent Event Strategy
8	The proportion of participants who achieve a scalp-specific IGA (ss-IGA) score of absence of disease (0) or very mild disease (1) at Week 16 among randomized participants with an ss-IGA score ≥3 at baseline	Difference in proportion of participants who achieve ss-IGA score of absence of disease (0) or very mild disease (1) at Week 16 between guselkumab group and placebo group.	A nonresponder status will be assigned to ss-IGA score of absence of disease (0) or very mild disease (1) after the occurrence of ICE 1 or 2. In addition, participants with missing ss-IGA score of absence of disease (0) or very mild disease (1) response at Week 16 or who do not return for evaluation at Week 16 will be considered to not have achieved IGA score of cleared (0) at Week 16. Observed value will be used for IGA score of cleared (0) response after the occurrence of ICE 3. For participants experiencing multiple ICEs, an ICE in categories 1 or 2 will supersede an ICE in category 3.
9	The proportion of participants who achieve a static Physician's Global Assessment of Genitalia (sPGA-G) score of clear (0) or minimal (1) at Week 16 among randomized participants with an sPGA-G score ≥3 at baseline	Difference in proportion of participants who achieve sPGA-G score of clear (0) or minimal (1) at Week 16 between guselkumab group and placebo group.	A nonresponder status will be assigned to sPGA-G score of clear (0) or minimal (1)) after the occurrence of ICE 1 or 2. In addition, participants with missing achieve sPGA-G score of clear (0) or minimal (1) response at Week 16 or who do not return for evaluation at Week 16 will be considered to not have achieved sPGA-G at Week 16. Observed value will be used for sPGA-G score of clear (0) or minimal (1) response after the occurrence of ICE 3. For participants experiencing multiple ICEs, an ICE in categories 1 or 2 will supersede an ICE in category 3.
10	The proportion of participants who achieve an intertriginous IGA (i-IGA) score of clear (0) or minimal (1) at Week 16 among randomized participants with an i-IGA score ≥3 at baseline	Difference in proportion of participants who achieve i-IGA score of clear (0) or minimal (1) at Week 16 between guselkumab group and placebo group.	A nonresponder status will be assigned to i-IGA score of clear (0) or minimal (1)) after the occurrence of ICE 1 or 2. In addition, participants with missing achieve i-IGA score of clear (0) or minimal (1) response at Week 16 or who do not return for evaluation at Week 16 will be considered to not have achieved i-IGA at Week 16. Observed value will be used for i-IGA score of clear (0) or minimal (1) response after the occurrence of ICE 3. For participants experiencing multiple ICEs, an ICE in categories 1 or 2 will supersede an ICE in category 3.
11	The proportion of participants who achieve a facial IGA (f-IGA) score of clear (0) or minimal (1) at Week 16 among randomized participants with	Difference in proportion of participants who achieve i-IGA score of clear (0) or minimal (1) at Week 16 between guselkumab group and placebo group.	A nonresponder status will be assigned to i-IGA score of clear (0) or minimal (1)) after the occurrence of ICE 1 or 2. In addition, participants with missing achieve i-IGA score of clear (0) or minimal (1) response at Week 16 or who do not return for evaluation at Week 16 will be considered to not have achieved i-IGA at Week 16. Observed value will be used for i-IGA score of clear (0) or minimal (1) response after the occurrence of ICE 3. For participants experiencing multiple ICEs, an ICE in categories 1 or 2 will supersede an ICE in category 3.

Table 8: Variables, Population-level Summary, and Intercurrent Event Strategy for each Major Secondary Endpoint (for Estimands 3-14)

Estimands	Variable (Endpoint)	Population-level summary	Intercurrent Event Strategy
	an f-IGA score ≥3 at baseline		
12	The change from baseline in PSSD symptom score at Week 16	Difference in mean change from baseline in PSSD symptom score at Week 16 between guselkumab group and placebo group.	Change from baseline in PSSD symptom score at Week 16 will be set to have zero change after the occurrence of ICE 1 or 2. Observed value will be used for PSSD symptom score after the occurrence of ICE 3. For participants experiencing multiple ICEs, an ICE in categories 1 or 2 will supersede an ICE in category 3.
13	The proportion of participants who achieve ≥ 4-point reduction (improvement) from baseline in the Psoriasis Symptom and Sign Diary (PSSD) itch score at Week 16, among participants with baseline PSSD itch ≥ 4 at baseline.	Difference in proportion of participants who achieve ≥ 4-point reduction (improvement) from baseline in the Psoriasis Symptom and Sign Diary (PSSD) itch score at Week 16, among participants with baseline PSSD itch ≥ 4 at baseline between guselkumab group and placebo group.	A nonresponder status will be assigned to PSSD itch score response after the occurrence of ICE 1 or 2. In addition, Participants with missing PSSD itch score responses at Week 16 or who do not return for evaluation at Week 16 will be considered to not have achieved PSSD itch response at Week 16. Observed value will be used for PSSD itch score response after the occurrence of ICE 3. For participants experiencing multiple ICEs, an ICE in categories 1 or 2 will supersede an ICE in category 3.
14	The proportion of participants with PSSD individual symptom scale score= 0 at Week 16, among participants with baseline PSSD >0 4 at baseline.	Difference in proportion of participants with PSSD individual symptom scale score=0 at week 16among participants with baseline PSSD >0 at baseline between guselkumab group and placebo group.	A nonresponder status will be assigned to PSSD symptom scale score response after the occurrence of ICE 1 or 2. In addition, Participants with missing PSSD symptom score responses at Week 16 or who do not return for evaluation at Week 16 will be considered to not have achieved PSSD symptom response at Week 16. Observed value will be used for PSSD symptom response after the occurrence of ICE 3. For participants experiencing multiple ICEs, an ICE in categories 1 or 2 will supersede an ICE in category 3.

5.4.1.3. Analysis Methods

5.4.1.3.1. Main Estimators (Analyses) for the Estimands

The major secondary endpoints, defined in Section 1.1, will be compared between guselkumab group and placebo group and will use the primary efficacy analysis set (FAS) and the estimands defined in Section 5.4.1.2.

The estimands 5,6,7,13 and 14 will be estimated by differences between guselkumab group and placebo group in the proportion of participants who achieve each endpoint and their associated 95% CIs calculated based on the Wald statistics. Each endpoint will be compared between guselkumab group and the placebo group using the CMH Chi-square test (2-sided) stratified by special site (scalp, face, intertriginous, genital) at a significance level of 0.05.

The estimands 8,9,10 and 11 will be estimated by differences between guselkumab group and placebo group in the proportion of participants who achieve each endpoint and their associated 95% CIs calculated. Each endpoint will be compared between guselkumab group and the placebo group using the Chi-squared test (2-sided) at a significance level of 0.05.

The estimands 3,4 and 12 will be estimated by differences between guselkumab group and placebo group in the mean change from baseline. Each endpoint will be compared between guselkumab group and the placebo group using MMRM model with explanatory factors as treatment group, visit, baseline score, special site (scalp, face, intertriginous, genital), interaction term of visit with treatment group, and an interaction term of visit with baseline score. The difference in the least squares means (LSmeans) and 95% confidence interval (CI) for the differences in LSmeans and p-values will be calculated based on the MMRM model, at a significance level of 0.05.

5.4.1.3.2. Data Handling Rules for Major Secondary Endpoints

5.4.1.3.2.1. Binary Estimands (5,6,7,8,9,10,11,13,14) – Non-responder Imputation (NRI).

Participants who have missing response at Week 16 (after accounting for the intercurrent events) will be considered non-responders at Week 16 (i.e., Non-responder Imputation (NRI)). Similarly, participants who have a missing score at week 16 (after accounting for the intercurrent events) will be considered non-responders for the endpoint at Week 16.

5.4.1.3.2.2. Continuous Estimands (3,4,12)

A missing score (after accounting for the intercurrent events) is not imputed and will be handled through the MMRM assuming missing at random (MAR).

5.4.1.3.3. Supplementary Estimands for the major Secondary Endpoints

In these supplementary estimands, all the intercurrent events are addressed by the **composite strategy**. The supplementary estimands for the major secondary endpoints acknowledge that having an intercurrent event is an unfavorable outcome. If a participant had any of the intercurrent events (ICE) prior to Week 16, the participant will be considered to be ‘Non responder’ in all

binary endpoints and zero change from baseline at week 16 in all continuous variables from the visit when first ICE occurred.

5.4.1.3.4. Summary of Analyses Related to Major Secondary Endpoints

Table 9 below provides an overview of all the analyses related to the major secondary endpoints, the estimands, the analysis sets, the data handling rules to be used, and the analysis methods and summary statistics.

Table 9: Summary of Analyses Related to major Secondary Endpoints

Endpoints (Analysis Set)	Missing data	Analysis method/Summary statistics
• IGA score of cleared (0) at Week 16 (FAS) • PASI 90 response at Week 16 (FAS) • PASI 100 response at Week 16 (FAS) • A ≥ 4-point reduction (improvement) from baseline in the Psoriasis Symptom and Sign Diary (PSSD) itch score at Week 16, among participants with baseline PSSD itch ≥ 4 at baseline (FAS Participants with a PSSD Itch Score >= 4 at Baseline) • A PSSD Individual Symptom Scale Score =0 at Week 16, among randomized participants with baseline PSSD symptom score >0 (Full Analysis Set Participants with Baseline PSSD Symptom Score > 0)	Missing data due to missed visits or missed data collection. Participants with missing data are considered to be non-responders' imputation (NRI)	• Summaries of the proportion of participants who achieved the endpoint • Treatment difference (guselkumab group-placebo group) and 95% CI • P-value from the CMH test (stratified by special site (scalp, face, intertriginous, genital)) will be used for the stratification
• Scalp-specific IGA (ss-IGA) score of absence of disease (0) or very mild disease (1) at Week 16, among randomized participants with an ss-IGA score ≥3 at baseline (Scalp Special Site Analysis Set with a ss-IGA Score >=3 at Baseline) • Static Physician's Global Assessment of Genitalia (sPGA-G) score of clear (0) or minimal (1) at Week 16 among randomized participants with an sPGA-G score ≥3 at baseline (Genital Special Site Analysis Set with a sPGA-G Score >=3 at Baseline) • Intertriginous IGA (i-IGA) score of clear (0) or minimal (1) at Week 16, among randomized participants with an i-IGA score ≥3 at baseline (Intertriginous Special Site Analysis Set with an i-IGA Score >=3 at Baseline) • Facial IGA (f-IGA) score of clear (0) or minimal (1) at Week 16 among randomized participants with an f-IGA score ≥3 at baseline (Facial Special Site Analysis Set with a f-IGA Score >=3 at Baseline)	Missing data due to missed visits or missed data collection. Participants with missing data are considered to be non-responders' imputation (NRI)	• Summaries of the proportion of participants who achieved the endpoint • Treatment difference (guselkumab group-placebo group) and 95% CI • P-value from chi-squared test will be used

Table 9: Summary of Analyses Related to major Secondary Endpoints

Endpoints (Analysis Set)	Missing data	Analysis method/Summary statistics
• Change from baseline in BSA affected at Week 16 • Change from baseline in PASI score at Week 16 • Change from baseline in PSSD total symptom score at Week 16 (Full Analysis Set (FAS) for all endpoints)	Missing data due to missed visits or missed data collection. Missing data is not imputed, but is handled through the MMRM assuming MAR.	• Descriptive summary statistics • MMRM model for ○ LS mean (95% CI) for each treatment group ○ Treatment differences in LS means (95% CI) • P-values for comparing LS means

5.4.1.3.4.1. Multiplicity Adjustment for Testing Procedures

This study has 12 major secondary endpoints (listed in section 1.1). The analyses of the major secondary endpoints will be performed only if the primary analysis is significant and in the fixed sequence testing approach as specified in Table 2. If a given comparison is not significant at the 2-sided α-level of 0.05, the remaining treatment group comparisons in this sequence will not be considered significant.

5.4.1.3.4.2. Level of Significance

The overall type I error will be controlled among the primary and major secondary endpoints at 5%.

5.4.2. Supportive Secondary Endpoint(s)

In addition to the primary and major secondary endpoints, other efficacy endpoints will also be analyzed.

This section outlines the definition and analyses of the other efficacy endpoints.

Other efficacy endpoints through Week 16 will be analyzed at Week 16 DBL and other efficacy endpoints through Week 48 will be analyzed at Final DBL.

5.4.2.1. Other efficacy endpoint through Week 16

1. Change from baseline in BSA ×IGA through Week 16.
2. Time to complete scalp psoriasis clearance (ss-IGA = 0) through week 16, among randomized participants with scalp psoriasis at baseline
3. Proportion of participants with complete scalp psoriasis clearance (ss-IGA = 0) over time among randomized participants with scalp psoriasis at baseline over time through Week 16.

4. Proportion of participants who achieve an ss-IGA score of absence of disease (0) or very mild disease (1) with at least 2-grade improvement from baseline at Week 16 among randomized participants with an ss-IGA score ≥2 at baseline.
5. Time to complete genital psoriasis clearance (sPGA-G = 0) through week 16, among randomized participants with genital psoriasis at baseline
6. Proportion of participants with complete genital psoriasis clearance (sPGA-G = 0) among randomized participants with genital psoriasis at baseline over time through Week 16.
7. Proportion of participants who achieve an sPGA-G score of clear (0) or minimal (1) with at least 2-grade improvement from baseline at Week 16 among randomized participants with an sPGA-G score ≥2 at baseline.
8. Time to complete intertriginous psoriasis clearance (i-IGA =0) through week 16, among randomized participants with intertriginous psoriasis at baseline
9. Proportion of participants with complete intertriginous psoriasis clearance (i-IGA = 0) among randomized participants with intertriginous psoriasis at baseline over time through Week 16
10. Proportion of participants who achieve an i-IGA score of clear (0) or minimal (1) with at least 2-grade improvement from baseline at Week 16 among randomized participants with an i-IGA score ≥2 at baseline.
11. Time to complete facial psoriasis clearance (f-IGA = 0), through week 16, among randomized participants with facial psoriasis at baseline.
12. Proportion of participants with complete facial psoriasis clearance (f-IGA = 0) among randomized participants with facial psoriasis at baseline over time through Week 16.
13. Proportion of participants who achieve an f-IGA score of clear (0) or minimal (1) with at least 2-grade improvement from baseline at Week 16 among randomized participants with an f-IGA score ≥2 at baseline.
14. The change from baseline in individual scale score of PSSD components at Week 16
15. The proportion of participants who achieve a PSSD individual scale score of 0 at Week 16 among randomized participants with scale score ≥1
16. The proportion of participants who achieve a PSSD symptom score = 0 at Week 16 among randomized participants with PSSD symptom score ≥1
17. The proportions of participants who achieve a PSSD symptom score =0 and a PSSD sign score =0 and the proportion of participants who achieve a PSSD individual
    scale score of 0 for participants with a baseline symptom score, sign score, and each PSSD individual baseline scale score that is ≥1 over time through Week 16
18. The proportion of participants with Dermatology Life Quality Index (DLQI) 0/1 at Week 16

19. The change from baseline in patient-reported outcomes measurement information system-29 (PROMIS-29) score over time through Week 16

5.4.2.2. Definition of other efficacy endpoint (s) through Week 16

Details refer to section 5.4.1.1. and 5.4.2.5.

5.4.2.3. Analysis method of other efficacy endpoint(s) through Week 16

Other efficacy endpoints through Week 16 will be tested regardless of the significance of the primary and major secondary endpoints; the testing of these endpoints will not be controlled for multiplicity. All statistical testing will be performed at the 2-sided 0.05 significance level. Nominal (unadjusted) p-values will be presented.

The analyses of these other efficacy endpoints through Week 16 will be based on FAS and special site analysis sets for the endpoints related to the special sites.

Descriptive statistics (i.e., N, mean, median, SD, IQ range, minimum, and maximum) will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Graphical data displays (e.g., line plots) may also be used to summarize the data.

The comparisons of interest will be between guselkumab group and the placebo group.

The primary estimand approach and analysis methods specified for the primary endpoint in Sections 5.3.2, and 5.3.3, will apply to all continuous endpoints, binary endpoints, and time to event endpoints.

For continuous endpoints the MMRM model will be used to test the difference between guselkumab group and the placebo group. This model relies on the Missing at Random (MAR) assumption for the missing responses. Under the assumption of MAR, the missing data will be accounted for through correlation of repeated measures in the model.

The explanatory variables of the MMRM model will include treatment group, visit, baseline score, special site (scalp, face, intertriginous, genital), interaction term of visit with treatment group, and an interaction term of visit with baseline score. For endpoints related to special sites, the MMRM will not include special site as an explanatory variable.

The estimates of the treatment difference between guselkumab group and the placebo group will be provided by the difference in the least squares means (LS means). The 95% confidence interval (CI) for the differences in LS means and p-values will be calculated based on the MMRM. An unstructured covariance matrix for repeated measure within a participant will be used. The F-test will use Kenward-Roger's approximation for degrees of freedom.

Participants with an intercurrent event in category 1or 2 prior to Week 16 will be considered to have zero change from baseline for that endpoint at Week 16. If a participant had any of the ICE category 3 prior to Week 16, observed value will be used from the visit.

For binary endpoints chi-square test or Cochran-Mantel-Haenszel chi-square test (as appropriate) will be used to compare the proportion of participants achieving selected endpoints between the guselkumab treatment group and the placebo group. The analyses will be stratified by special site (scalp, face, intertriginous, genital). In case of rare events, Fisher's exact test will be used for treatment comparisons.

Participants with an intercurrent event in category 1 or 2 prior to Week 16 will be considered non-responder for the binary endpoint at Week 16. If a participant had any of the ICE category 3, observed value will be used from the visit.

For time to event endpoints, life table estimates will be provided for the response rate (95% CI) and the time to achieve the endpoint by Week 16. P-value will be calculated based on log-rank test.

For participants experiencing ICE's 1 or 2 will be censored. Observed value will be used for the response after the occurrence of ICE 3. For participants experiencing multiple ICEs, an ICE in categories 1 or 2 will supersede an ICE in category 3. Participants who do not achieve the endpoint by Week 16 will be censored for the analysis.

5.4.2.4. Other efficacy endpoints through Week 48

The other efficacy endpoints through Week 48 are listed below. The analyses will be based on full analysis set (FAS). Endpoints after Week 16 through Week 48 will be descriptively summarized by visit. The same missing data handling rules used in Week 16 DBL main analysis will be applied for all endpoints in the final DBL.

1. Change from baseline in BSA ×IGA over time through Week 48
2. The proportion of participants who achieve National Psoriasis Foundation (NPF)target response (i.e., BSA ≤1%) over time through Week 48
3. The proportion of participants who achieve NPF acceptable response (i.e., BSA ≤3%) over time through Week 48 among those with baseline BSA >3%
4. The proportion of participants who achieve PASI 50/75/90/100 over time through Week 48
5. The proportion of participants who achieve IGA 0 over time through Week 48
6. The proportion of participants who achieve IGA 0/1 over time through Week 48
7. Time to achievement of NPF target response (i.e., BSA ≤1%)
8. Time to achievement of NPF acceptable response (i.e. BSA ≤3%)

9. The proportion of patients who achieve IGA 0/1 at Week 16 and who maintain IGA 0/1 response at Week 48

10. The proportion of participants achieving palmoplantar IGA (pp-IGA) of clear (0) or almost clear/minimal (1) with at least 2-point improvement over time through Week 48 among randomized participants with a pp-IGA score ≥2 at baseline

11. The proportion of participants achieving pp-IGA of clear (0) over time through Week 48 among randomized participants with palmoplantar psoriasis at baseline

12. The change from baseline in the Nail Psoriasis Severity Index (NAPSI) over time through Week 48 among randomized participants with nail psoriasis at baseline

13. The percent improvement from baseline in NAPSI over time through Week 48 among randomized participants with nail psoriasis at baseline

14. The proportion of participants achieving NAPSI 50/75/90/100 response over time through Week 48 among randomized participants with nail psoriasis at baseline

15. The proportion of participants achieving NAPSI 0 over time through Week 48 among randomized participants with nail psoriasis at baseline.

16. The change from baseline in Psoriatic Arthritis Impact of Disease score (PsAID-12) over time through Week 48

17. The proportion of participants with a score suggestive of PsA, i.e., ≥3 on the Psoriasis Epidemiology Screening Tool (PEST) over time through Week 48 among randomized participants with screening PEST score <3

18. The change from baseline in PSSD symptom score over time through Week 48

19. The proportion of participants who achieve ≥4-point reduction (improvement) in PSSD itch score from baseline over time through Week 48 among participants with a PSSD itch score ≥4 at baseline.

20. The proportion of participants with PSSD Individual Symptom Scale Score =0 over time through Week 48 among participants with PSSD >0 at baseline

21. The change from baseline in individual scale score of PSSD components over time through Week 48.

22. The proportion of participants who achieve a PSSD individual scale score of 0 over time through Week 48 among randomized participants with scale score ≥1

23. The proportion of participants who achieve a PSSD symptom score = 0 over time through Week 48 among randomized participants with PSSD symptom score ≥1

24. The proportions of participants who achieve a PSSD symptom score =0 and a PSSD sign score =0 and the proportion of participants who achieve a PSSD individual scale score of 0 for participants with a baseline symptom score, sign score, and each PSSD individual baseline scale score that is ≥1 over time through Week 48

25. The proportion of participants with Dermatology Life Quality Index (DLQI) 0/1 over time through Week 48

26. The proportion of participants with DLQI 0 over time through Week 48

27. The change from baseline in PROMIS-29 score over time through Week 48

28. Change from baseline in Body Surface Area (BSA) affected over time through Week 48

29. Change from baseline in total Psoriasis Area Severity Index (PASI) score over time through Week 48

5.4.2.5. Definition of other efficacy endpoint (s) through Week 48

5.4.2.5.1. Dermatology Life Quality Index (DLQI)

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

A score of ≤1 indicates no effect at all of disease on participant's health related quality of life, and a reduction of 5 points or more in total DLQI score is considered clinically meaningful improvement.

For a partially answered questionnaire (eg, not all 10 answers in the DLQI questionnaire were available):

- If one question's answer is not available, this question will be scored 0. The total score will then be calculated.

- If two or more questions' answers are unavailable, the questionnaire is not scored. Hence, the total score and each of the 6 component scores will be set to missing.

- If one question from one of the 6 component scores is missing, the affected component score will be set to be missing.

5.4.2.5.2. Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29)

The PROMIS-29 is a 29-item generic HRQoL survey, assessing each of the 7 PROMIS domains (depression; anxiety; physical function; pain interference; fatigue; sleep disturbance; and ability to participate in social roles and activities) with 4 questions. The questions are ranked on a 5-point Likert Scale. There is also one 11-point rating scale for pain intensity.

The total raw score will be converted into a T-score for each participant based on the table in Appendix 9. The raw score of each domain is converted into a standardized score with a mean of 50 and a standard deviation (SD) of 10 (T-Score). The standardized T-score is reported as the final score for each participant. Pain Intensity is presented as raw responses (0-10). For PROMIS domains of Depression, Anxiety, Physical Function, Pain Interference, Fatigue, a score of 50 is the average for the United States general population with a standard deviation of 10, because testing was performed on a large sample of the general population. However, the other two domains (Ability to Participate in Social Roles and Activities and Sleep Disturbance) were not centered in a national sample. For these two domains, a score of 50 represents the average of the calibration sample which was generally more enriched for chronic illness, and a score of 50 likely represents somewhat sicker people than the general population. A higher PROMIS T-score represents more of the concept being measured. For negatively worded concepts like Anxiety, a T-score of 60 is one SD worse than average. By comparison, an Anxiety T-score of 40 is one SD better than average. However, for positively worded concepts like Physical Function, a T-score of 60 is better than average while a T-score of 40 is better. Participants will undergo this assessment at time points according to the SoA in the protocol.

5.4.2.5.3. Psoriasis Epidemiology Screening Tool (PEST)

The Psoriasis Epidemiology Screening Tool (PEST) is a validated screening tool for psoriatic arthritis. It is a 5-item questionnaire developed to help identify PsA at an early stage. In this study, the PEST will be administered at screening to those who do not report a prior history of confirmed PsA. Those with scores ≥3 on screening PEST, may have undiagnosed PsA and will proceed with PsAID-12 at baseline (Week 0) and all subsequent visits. Those who score < 3 on PEST at screening will continue to receive PEST throughout the study.

5.4.2.5.4. PsAID-12

The PsAID-12 is made up of 0-10 numeric rating scale (NRS) questions, with a final result included between 0 (no difficulty)-10 (extreme difficulty). The 12 domains examine different perspectives, both physical and psychological, that are considered important in patients with PsA. Each domain has a different weight: pain, fatigue, and skin problems are those with a greater effect. The PsAID-12 will be administered to all patients with known prior confirmed diagnosis of psoriatic arthritis as well as those who screen positive with score ≥3 on PEST at the screening visit.

5.4.2.5.5. Palmoplantar Investigator's Global Assessment (pp-IGA)

The pp-IGA is used to evaluate disease severity of palmoplantar psoriasis. The lesions are assessed in terms of the clinical signs of coloration, thickening, and scaling, which are scored using a 5-point scale: clear (0), almost clear/minimal (1), mild (2), moderate (3), and severe (4).

5.4.2.5.6. Nail Psoriasis Severity Index (NAPSI)

The NAPSI is an index used for assessing and grading the severity of nail psoriasis. Each of the participant's 10 nails is divided into quadrants and is graded for nail matrix psoriasis (pitting, leukonychia, red spots in the lunula, and nail plate crumbling) and nail bed psoriasis (onycholysis, splinter hemorrhages, oil drop discoloration, and nail bed hyperkeratosis). Each quadrant is evaluated for the presence of any of the nail matrix and nail bed features, respectively, with scores ranging from 0 (none of the quadrants) to 4 (all 4quadrants) impacted. The total individual nail score is the sum of the nail matrix and nail bed score and ranges from 0 to 8. The sum of these scores across all 10 nails represents the total NAPSI score (ranging from 0 to 80 for full hand nails)

NAPSI 50 Responder

Participants with ≥50% improvement in NAPSI from baseline will be considered NAPSI 50 responders.

NAPSI 75 Responder

Participants with ≥75% improvement in NAPSI from baseline will be considered NAPSI 75 responders.

NAPSI 90 Responder

Participants with ≥90% improvement in NAPSI from baseline will be considered NAPSI 90 responders.

NAPSI 100 Responder

Participants with 100% improvement in NAPSI from baseline will be considered NAPSI 100 responders.

5.5. Tertiary/Exploratory Endpoint(s) Analysis

No tertiary/exploratory endpoints in this study.

5.6. Other Safety Analyses

Safety will be assessed by summarizing the occurrences and type of AEs, vital signs (pulse, blood pressure, and weight), examining the changes in the laboratory parameters.

In all the safety analysis, participants 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 treatments they are randomized to.

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages.

There are 2 DBLs in this study, respectively, at Week 16, and final DBL at Week 56. Depending on the safety data categories, the cumulative safety data will be analyzed through different study periods which may include, but are not limited to safety data through Week 16, through Week 56. Tabular summaries of safety events for key study periods are in general presented as follows:

Summaries Through Week 16

Safety data through Week 16 will be analyzed according to the following treatment groups:

1. **Placebo**: Participants who received placebo only and no guselkumab through Week 16.
2. **Guselkumab** CCI **at Weeks 0, 4, and then** CCI Participants who received guselkumab CCI CCI through Week 16.

For participants who started treatment with placebo only but later received guselkumab prior to Week 16 inadvertently, the safety events/measurements on and after the first dose of guselkumab, will be excluded from the data summaries through Week 16. Only the safety events/measurements that occurred while the participants had been receiving placebo only will be included in the data summaries through Week 16.

Summaries Through Week 56

Safety data through Week 56 will be analyzed according to the following treatment groups:

1. **Placebo → Guselkumab** CCI CCI Participants who started treatment with placebo and later received treatment with guselkumab (due to crossed over or inadvertently) at Weeks 16 and 20 then CCI through Week 56. All the safety events/measurements that occurred on and after the first dose of guselkumab up to Week 56 will be included in this group.
2. **Guselkumab** CCI Participants who received guselkumab CCI at Week 0, 4 and then CCI (CCI through Week 56 for those randomized to guselkumab.

5.6.1. Extent of Exposure

The extent of exposure will be summarized for all treated participants. Descriptive statistics will be presented for number of study agent administrations and cumulative total dose by treatment received.

The exposure data will be summarized for the study periods of:

- Through Week 16
- Through Week 56

Study agent lots received by treatment, including matching placebo for active treatment will also be summarized. In addition, the average exposure (number of administrations) and average duration of follow-up (weeks) will also be summarized by treatment group in the safety tables through different study time periods.

5.6.2. Adverse Events

Adverse Events (AEs) that occurred any time over the study will be reported and coded using Medical Dictionary for Regulatory Activities (MedDRA). Analyses of AEs will be performed on those events that are considered treatment emergent. Treatment emergent AEs are those AEs that occurred after the start of initial study agent administration and those AEs that were present at baseline but worsened in severity after the start of initial study agent administration. Treatment emergent AEs will be summarized by MedDRA system organ class, preferred term, and actual treatment group. The numbers of participants reporting at least 1 event of the following treatment emergent AE categories will be summarized:

- Any AEs
- Serious adverse events (SAEs)
- AEs that are reasonably related to study agent
- AEs of severe intensity
- AEs that led to permanent discontinuation of study agent administration
- Injection-site reactions
- AEs of psoriasis

These summary tables will provide the count and percentage of participants with 1 or more of the specified AEs by treatment group. To adjust for the different duration of follow-up among treatment groups, the AE rates per hundred participant-years of follow-up will also be provided for the above AE categories, Malignancy, Tuberculosis, MACE, infections, serious infections and IBD.

All AE summary tables will include average weeks of follow-up and average number of study agent administrations for each treatment group.

In addition to the summary tables, listings of participants with the following AEs will also be provided:

- SAEs
- AEs leading to permanent discontinuation of study agent
- Opportunistic infection
- Malignancies (non-melanoma skin cancer and other malignancies)
- Death
- Suicidal ideation and behavior
- Possible serum sickness-like reactions and anaphylactic reactions.

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

Adverse events of psoriasis include any event of erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, inverse psoriasis, palmo-plantar psoriasis and worsening or exacerbation of psoriasis.

In addition, impact of weight on safety will be evaluated for selected treatment emergent AE categories based on baseline weight (≤ 90 kg, >90 kg).

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

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Tests

Blood samples for hematology and clinical chemistry will be collected based on the time and events schedule specified in the protocol. The clinical laboratory parameters to be evaluated by the central laboratory include but are not limited to:

Laboratory Assessments	**Parameters**		
Hematology	Platelet count Red blood cell count Hemoglobin	Red Blood Cell (RBC) Indices: MCV MCH	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td></td><td>Hematocrit</td><td>% Reticulocytes</td><td>Monocytes
Eosinophils
Basophils</td></tr>
<tr><td></td><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.</td></tr>
<tr><td>Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Calcium
Chloride
Bicarbonate
Blood urea nitrogen (BUN)
Creatinine
Glucose (non-fasting, acceptable)
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Gamma-glutamyltransferase (GGT)</td><td>Total bilirubin
Alkaline phosphatase
Creatine phosphokinase (CPK)
Albumin
Total protein</td></tr>
<tr><td></td><td colspan="3">Note: Details of liver chemistry stopping criteria and required actions and follow-up are given in protocol Appendix 7: Liver Safety.

Potential Hy's Law case (ALT or AST ≥3 x ULN and Tbili ≥2 x ULN) reporting requirements are defined in the protocol section 8.3.1.</td></tr>
<tr><td>Other</td><td colspan="3">• Lipid Panel (fasting required): Total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides
• Serum Pregnancy Testing for women of childbearing potential only
• High-sensitivity C-reactive protein (hsCRP)
• Serology (HIV antibody, Hepatitis C virus antibody, and Hepatitis B panel which includes: hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [anti-HBs], and hepatitis B core antibody [anti-HBc total])
• Interferon gamma release assay testing, which includes either QuantiFERON-TB® test or T-SPOT.TB® (for tuberculosis)
• Follicle-stimulating hormone (screening only to confirm potential post-menopausal status)
• Hemoglobin A1c (HbA1c)
• Hepatitis B DNA (screening only for those whose Hepatitis B serology results with HbsAg negative, anti-HBs negative and anti-Hbc total positive)
• Hepatitis C RNA (screening only for those who are Hepatitis C antibody positive or with history of Hepatitis C treatment)</td></tr>
</table>

Laboratory Assessments	Parameters
	• Human immunodeficiency virus RNA(screening only; for those whose HIV screen is positive)

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

- Plots of the observed values and changes from baseline over time for selected clinical laboratory parameters
- Number of participants with post-baseline values by maximum toxicity grade according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) for parameters with NCI-CTCAE criteria defined
- Listings of participants with any post-baseline lab value of NCI-CTCAE toxicity Grade 3 or higher

5.6.3.2. Vital Signs and Physical Examination Findings

Vital signs will be measured at visits as per the schedule of events in the protocol. Descriptive statistics of the observed value and change from baseline of the vital signs will be summarized by treatment group.

5.6.3.3. Electrocardiogram

No analysis is planned.

5.6.3.4. Other Safety Parameters

No analysis is planned.

5.7. Other Analyses

5.7.1. Pharmacokinetics

Blood samples for measuring serum guselkumab concentrations will be collected from all participants at scheduled visits as indicated in the Schedule of Events in the protocol.

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

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

- Summary of serum guselkumab concentrations at each visit by treatment group

- Participants with serum guselkumab concentration below the lowest quantifiable concentration in a sample will be summarized by treatment group overtime.
- Summary of serum guselkumab concentrations overall and by baseline weight (≤90kg, >90 kg) will be summarized by treatment group overtime.
- Plot of median serum guselkumab concentrations over time by treatment group

In addition, the relationship between serum guselkumab concentrations and safety or efficacy may be explored.

For summary statistics of serum guselkumab concentrations, concentration values below the lower limit of quantification will be treated as zero. Once a Participant meets one of the following dosing deviation criteria, the participant's data will be excluded from the by-visit data analyses from that point onwards.

Dosing deviation criteria:

- Discontinue CC guselkumab administrations.
- Skipped an CC guselkumab administration.
- Received an incomplete/ incorrect CC dose.
- Received an incorrect CC study agent.
- Received an additional CC guselkumab dose.

In addition, if a participant has an administration outside of visit windows (Section 5.1.1), the concentration data collected at and after that visit will be excluded from the by-visit data analyses. Additional exclusions for incongruous PK data to be implemented based on Janssen SOP-07948.

Population PK analyses will be performed to characterize the disposition characteristics of guselkumab based on the guselkumab concentration data from PSO studies. Data may be combined with other selected studies to support a relevant structural model. A detailed analysis plan for population PK analysis will be developed separately, and a stand-alone technical report will be written to summarize the results of the population PK analysis.

PK analyses presentation

PK analyses will be summarized through the following time periods:

- Through Week 16
- Through Week 48

For the analyses, a Participant is included in one and only one treatment group on the basis of the treatment regimen followed. The description of treatment groups are as follows:

1. **Placebo → Guselkumab** CCI CCI Participants randomized to placebo and were switched over to Guselkumab CCI CCI (due to CO) at Week 16.

2. **Guselkumab [CCI] at Week 0, Week 4, and then [CCI]** Participants randomized to guselkumab [CCI] at Week 0, Week 4, and then [CCI] and received guselkumab [CCI] [CCI] throughout.

5.7.2. Immunogenicity (Antibodies to Guselkumab)

Blood samples will be collected to examine the formation of antibodies to guselkumab at the specified visits as shown in the schedule of events of the protocol. Serum samples will also be collected at the final visit from participants who terminate study participation early.

5.7.2.1. Immunogenicity Analysis

The antibodies to guselkumab will be summarized based on Immunogenicity Analysis Set (Section 4). Participants will be analyzed according to the treatment groups that they actually received. No imputation for missing concentration data will be performed.

The following analysis of antibodies to guselkumab will be performed by treatment group:

- Summary of antibodies to guselkumab status
- Summary of neutralizing antibodies to guselkumab status
- List of participants positive for antibodies to guselkumab

In addition, to explore the relationship between antibodies to guselkumab status and serum guselkumab concentrations, efficacy and safety, the following analysis may be performed as appropriate:

- Summary of clinical response (e.g., IGA 0/1 response) by antibody to guselkumab status
- Summary of injection-site reactions by antibody to guselkumab status
- Summary of serum guselkumab concentrations by antibody to guselkumab status
- Plots of median trough serum guselkumab concentrations over time by antibody to guselkumab status

Immunogenicity analyses presentation

Immunogenicity analyses will be summarized through the following time periods:

- Through Week 16
- Through Week 48

For the immunogenicity analyses, the description of treatment groups is as follows:

1. **Placebo → Guselkumab [CCI] [CCI]** Participants randomized to placebo and were switched over to Guselkumab [CCI] [CCI] (due to CO) at Week 16.
2. **Guselkumab [CCI] at Week 0, Week 4, and then [CCI]** Participants randomized to guselkumab [CCI] at Week 0, Week 4, and then [CCI] and received guselkumab [CCI] [CCI] throughout with an additional dose at Week 4.

5.7.2.2. Other Immunogenicity Analyses

No other immunogenicity analysis is planned.

5.7.3. Pharmacodynamics

Samples for serum biomarkers will be collected for all participants as indicated in the Schedule of Activities in the protocol. The analyses on PD biomarkers are to better understand the biology of PSO, to provide a biological assessment of the participants' response to treatment with guselkumab, to analyze differences between responders and non-responders, and to determine if the markers can be used to classify participants as potential responders prior to treatment.

All PD analyses will be based on the PD Analysis Set (Section 4). Participants will be analyzed according to the treatment groups that they received. No imputation for missing concentration data will be performed. Detailed analysis plan and the PD analyses results will be provided in an independent technical report.

5.7.4. Pharmacokinetic/Pharmacodynamic Relationships

If data permit, the relationships between serum guselkumab concentration and efficacy may be analyzed graphically. If any visual trend is observed, a suitable population PK/PD model may be developed to describe the exposure-response relationship. Details will be given in a population PK/PD analysis plan and results of the population PK/PD analysis will be presented in a separate technical report.

5.7.5. Biomarkers Analyses

Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

DNA samples may be analyzed if it is hypothesized that this may help resolve issues with the clinical data. DNA samples will be used for research related to guselkumab or psoriasis. They may also be used to develop tests/assays related to guselkumab and psoriasis. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome (as appropriate) in relation to guselkumab or psoriasis clinical endpoints. Results will be presented in a separate report.

5.7.6. Health Economics

No health economics measurement is collected in this study.

5.7.7. Other Variables and/or Parameters

5.7.7.1. Definition

5.7.7.2. Analysis Method

5.7.8. Definition of Subgroups

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

Baseline demographics

- Sex (male, female)
- Race/ethnicity (White, Black, Asian, Hispanic or Latino, Multi-Racial, Middle Eastern, American Indian/Indigenous/Alaskan Native, Pacific Islander/Native Hawaiian, Other)
- Geographic location ((United States, Canada)
- Baseline Age (≤ 30, >30 to ≤45, >45)
- Baseline weight (≤ 90 kg, >90 kg)
- Baseline weight by quartiles
- BMI (Normal [<25], Overweight [25 to <30], Obese [≥30])

Baseline disease characteristics:

- Age at diagnosis (years) (<25, ≥25)
- Psoriasis disease duration (years) (≤ 2, >2 to ≤5, >5)
- Psoriatic arthritis (3 groups: Yes Rheumatologist confirmed; PEST positive at screening, PEST negative at screening)
- Special site as randomized (Scalp, Face, Intertriginous, Genital)
- Additional special site (, Palmoplantar, Nail)
- Baseline DLQI (<10, ≥10)
- Baseline PASI (<10, ≥10 to <15, >=15)
- Baseline BSA (>=2 to <5, >=5 to <10, >=10 to <=15)

Psoriasis medication history:

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

- Never used
- Ever Used

- Advanced Orals (apremilast, deucravacitinib,)
  - Never used
  - Ever used
- Topicals
  - Never used
  - Ever used
- Participants who had an inadequate response to or intolerance to any of the following phototherapy: Ultraviolet B light [UVB] or psoralen and ultraviolet A light therapy [PUVA]
  - Yes
  - No
- Participants who had an inadequate response to, or intolerance to any of the conventional systemic therapies (PUVA, MTX, acitretin or cyclosporine)
  - Yes
  - No
- Participants who had an inadequate response to or intolerance to any of the conventional systemics, phototherapy, or apremilast
  - Yes
  - No
- Participants who had an inadequate response to or intolerance to any of the advanced oral systemic therapies (apremilast, deucravacitinib,)
  - Yes
  - No

5.8. Interim Analyses

No interim analysis is planned for this study.

5.8.1. Data Monitoring Committee (DMC) or Other Review Board

No data monitoring committee or other review board is planned for this study.

6. SUPPORTING DOCUMENTATION

No data monitoring committee or other review board is planned for this study.

6.1. Appendix 1 List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomic and therapeutic class
BMI	body mass index
BSA	body surface area
CI	confidence interval
CMH	Cochran-Mantel Haenszel
CRO	contract research organization
DBL	Database lock
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
eCRF	electronic case report form
FAS	full analysis set
f-IGA	Facial Psoriasis Investigator's Global Assessment
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
hsCRP	high sensitivity C-Reactive Protein
ICE	Intercurrent Events
ICF	informed consent form
ICH	International Conference on Harmonisation
IGA	Investigator Global assessment
IgG1λ	immunoglobulin G1 lambda
i-IGA	Intertriginous Psoriasis Investigator's Global Assessment
IL	interleukin
INR	international normalized ratio
IPC	International Psoriasis Council
IQ	interquartile
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	MMRM mixed model for repeated measures
MTX	methotrexate
NCI-CTCAE	National Cancer Institute –Common Terminology Criteria for Adverse Event
NAPSI	Nail Psoriasis Severity Index
NPF	National Psoriasis Foundation
NRS	numeric rating scale
PASI	Psoriasis area and Severity Index
PD	pharmacodynamic(s)
PEST	Psoriasis Epidemiology Screening Tool
PIDASI	Post-inflammatory Dyspigmentation Area and Severity Score
PIPA	Post-inflammatory Pigment Alteration
PK	pharmacokinetic(s)
PP	per protocol
pp-IGA	Palmoplantar Investigator's Global Assessment
PRP	Patient-reported outcomes
PROMIS-29	Patient-Reported Outcomes Measurement Information System-29
PsA	psoriatic arthritis
PsAID12	Psoriatic Arthritis Impact of Disease 12
PSSD	Psoriasis Symptoms and Signs Diary

PUVA	Psoralen plus ultraviolet A
CCI	CCI
QuantiFERON-TB®	QuantiFERON-TB® Gold In Tube test (for tuberculosis)
RBC	Red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
C	CCI ly)
SD	standard deviation
SDIEQ	Skin Discoloration Impact Evaluation Questionnaire
sPGA-G	static Physician's Global Assessment of Genitalia
SSA	scalp surface area
ss-IGA	scalp surface –Investigator Global Assessment
SoA	Schedule of Activities
Tbili	total bilirubin
ULN	upper limit of normal
USA	United States of America
UVB	Ultraviolet B light
WBC	White blood cell

6.2. Appendix 2 Demographics and Baseline Characteristics

Demographic and baseline characteristic variables will be descriptively summarized by randomized treatment group. No formal statistical comparison is planned. P-values will not be provided.

Demographic variables to be summarized will include sex, race, age, height, baseline weight, and baseline body mass index (BMI). Baseline characteristic variables to be summarized will include, but not be limited to, baseline disease characteristics (e.g., Psoriasis disease duration (yrs), Age at diagnosis (yrs), Participants with scalp psoriasis at baseline, Participants with facial psoriasis at baseline, Participants with intertriginous psoriasis at baseline, Participants with genital psoriasis at baseline, Special Site as Randomized, PASI score, NAPSI score, IGA score, BSA [%], ss-IGA score , f-IGA score, i-IGA score, and sPGA-G score.

In addition, summaries of participants' medical history and current diagnoses, alcohol intake, and smoking status will be provided by the treatment group. If imbalances are found at baseline, then additional analyses may be performed adjusting for baseline differences.

6.3. Appendix 3 Protocol Deviations

Participants with major protocol deviations, defined as having the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category through Week 16 and through the end of study. The major protocol deviations will be grouped into the following 5 categories:

- Entered the study without satisfying study selection criteria
- Developed study withdrawal criteria but not withdrawn
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

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

6.4. Appendix 4 Prior and Concomitant Medications

Pre study therapies that treat psoriatic disease and any vaccines including those authorized for emergency use (e.g., COVID-19) administered up to 30 days before first dose of study intervention must be recorded at screening as prior medications/treatments.

Medications/treatments taken after the first dose of study intervention has been administered will be documented as concomitant medications/treatments. Concomitant therapies, including any vaccinations or vaccines authorized for emergency use (e.g., COVID-19) must be recorded throughout the study beginning with the start of the first dose of study intervention to 12 weeks after the last dose of study intervention.

Participants' psoriasis medication history with topical agents, phototherapy, conventional systemic therapies and advanced orals, will be summarized by treatment group for all randomized Participants. If data are available, total cumulative duration of treatment with these medications will be summarized. In addition, reasons for which Participants discontinued previous topical, phototherapy, conventional systemic and advanced orals (Intolerance, inadequate response, or other) will be summarized by randomized treatment group.

The number of Participants who received concomitant treatment of moisturizer for psoriasis will be summarized by randomized treatment group. Participants who received concomitant corticosteroids for indications other than psoriasis will be listed. Participants with concomitant prophylactic treatments for latent tuberculosis infection will also be listed

6.5. Appendix 5 Medical History

Summaries of participants' medical history, general medical history, alcohol intake, and smoking status will be provided by the treatment group.

6.6. Appendix 6 Intervention Compliance

Treatment compliance will be assessed by protocol deviations related to administration related to incorrect study agent or dose received and missed administrations.

6.7. Appendix 7 Adverse Events of Special Interest

Adverse events of special interest will be tabulated by actual treatment group based on safety analysis set.

6.8. Appendix 8 Laboratory Toxicity Grading

The grading scale use for lab assessments is based on 'Common Terminology Criteria for Adverse Events (CTCAE) v5.0'.

If a laboratory value falls within the grading as specified below but also within the local laboratory normal limits, the value is considered to be normal and will be reset to grade 0.

Pre-baseline measurements will use the same grading ranges as applied to baseline measurements. In case a test has two sets of ranges – one for baseline normal and one for baseline abnormal, the one for baseline normal will be applied for all measurements taken pre-baseline and on baseline.

Text in gray italic in the table is present in the grading scale but is not applied by Janssen when grading lab data.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Blood and lymphatic system disorders					
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hemoglobin (Hgb) <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hemoglobin (Hgb) <8.0 g/dL; <4.9 mmol/L; <80 g/L; *transfusion indicated*	*Life-threatening consequences; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading.
Leukocytosis	-	-	>100,000/mm3; >100 x 10e9 /L	*Clinical manifestations of leucostasis; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading; Added ranges in SI unit (x 10e9 /L)
Investigations					
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; *bleeding*	-	Clinical signs and symptoms are not taken into consideration for grading.
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal;	>1.5 - 3.0 x ULN if baseline was normal;	>3.0 - 10.0 x ULN if baseline was normal;	>10.0 x ULN if baseline was normal;	Ranges defined for "abnormal baseline" are

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
	> 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x baseline if baseline was abnormal	applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	
Creatinine increased	Creatine Kinase >ULN - 1.5 x ULN	Creatine Kinase >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	Creatine Kinase >3.0 x baseline; >3.0 - 6.0 x ULN	Creatine Kinase >6.0 x ULN	
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN; if abnormal, 50 - <75% decrease from baseline	<0.25 x LLN; if abnormal, 75% decrease from baseline; absolute value <50 mg/dL	Ranges defined for "abnormal" are applied only on values < LLN. Grade 0 will be assigned to values > ULN.
GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Haptoglobin decreased	<LLN	-	-	-	
Hemoglobin increased	Increase in >0 - 2 g/dL; Increase in >0 - 20 g/L	Increase in >2 - 4 g/dL; Increase in >20 - 40 g/L	Increase in >4 g/dL; Increase in >40 g/L	-	The increase indicates the level of increase above normal (above ULN). Applied as, e.g. grade 1 (g/dL): >ULN – ULN+2 g/dL; Added ranges in SI unit (g/L).
INR increased	>1.2 - 1.5; *>1 - 1.5 x baseline if on anticoagulation; monitoring only indicated*	>1.5 - 2.5; *>1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated*	>2.5; *>2.5 x baseline if on anticoagulation; bleeding*	-	Concomitant therapy or clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; *>2.0 - 5.0 x ULN and asymptomatic*	>2.0 - 5.0 x ULN with signs or symptoms; *>5.0 x ULN and asymptomatic*	>5.0 x ULN and with signs or symptoms	"Asymptomatic" ranges are not taken into consideration for grading, i.e. worst case grading is applied.
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3; >4 - 20 x 10e9 /L	>20,000/mm3; >20 x 10e9 /L	-	Added ranges in SI unit (x 10e9 /L).
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	Both Neutrophils and segmented neutrophils are graded using these criteria.
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; *>2.0 - 5.0 x ULN and asymptomatic*	>2.0 - 5.0 x ULN *with signs or symptoms; >5.0 x ULN and asymptomatic*	>5.0 x ULN *and with signs or symptoms*	"Asymptomatic" ranges are not taken into consideration for grading, i.e. worst case grading is applied.
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	
Metabolism and nutrition disorders					
Acidosis	pH <normal, but >=7.3	-	pH <7.3	*Life-threatening consequences*	pH <normal is implemented as pH <LLN. Clinical signs and symptoms are not taken into consideration for grading.
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	*Life-threatening consequences*	pH >normal is implemented as pH >ULN. Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; *symptomatic*	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; *hospitalization indicated*	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading. Note: For Hypercalcemia or Hypocalcemia in the CTCAE Lab Toxicity grading scale, the reference ranges from serum calcium (ULN /LLN) from the local or central lab are being utilized.
Hyperkalemia	Potassium >ULN - 5.5 mmol/L	Potassium >5.5 - 6.0 mmol/L; *intervention initiated*	Potassium >6.0 - 7.0 mmol/L; *hospitalization indicated*	Potassium >7.0 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypermagnesemia	Magnesium >ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	Magnesium >3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	Magnesium >8.0 mg/dL; >3.30 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypernatremia	Sodium >ULN - 150 mmol/L	Sodium >150 - 155 mmol/L; *intervention initiated*	Sodium >155 - 160 mmol/L; *hospitalization indicated*	Sodium >160 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypertriglyceridemia	Triglycerides 150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	Triglycerides >300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	Triglycerides >500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	Triglycerides >1000 mg/dL; >11.4 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypoalbuminemia	Albumin <LLN - 3 g/dL; <LLN - 30 g/L	Albumin <3 - 2 g/dL; <30 - 20 g/L	Albumin <2 g/dL; <20 g/L	*Life-threatening consequences; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; *symptomatic*	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; *hospitalization indicated*	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading. Note: For Hypercalcemia or Hypocalcemia in the CTCAE Lab Toxicity grading scale, the reference ranges from serum calcium (ULN /LLN) from the local or central lab are being utilized.
Hypoglycemia	Glucose <LLN - 55 mg/dL; <LLN - 3.0 mmol/L	Glucose <55 - 40 mg/dL; <3.0 - 2.2 mmol/L	Glucose <40 - 30 mg/dL; <2.2 - 1.7 mmol/L	Glucose <30 mg/dL; <1.7 mmol/L; *life-threatening consequences; seizures*	Clinical signs and symptoms are not taken into consideration for grading. Urine glucose is not graded.
Hypokalemia	*Potassium <LLN - 3.0 mmol/L*	*Symptomatic with* Potassium <LLN - 3.0 mmol/L; intervention indicated	Potassium <3.0 - 2.5 mmol/L; *hospitalization indicated*	Potassium <2.5 mmol/L; *life-threatening consequences*	"Symptomatic" ranges are applied for grade 2, grade 1 not assigned, i.e. worst case applied. Clinical signs and symptoms are not taken into consideration for grading of grade 3 and 4.
Hypomagnesemia	Magnesium <LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	Magnesium <1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	Magnesium <0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	Magnesium <0.7 mg/dL; <0.3 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hyponatremia	Sodium <LLN - 130 mmol/L	*Sodium 125-129 mmol/L and asymptomatic*	*Sodium 125-129 mmol/L symptomatic;* *120-124 mmol/L regardless of symptoms*	Sodium <120 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
			Sodium <130-120 mmol/L		Worst case ("<130-120 mmol/L" for grade 3 added by Janssen) is applied across grade 2/3 ranges: 120-129 mol/L assigned to grade 3, grade 2 not used.
Renal and urinary disorders					
Proteinuria	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs; urinary protein ≥ULN - <1000 mg/day	**Adult:** 2+ and 3+ proteinuria; urinary protein 1.0 - <3.5 g/24 hrs; urinary protein 1000 - <3500 mg/day **Pediatric:** Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9; Urine P/C (Protein/Creatinine) 56.5 – 214.7 g/mol	**Adult:** 4+ proteinuria; urinary protein >=3.5 g/24 hrs; urinary protein >=3500 mg/day; **Pediatric:** Urine P/C (Protein/Creatinine) ratio >1.9; Urine P/C (Protein/Creatinine) >214.7 g/mol	-	In case both 24-h urine collection and dipstick are collected, then worst case is taken, as opposed to having 24-h urine collection take precedence over dipstick. Added ranges in SI unit for urinary protein (mg/day) and for urine P/C (g/mol). Pediatric grading is applied to age range [0-18]. Adult grading is applied for ages [>18].

* Grade 0 is assigned to a lab assessment when the lab test is described in the table, but the lab value is not assigned a grade 1 or higher.

6.9. Appendix 9 PROIMIS-29 T-score

PROMIS 29 – PROFILE v2.1
PROMIS 29 + 2 PROFILE v2.1 (PROPr)

CCI

CCI

7. REFERENCES

Kim, Y. W., and S. Won. "Adjusted proportion difference and confidence interval in stratified randomized trials." PharmaSUG, Chicago, May (2013): 12-15.