Janssen Research & Development *

Clinical Protocol

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Guselkumab Administered Subcutaneously in Subjects with Active Psoriatic Arthritis

Discover 2

Protocol CNTO1959PSA3002; Phase 3
AMENDMENT 1

CNTO 1959 (guselkumab)

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312)

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Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-125132842: 3.0

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	16 March 2017
Amendment 1	23 January 2018

Amendments below are listed beginning with the most recent amendment.

Amendment 1 (23 January 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is due to FDA feedback and correction of errors.

Applicable Section(s)	Description of Change(s)
Rationale: To update the footnotes in Table 1 to correct minor errors and provide clarification.	
Table 1, Time and Events Schedule from screening through Week 24	Footnote 'b' was modified to have a visit window of ±4 days instead of 7 and text was clarified: Through Week 24, **study visits** will have a visit window of ±**4** days. Footnote 'p' language was revised for clarification (deleted text is striked-through): "All patient questionnaires should be completed before any other tests, procedures, or evaluations on the day of the visit for baseline and post-baseline visits. ~~The questionnaires and site assessments will be completed/recorded on the tablet.~~" Footnotes 'q' and 'r': "will/must" was changed to "should". Footnote 'v' was cited to the following rows: Hepatitis B and C Serologies, HIV Antibody Test, C-reactive Protein, Rheumatoid factor, and Follicle Stimulating Hormone.
Rationale: To update the footnotes in Table 1 to provide clarification.	
Table 1, Time and Events Schedule from screening through Week 24	Footnote 'x' was modified as follows: *Original text:* Prior to randomization, FSH is required for selected female subjects to determine childbearing potential. This test is only required for a female subject of any age with amenorrhea for at least 6 months. This test should NOT be done for any female subject of childbearing potential or female subjects >45 years of age with amenorrhea for at least 12 months. Refer to Inclusion Criterion 10 for details. *Modified text (deleted text is striked-through and new text in bold and underlined):* Prior to randomization, FSH is **only** required for ~~selected~~ female subjects **with amenorrhea for less than 12 months**~~to determine childbearing potential~~. ~~This test is only required for a female subject of any age with amenorrhea for at least 6 months.~~ **Two FSH measurements are needed to confirm amenorrhea in these subjects.** This test should NOT be done for any female subject of childbearing potential or female subjects ~~>45 years of age~~ with amenorrhea for at least 12 months. Refer to Inclusion Criterion 10 for details.
Rationale: To update Table 1 footnote and study procedures to state that the eC-SSRS will be completed at screening after the Independent Joint Assessor has completed the Joint Count assessment so that the site user can determine subject's eligibility prior to the subject completing the PRO assessment. Also, to clarify that the eC-SSRS will be performed first of the PRO assessments at baseline and all post-baseline visits.	

Applicable Section(s)	Description of Change(s)
Table 1, Time and Events Schedule from screening through Week 24, footnote i; Sections 9.1.3 Screening Phase; and 9.7.2 eC-SSRS	*Original text:* The eC-SSRS will be performed first at the screening visit (after signing informed consent) if the screening visit is a single visit. If the screening visit is divided into more than 1 visit, the eC-SSRS will be performed first at the second screening visit (after the subject is determined to be eligible by the central laboratory test results). The eC-SSRS will be performed first at Week 0/baseline, before study agent administration. At all post baseline visits, the eC-SSRS will be the first assessment/questionnaire that the subject must complete. *Modified text (deleted text is striked-through and new text in bold and underlined):* The eC-SSRS **should**~~will~~ be performed ~~first~~ **after the joint assessment** at the screening visit (after signing informed consent) ~~if the screening visit is a single visit. If the screening visit is divided into more than 1 visit, the eC-SSRS will be performed first at the second screening visit (after the subject is determined to be eligible by the central laboratory test results)~~. At Week 0/baseline **and at all post-baseline visits**, the eC-SSRS ~~will~~**should** be the first assessment/questionnaire that the subject ~~must~~ complete**s** **prior to study agent administration (see Section 9.7.2 for details)**.
Rationale: To correct minor errors.	
Table 1, footnotes l and u; Table 2, footnote j; Exclusion criterion 30; and Section 9.1.3 Screening phase	Reference to Inclusion Criterion 13 was changed to Criterion 14.
Rationale: To update the footnotes in Table 2 to correct minor errors.	
Table 2, Time and Events Schedule from Week 28 through Week 112	Footnote 'a' was clarified and now reads (new text in bold and underlined): Through Week 100, study visits will have a visit window of ±7 days; Week 112 visit **or the final safety visit (12 weeks after the last dose in subjects who discontinued study treatment)** will have a visit window of ±14 days. Footnote 'n' language was clarified and now reads (deleted text is striked-through): All patient questionnaires should be performed before any other tests, procedures, or evaluations on the day of the visit. ~~The patient questionnaires and site assessments will be completed/recorded on the tablet~~. Footnote 'o': the word "must" was changed to "should". Footnote 'q' was added to C-reactive Protein.

Applicable Section(s)	Description of Change(s)
Rationale: To delete redundancies.	
Section 1.2.3.2 Rationale for Guselkumab 100 mg Every 4 weeks Dose Regimen	*Deleted text:* Although subjects who had higher systemic exposure of guselkumab (serum guselkumab concentrations at the fourth quartile level) had 12-13% higher rates of infections when compared with subjects who had serum guselkumab concentrations in the lower 3 quartiles, a pattern of increasing rates of these events with higher exposure was not present across the first, second, and third quartile levels. Moreover, the clinical relevance of this finding appears to be limited, given that the vast majority of infections were non-serious and mild to moderate in intensity and that the frequency of the infections requiring treatment was generally similar across all 4 exposure quartiles.
Rationale: To correct error noted in hemoglobin level.	
Section 4.1 Inclusion criteria	*Original text in inclusion criterion 17 from:* a. Hemoglobin ≥8.5 g/dL (SI: ≥100 g/L) *Modified text (deleted text is striked-through and new text in bold and underlined):* a. Hemoglobin ≥8.5 g/dL (SI: ≥**85** ~~100~~ g/L)
Rationale: To correct error noted in visit windows.	
Section 7 Treatment Compliance	*Original text:* All post-baseline visits will have a visit window of ±7 days counting from Week 0 as Day 1. The safety follow-up visit at 12 weeks after the last dose will have a visit window of ±14 days. *Modified text (deleted text is striked-through and new text in bold and underlined):* All post-baseline visits ~~through Week 100~~ **up to and including Week 24** will have a visit window of ±~~7~~**4** days counting from Week 0 as Day 1. **After Week 24, all visits will have a visit window of ±7 days. The Week 112 visit or the final** safety ~~follow-up~~ visit ~~at~~ **(**12 weeks after the last dose **in subjects who discontinued study treatment)** will have a visit window of ±14 days.
Rationale: To revise for clarification.	
Sections 4.2 Exclusion Criteria #13; 9.1.3 Screening Phase; 9.1.4 Treatment Phase; 9.7.2 eC-SSRS; 10.2 Discontinuation of Study Treatment	The eC-SSRS ideation level language was revised for better clarity. The *Baseline/Screening* version name was changed to *Lifetime* version. The *Since Last Visit* version was changed to *Since Last Contact* version Clarified that the eC-SSRS measures five possible levels of suicidal ideation and four possible suicidal behaviors.
Rationale: To allow for a reduction in steroid dose after Week 24, as it may be medically appropriate.	
Section 8.2.1 Oral Corticosteroids	The following text regarding reduction of steroid dose after Week 24 has been added: **After Week 24 and through Week 52, a one-time dose decrease in oral corticosteroids is allowed.**

Applicable Section(s)	Description of Change(s)
Rationale: To clarify requirements for hand and foot radiographs at screening.	
Sections 9.1.1 Overview; 9.1.3 Screening; 9.2.1.6 Imaging Evaluation	The requirement for hand and foot radiographs at screening was changed to: All eligible subjects should have radiographs taken approximately 2 weeks but not greater than 4 weeks prior to randomization. The word "will" was changed to "should". For posterior-anterior view chest radiograph, the text "as per country regulations where applicable" was deleted.
Rationale: To revise for clarification.	
Section 9.1.3 Screening Phase	*Original text:* The electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) (Baseline/Screening version) will be the first assessment performed at the screening visit (after signing informed consent) if the screening visit is a single visit. If the screening visit is divided into more than 1 visit, the eC-SSRS will be performed as the first assessment at the visit that occurs after the subject is determined to be eligible by the central laboratory test results. *Modified text (deleted text is striked-through and new text in bold and underlined):* **If the screening is a single visit, t**~~T~~he electronic Columbia-Suicide Severity Rating Scale (eC SSRS) (**Lifetime**~~Baseline/Screening~~ version) **should**~~will~~ be **performed** **after the joint assessment** ~~the first assessment performed at the screening visit~~ (after signing informed consent) ~~if the screening visit is a single visit~~. If the screening visit is divided into more than 1 visit, the eC-SSRS **should**~~will~~ be performed **after the joint assessment and** ~~as the first assessment at the visit that occurs after~~ the subject is determined to be eligible by the central laboratory test results.
Rationale: To revise for clarification.	
Section 9.2.1.10 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) Composite Score (GRACE)	*Original text:* **9.2.1.10. Arithmetic Mean of the Desirability Function and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAppa) Composite Score (GRACE) Index** The Arithmetic Mean of the Desirability Function is calculated by transforming the following variables, using predefined algorithms and expressing the total score as a mean with a score range of 0–1, where 1 indicates a better state than 0:[23,22] • Tender joint count (0-68) • Swollen joint count (0-66) • HAQ (0-3) • Patient's global assessment of disease activity by VAS (arthritis and psoriasis, 0-100 mm) • Patient's assessment of skin disease activity by VAS (0-100 mm) • Patient's global assessment of disease activity (arthritis) by VAS (0-100 mm) • PASI (0-72) • Psoriatic arthritis Quality of Life Index (PsAQoL) which is determined from a transformation algorithm in which: - PsAQoL = 25.355 + (2.367 × HAQ) – (0.234 × PCS) – (0.244 × MCS) - GRACE index = (1-AMDF) $\times 10^{24}$

Applicable Section(s)	Description of Change(s)
	Modified text (deleted text is striked-through and new text in bold and underlined): **9.2.1.10. ~~Arithmetic Mean of the Desirability Function and~~ Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) Composite Score (GRACE) ~~Index~~** **The GRAPPA Composite score (GRACE) is a composite score of Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), derived as *GRACE Index = (1 - AMDF) x 10*, where, AMDF is the Arithmetic Mean of the Desirability Function (AMDF).[22-24]** The ~~Arithmetic Mean of the Desirability Function~~ **AMDF** is calculated by transforming the following variables, using predefined algorithms and expressing the total score as a mean with a score range of 0–1, where 1 indicates a better state than 0: [22, 23] • Tender joint count (0-68) • Swollen joint count (0-66) • HAQ-**DI score** (0-3) • Patient's global assessment of disease activity ~~by VAS~~ (arthritis and psoriasis, 0-100 ~~mm~~**VAS**) • Patient's assessment of skin disease activity ~~by VAS~~ (0-100 ~~mm~~**VAS**) • Patient's global assessment of disease activity (arthritis) ~~by VAS (0-100 mm)~~ • PASI **score** (0-72) • Psoriatic arthritis Quality of Life Index (PsAQoL)~~-~~**which is derived as follows**:~~which is determined from a transformation algorithm in which:~~ - PsAQoL = 25.355 + (2.367 × HAQ-**DI**) – (0.234 × **SF-**PCS) – (0.244 × **SF-**MCS), ***where,*** ○ **HAQ-DI: HAQ-DI score (0-3)** ○ **SF-PCS: PCS score of SF-36 Health Survey** ○ **SF-MCS: MCS score of SF-36 Health Survey** - ~~GRACE index = (1-AMDF) ×10[24]~~
Rationale: To revise for clarification.	
Section 9.7.1 Evaluation of Safety	*Original text:* • FSH is optional. It is only needed for determining childbearing potential of a female subject of any age with amenorrhea for at least 6 months. A female subject of any age with amenorrhea for at least 6 months who also has FSH >40 IU/L is considered not of childbearing potential. FSH is not needed for female subjects >45 years of age with amenorrhea for at least 12 months or any female subject of childbearing potential. Refer to Inclusion Criterion 10 for detail. *Modified text (deleted text is striked-through and new text in bold and underlined):* • FSH is optional. It is only needed for determining childbearing potential of a female subject of any age with amenorrhea for ~~at least 6 months~~**less than 12 months. In the absence of 12 months of amenorrhea, 2 FSH measurements are needed**. ~~A female subject of any age with amenorrhea for at least 6 months who also has FSH >40 IU/L is considered not of childbearing potential.~~ FSH is not needed for female subjects~~>45 years of age~~ with amenorrhea for at least 12 months or any female subject of childbearing potential. Refer to Inclusion Criterion 10 for detail.

Applicable Section(s)	Description of Change(s)
Rationale: To revise to allow for telephone system.	
Section 9.7.2 eC-SSRS	*Original text:* Subjects will complete the eC-SSRS questionnaire using the Sponsor-provided electronic tablets. Study site personnel will train the subjects on how to use the electronic device. The eC-SSRS will be provided in the local languages in accordance with local guidelines. The eC-SSRS will be performed during each evaluation visit according to the Time and Events schedule. During a visit, subjects will be directed to a private, quiet place with the electronic device to complete the assessment. *Modified text (deleted text is striked-through and new text in bold and underlined):* Subjects will complete the eC-SSRS questionnaire using the Sponsor-provided electronic tablets **(or through an Interactive Voice Response System [IVRS], if available**). Study site personnel will train the subjects on how to use the electronic device **and/or a telephone system**. The eC-SSRS will be provided in the local languages in accordance with local guidelines. The eC-SSRS will be performed during each evaluation visit according to the Time and Events schedule. During a visit, subjects will be directed to a private, quiet place with the electronic device **and/or a telephone** to complete the assessment.
Rationale: Treatment failure criteria was amended to include study termination for any reason. Treatment failure criteria amended to remove early escape criteria met at Week 16 and initiated or increased the dose of one of the permitted concomitant medications. Additional sensitivity/supplemental analyses as well as tipping point analysis will be defined in the SAP.	
Synopsis; Section 11.3.1 Primary Endpoint Analyses	*Original text:* The primary endpoint to be analyzed for the primary analysis is proportion of subjects who achieved an ACR 20 response at Week 24 and who had not met the following treatment failure criteria prior to Week 24. Subjects who met the following treatment failure prior to Week 24 will be considered as ACR 20 non-responder at Week 24 regardless of the observed ACR 20 response status. Subjects who meet the following treatment failure criteria include subjects who: 1. Discontinued study agent injections due to lack of efficacy. 2. Initiated or increased the dose of non-biologic DMARDs (MTX, SSZ, HCQ, LEF) or oral corticosteroids over baseline for PsA. 3. Initiated protocol prohibited medications/therapies for PsA. 4. Met early escape criteria at Week 16 and initiated or increased the dose of one of the permitted concomitant medications. The treatment effect of each guselkumab group versus placebo will be tested using a CMH test stratified by baseline non-biologic DMARD (MTX, SSZ, HCQ, LEF) use (yes/no) and the most recent available CRP value prior to randomization (<2.0 mg/dL or ≥2.0 mg/dL). The magnitude of the effect will be estimated by the difference in ACR 20 response rates between the guselkumab and placebo groups with the 95% confidence interval calculated based on Wald statistics. In the primary efficacy analysis, data from all randomized subjects who received at least 1 administration of study treatment (full analysis set) will be analyzed according to their assigned treatment group regardless of their actual treatment received. In general, subjects with missing data for ACR 20 at Week 24 will be considered non-responders at Week 24.

Applicable Section(s)	Description of Change(s)

[…]

Sensitivity Analysis

To evaluate the robustness of the primary analysis results, sensitivity analyses will be performed., including, but not limited to, the following:

1. A similar analysis, however, if subjects meet treatment failure rules, ACR 20 response will be assumed to be missing. Subjects with missing ACR 20 response will be imputed by Multiple-Imputation (MI) method under the assumption of Missing At-Random.
2. A similar analysis, however, ACR 20 response using all observed data regardless of meeting treatment failure criteria. Subjects with missing ACR 20 response will be imputed by Multiple-Imputation (MI) method under the assumption of Missing At-Random. And 2-dimensional tipping point analyses based on MI will be included to assess the robustness of the assumption regarding the missing data mechanism.

Additional sensitivity analyses may be specified in the SAP to further address the robustness of the primary analysis.

Modified text (deleted text is striked-through and new text in bold and underlined):

The primary endpoint to be analyzed for the primary analysis is proportion of subjects who achieved an ACR 20 response at Week 24 ~~and who had not met the following treatment failure criteria prior to Week 24. Subjects who met the following treatment failure prior to Week 24 will be considered as ACR 20 non-responder at Week 24 regardless of the observed ACR 20 response status~~. **Note that the intercurrent event of Treatment Failure prior to Week 24 (defined below) will be treated as non-response for the primary analysis, regardless of the observed ACR 20 response status.**

Treatment Failure Criteria

Subjects who meet the following treatment failure criteria include subjects who:

1. Discontinued study agent injections due to lack of efficacy.
2. **Terminate study participation for any reason.**
3. ~~2~~. Initiated or increased the dose of non-biologic DMARDs (MTX, SSZ, HCQ, LEF) or oral corticosteroids over baseline for PsA.
4. ~~3~~. Initiated protocol prohibited medications/therapies for PsA.

~~4. Met early escape criteria at Week 16 and initiated or increased the dose of one of the permitted concomitant medications.~~

Subjects with missing data at Week 24 will be considered non-responders.

The treatment effect of each guselkumab group versus placebo will be tested using a CMH test stratified by baseline non-biologic DMARD (MTX, SSZ, HCQ, LEF) use (yes/no) and the most recent available CRP value prior to randomization (<2.0 mg/dL or ≥2.0 mg/dL). The magnitude of the effect will be estimated by the difference in ACR 20 response rates between the guselkumab and placebo groups with the 95% confidence interval calculated based on Wald statistics.

~~In the primary efficacy analysis, data from all randomized subjects who received at least 1 administration of study treatment (full analysis set) will be analyzed according to their assigned treatment group regardless of their actual treatment received. In general, subjects with missing data for ACR 20 at Week 24 will be considered non-responders at Week 24.~~

Applicable Section(s)	Description of Change(s)
	[…] ~~**Sensitivity Analysis**~~ To evaluate the robustness of the primary endpoint analysis results, **the exhaustive scenario tipping point** sensitivity analyses will be performed **by varying the amount of non-responder imputation for missing data**. ~~including, but not limited to, the following:~~ **Additional supplemental estimand and sensitivity analyses which vary how intercurrent events (eg, treatment failures) are handled, how observed data are used, and how missing data are treated will be specified in the SAP to further address the robustness of treatment effect of ACR 20 at Week 24 for the primary and alternative estimands (which will also be defined in the SAP).**
Rationale: Subjects must sign the ICF independently and be able to read and write to participate in this study.	
Sections 16.2.3 Informed Consent; 16.2.4 Privacy of Personal Data	*Original text:* Each subject (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the Sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy. Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized Sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access. The subject or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

Applicable Section(s)	Description of Change(s)
	Subjects will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the subject or his or her legally acceptable representative will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the subject. If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject or legally acceptable representative is obtained. A limited number of study sites may be asked by the Sponsor to obtain informed consent using a validated electronic system instead of a paper-based process. If both parties (Sponsor and the study site) agree, and if participation is allowed by local regulations and IEC/IRB requirements, the means to facilitate such a process will be provided to the sites by Sponsor. The actual mechanism of consenting will be facilitated by the use of an eTablet device (eg, iPad®), but overall the consent process will remain the same, as described in this section. At these study sites, subjects will still be required to review the entire informed consent as a written document on the eTablet and then to apply their handwritten signature electronically by the use of a stylus directly onto the eTablet. *Modified text (deleted text is striked-through, new text in bold and underlined):* Each subject ~~(or a legally acceptable representative)~~ must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the Sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy. Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects ~~or their legally acceptable representatives~~ the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized Sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject ~~or legally acceptable representative~~ is authorizing such access. The subject ~~or legally acceptable representative~~ will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of ~~either~~ the subject's ~~or his or her legally acceptable representative's~~ personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

Applicable Section(s)	Description of Change(s)
	Subjects will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the subject ~~or his or her legally acceptable representative~~ will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the subject. ~~If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject or legally acceptable representative is obtained~~ **The subject must be able to read and write and should personally sign the ICF. An impartial witness or legally acceptable representative should not sign the ICF on the subject's behalf.** A limited number of study sites may be asked by the Sponsor to obtain informed consent using a validated electronic system instead of a paper-based process. If both parties (Sponsor and the study site) agree, and if participation is allowed by local regulations and IEC/IRB requirements, the means to facilitate such a process will be provided to the sites by Sponsor. The actual mechanism of consenting will be facilitated by the use of an eTablet device (eg, iPad®), but overall the consent process will remain the same, as described in this section. At these study sites, subjects will still be required to review the entire informed consent as a written document on the eTablet and then to apply their handwritten signature electronically by the use of a stylus directly onto the eTablet. **Alternately, the site will also have the option to print the electronic version of the ICF and apply a handwritten signature .** *Section 16.2.4* *Original text:* The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries. *Modified text (deleted text is striked-through, new text in bold and underlined):* The informed consent obtained from the subject ~~(or his or her legally acceptable representative)~~ includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify the sample storage period.	
Section 16.2.5 Long-Term Retention of Samples	*Original text:* Samples collected in this study may be stored for up to 15 years. *Modified text (deleted text is striked-through, new text in bold and underlined):* Samples collected in this study may be stored for up to 15 years, **starting from last patient, last visit.**
Rationale: To revise for clarification.	
Section 17.4 Source Documentation	Revised language to clarify eC-SSRS questionnaires can be completed through IVRS as an alternative method. Clarified that the at-home administrations occur at Weeks 56, 60, 64, 72, 80, 88, 92, and 96.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Guselkumab Administered Subcutaneously in Subjects with Active Psoriatic Arthritis

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

EudraCT NUMBER: 2016-001224-63

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Primary Objective

The primary objective of this study is to evaluate the efficacy of guselkumab treatment in subjects with active psoriatic arthritis (PsA) by assessing the reduction in signs and symptoms of PsA.

Secondary Objectives

The secondary objectives are to assess the following for guselkumab treatment:

- Efficacy in improving psoriatic skin lesions
- Improvement in physical function
- Inhibition of progression of structural damage
- Efficacy in improving general and disease specific health-related quality of life and patient-reported health outcomes
- Safety
- Pharmacokinetics, pharmacodynamics, and immunogenicity

Primary Endpoint

The primary endpoint is the proportion of subjects who achieve an American College of Rheumatology (ACR) 20 response at Week 24.

Major Secondary Endpoints

1. Change from baseline in Disability Index of the Health Assessment Questionnaire (HAQ-DI) score at Week 24.
2. Proportion of subjects who achieve an ACR 50 response at Week 24.
3. Proportion of subjects with a psoriasis response of an Investigator's Global Assessment (IGA) (ie, an IGA psoriasis score of 0 [cleared] or 1 [minimal] AND ≥2-grade reduction from baseline) at Week 24 among the subjects with ≥3% body surface area (BSA) psoriatic involvement and an IGA score of ≥2 (mild) at baseline.
4. Proportion of subjects who achieve an ACR 20 response at Week 16.

5. Change from baseline in modified van der Heijde-Sharp (vdH-S) score at Week 24.
6. Proportion of subjects with resolution of enthesitis at Week 24 among the subjects with enthesitis at baseline.
7. Proportion of subjects with resolution of dactylitis at Week 24 among the subjects with dactylitis at baseline.
8. Change from baseline in enthesitis score (based on Leeds Enthesitis Index [LEI]) at Week 24 among the subjects with enthesitis at baseline.
9. Change from baseline in dactylitis score at Week 24 among the subjects with dactylitis at baseline.
10. Change from baseline in 36-item Short Form Health Survey Physical Component Summary (SF-36 PCS) at Week 24.
11. Change from baseline in Disease Activity Score 28 (DAS28) C-reactive protein (CRP) at Week 24.
12. Change from baseline in SF-36 Mental Component Summary (MCS) at Week 24.
13. Proportion of subjects who achieve an ACR 50 response at Week 16.
14. Proportion of subjects who achieve an ACR 70 response at Week 24.

Other Secondary Endpoints

Endpoints Related to Reduction of Signs and Symptoms and Physical Function

1. Proportions of subjects who achieve an ACR 20, ACR 50, and ACR 70 responses by visit over time through Week 100.
2. Percent change from baseline in ACR components by visit over time through Week 100.
3. Change from baseline in HAQ-DI score by visit over time through Week 100.
4. Proportion of subjects who achieve a clinically meaningful improvement (a ≥0.35 improvement from baseline) in HAQ-DI score by visit over time through Week 100 among those subjects with HAQ-DI score ≥ 0.35 at baseline.
5. Proportion of subjects who achieve a DAS28 (CRP) response by visit over time through Week 100.
6. Proportion of subjects who achieve a DAS28 (CRP) remission by visit over time through Week 100.
7. Change from baseline in DAS28 (CRP) by visit over time through Week 100.
8. Proportion of subjects who achieve a response based on modified Psoriatic Arthritis Response Criteria (PsARC) by visit over time through Week 100.
9. Proportion of subjects with resolution of enthesitis by visit by visit over time through Week 100 among the subjects with enthesitis at baseline.
10. Proportion of subjects with resolution of dactylitis by visit by visit over time through Week 100 among the subjects with dactylitis at baseline.
11. Change from baseline in enthesitis score (based on LEI) by visit over time through Week 100 among the subjects with enthesitis at baseline.

12. Change from baseline in dactylitis score by visit over time through Week 100 among the subjects with dactylitis at baseline.

13. Change from baseline in Psoriatic ArthritiS Disease Activity Score (PASDAS) by visit over time through Week 100.

14. Change from baseline in Group for Research and Assessment of Psoriasis and Psoriatic Arthritis GRAppa Composite Score Index by visit over time through Week 100.

15. Change from baseline in Work Productivity and Activity Impairment Questionnaire scores by visit over time through Week 100.

16. Change from baseline in modified Composite Psoriatic Disease Activity Index (mCPDAI) score by visit over time through Week 100.

17. Change from baseline in Disease Activity Index for Psoriatic Arthritis score by visit over time through Week 100.

18. Proportion of subjects who maintain an ACR 20 response at Week 52 and Week 100 among the subjects who achieved an ACR 20 response at Week 24.

19. Proportion of subjects who maintain an ACR 50 response at Week 52 and Week 100 among the subjects who achieved an ACR 50 response at Week 24.

20. Proportion of subjects who maintain an ACR 70 response at Week 52 and Week 100 among the subjects who achieved an ACR 70 response at Week 24.

21. Proportion of subjects who maintain a HAQ-DI response (ie, ≥0.35 improvement from baseline in HAQ-DI score) at Week 52 and Week 100 among the subjects who achieved a HAQ-DI response at Week 24.

22. Proportion of subjects who achieve minimal disease activity by visit over time through Week 100.

23. Proportions of subjects who achieve a ≥20%, ≥50%, ≥70%, and ≥90% improvement from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score by visit over time through Week 100 among the subjects with spondylitis and peripheral joint involvement as their primary arthritic presentation of PsA.

Endpoints Related to Skin Disease

1. Proportions of subjects who achieve ≥ 75%, ≥ 90%, and 100% improvement in Psoriatic Area and Severity Index (PASI) score from baseline by visit over time through Week 100 among the subjects with ≥3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline.

2. Proportion of subjects with an IGA score of 0 (cleared) by visit over time through Week 100 among the subjects with ≥3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline.

3. Change from baseline in PASI score by visit over time through Week 100 among the subjects with ≥3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline.

4. Proportion of subjects who achieve a Dermatology Life Quality Index (DLQI) score of 0 or 1 by visit over time through Week 100 among the subjects with baseline DLQI score >1 and with ≥ 3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline.

5. Proportion of subjects who achieve ≥ 5-point improvement from baseline in DLQI score by visit over time through Week 100 among the subjects with baseline DLQI score ≥ 5 and with ≥ 3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline.

6. Change from baseline in DLQI score by visit over time through Week 100 among the subjects with ≥ 3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline.

7. Proportion of subjects who achieve both PASI 75 and ACR 20 responses by visit over time through Week 100 among the subjects with ≥3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline.

8. Proportion of subjects who achieve both PASI 75 and modified PsARC response by visit over time through Week 100 among the subjects with ≥3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline.

Endpoints Related to Joint Structural Damage

1. Change from baseline in modified vdH-S score by visit over time through Week 100.

2. Change in total modified vdH-S score from Week 24 to Week 52, from Week 24 to Week 100, and from Week 52 to Week 100.

3. Change from baseline in modified vdH-S erosion score by visit over time through Week 100.

4. Change in modified vdH-S erosion score from Week 24 to Week 52, from Week 24 to Week 100, and from Week 52 to Week 100.

5. Change from baseline in modified vdH-S joint space narrowing (JSN) score by visit over time through Week 100.

6. Change in modified vdH-S JSN score from Week 24 to Week 52, from Week 24 to Week 100, and from Week 52 to Week 100.

7. Change from baseline in modified vdH-S score by region and type of damage (ie, hand erosion, hand JSN, foot erosion, foot JSN subscores) by visit over time through Week 100.

8. Proportion of subjects with a change of ≤0 from baseline and proportion of subjects with a change of ≤ 0.5 from baseline in modified vdH-S score by visit over time through Week 100.

9. Proportion of subjects with a change of ≤0 from baseline and proportion of subjects with a change of ≤ 0.5 from baseline in modified vdH-S erosion score at by visit over time through Week 100.

10. Proportion of subjects with a change of ≤0 from baseline and proportion of subjects with a change of ≤ 0.5 from baseline in modified vdH-S JSN score by visit over time through Week 100.

11. Proportion of subjects with radiographic progression (based on the smallest detectable change [SDC]) from baseline by visit over time through Week 100.

12. Proportion of subjects with radiographic joint erosion progression (based on SDC) from baseline by visit over time through Week 100.

13. Proportion of subjects with radiographic JSN progression (based on the SDC) from baseline by visit over time through Week 100.

14. Proportion of subjects with pencil in cup or gross osteolysis deformities by visit over time through Week 100.

Endpoints Related to Health Related Quality of Life

1. Change from baseline in PCS score of the SF-36 by visit over time through Week 100.
2. Change from baseline in MCS score of the SF-36 by visit over time through Week 100.
3. Change from baseline in domain scales scores of SF-36 by visit over time through Week 100.
4. Proportion of subjects who achieve ≥ 5-point improvement from baseline in SF-36 MCS score by visit over time through Week 100.
5. Proportion of subjects who achieve ≥ 5-point improvement from baseline in SF-36 PCS score by visit over time through Week 100.
6. Change from baseline in Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue) by visit over time through Week 100.
7. Proportion of subjects who achieve ≥ 4-point improvement from baseline in FACIT-Fatigue score improvement by visit over time through Week 100.
8. Change from baseline in EuroQol five-dimension questionnaire (EQ-5D) Visual Analogue Scale and in EQ-5D index scores by visit over time through Week 100.

Hypothesis

The primary hypothesis is the guselkumab 100 mg every 4 weeks (q4w) treatment group is superior to placebo as assessed by the proportion of subjects achieving an ACR 20 response at Week24.

OVERVIEW OF STUDY DESIGN

This is a Phase 3 randomized, double-blind, placebo-controlled, multicenter, 3-arm study of guselkumab in subjects with active PsA who are biologic naïve* and have had inadequate response to standard therapies (eg, non-biologic disease-modifying antirheumatic drugs [DMARDs], apremilast, nonsteroidal anti inflammatory drugs [NSAIDs]).

* Subjects may not have previously received any biologic treatment including, but not limited to, guselkumab, ustekinumab, secukinumab (AIN457), anti-tumor necrosis factor alpha (TNFα) agents (such as adalimumab, etanercept, infliximab, golimumab subcutaneous [SC] or intravenous [IV], certolizumab pegol, or their respective biosimilars), tildrakizumab (MK3222), ixekizumab (LY2439821), brodalumab (AMG827), risankizumab (BI-655066), or other investigative biologic treatment for PsA or psoriasis.

Stable doses (as defined below) of concomitant NSAIDs, oral corticosteroids, and selected non-biologic DMARDs (limited to methotrexate [MTX], sulfasalazine [SSZ], hydroxychloroquine [HCQ], leflunomide LEF) will be allowed but are not required:

- NSAIDs and other analgesics: the marketed dose approved in the country where the study is being conducted
- Oral Corticosteroids: equivalent to ≤10 mg/day of prednisone
- Selected Non-biologic DMARDs:
  - MTX: ≤25 mg/week
  - SSZ: ≤3 g/day

- HCQ: ≤400 mg/day
- LEF: ≤20 mg/day

The study will include approximately 684 subjects.

Subjects who satisfy all inclusion and exclusion criteria will be randomly assigned to one of the following 3 treatment groups in a 1:1:1 ratio using permuted block randomization stratified by baseline non-biologic DMARD (MTX, SSZ, HCQ, LEF) use (yes/no) and the most recent available CRP value prior to randomization (<2.0 mg/dL vs ≥2.0 mg/dL):

- **Group I** (n=228): Subjects will receive SC guselkumab 100 mg q4w from Week 0 through Week 100.
- **Group II** (n=228): Subjects will receive SC guselkumab 100 mg at Weeks 0 and 4 then every 8 weeks (q8w) (Weeks 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, and 100) and placebo injections at other visits (Weeks 8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, and 96) to maintain the blind.
- **Group III** (n=228): Subjects will receive SC placebo q4w from Week 0 to Week 20 and will cross over at Week 24 to receive SC guselkumab 100 mg q4w from Week 24 through Week 100.

At Week 16, all subjects in Groups I, II and III with <5% improvement from baseline in both tender and swollen joint counts will be considered as meeting early escape criteria. These subjects will remain on the dosing regimen they were to randomized at Week 0. At Week 16, subjects who meet early escape criteria will be allowed to initiate or increase the dose of one of the permitted concomitant medications up to the maximum allowed dose as specified above, as selected by the investigator. Titration to a stable dose of the medication should be completed for subjects qualifying for early escape by the Week 24 visit.

At Week 24, all subjects in the placebo group (Group III) will cross over to receive guselkumab 100 mg SC q4w through Week 100; this will allow for collection of additional safety data for the 100 mg SC q4w dose. Subjects in the guselkumab groups (Groups I and II) will remain on the dosing regimen they were randomized to at Week 0, through Week 100.

Subjects will be followed for adverse events and serious adverse events up to 12 weeks following the last study agent administration. The end of the study is defined as the time the last subject completes the last study visit. For subjects who complete the Week 100 visit, the last study visit is the Week 112 visit. For subjects who discontinue study agent prior to Week 100, the last study visit is the final safety visit.

An independent Data Monitoring Committee will be established to monitor unblinded data on an ongoing basis through at least the Week 24 DBL to ensure the continuing safety of the subjects enrolled in this study.

Samples for the analysis of pharmacodynamic biomarkers will be collected from all subjects.

A pharmacogenomic blood sample will be collected from subjects who consent separately to this component of the study where local regulations permit. Subject participation in pharmacogenomic research is optional.

Three DBLs are scheduled at Weeks 24, 52, and 112.

SUBJECT POPULATION

The target study population is subjects with active PsA who are biologic naïve (see above) and have had inadequate response to standard therapies (eg, non-biologic DMARDs, apremilast, and/or NSAIDs). This population is considered appropriate to provide relevant efficacy and safety information for the intended use of guselkumab in PsA. Additionally, a biologic naïve population with a CRP ≥0.6 mg/dL is required

to enrich the population for radiographic progression and increase the power for detection of treatment effect on radiographic endpoints.

Subjects must also meet all inclusion and exclusion criteria.

DOSAGE AND ADMINISTRATION

Guselkumab 100 mg and matching liquid placebo for guselkumab will be provided in a single-use prefilled syringe (PFS) assembled with the UltraSafe PLUS™ Passive Needle Guard (PFS-U).

Study agent will be administered at the site by a health care professional until the subject (or caregiver) is trained for self-administration. Study agent will be administered by site personnel at Weeks 0 and 4. Beginning at Week 8, at the discretion of the investigator and subject, and after appropriate and documented training, subjects will self-administer study agent at the investigative site under the supervision of a health care professional. The option to begin self-administration of study agent at home will begin after Week 52. Subjects unable to have injection(s) administered away from study site will be required to return to the site for administration of study agent injection(s) by a health care professional. After Week 52, subjects will have study visits and assessments at Weeks 68, 76, 84, 100, and 112.

Safety and efficacy assessments, including blood samples for clinical laboratory and pharmacokinetics/immunogenicity, should be performed before study agent administration.

The three dose groups (Groups I, II, and III) are described above.

EFFICACY EVALUATIONS

Psoriatic Arthritis Response Evaluations

- Joint Assessment
- Nonevaluable Joints
- American College of Rheumatology Response (ACR)
- Dactylitis Assessment
- Enthesitis Assessment
- Imaging Evaluation
- Disability Index of the Health Assessment Questionnaire
- Minimal Disease Activity
- Psoriatic Arthritis Disease Activity Score
- Group for Research and Assessment of Psoriasis and Psoriatic Arthritis Composite Score (GRACE)
- Disease Activity Index Score 28
- Modified Composite Psoriatic Disease Activity Index
- Disease Activity Index for Psoriatic Arthritis
- Modified Psoriatic Arthritis Responder Criteria
- Bath Ankylosing Spondylitis Disease Activity Index

Psoriasis Response Evaluations

- Investigator's Global Assessment of Psoriasis
- Psoriasis Area and Severity Index
- Dermatology Life Quality Index

Other Patient Reported Outcomes

- 36-Item Short-form Health Survey
- EQ-5D Questionnaire
- Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT)

HEALTH ECONOMICS EVALUATIONS

The Work Productivity and Activity Impairment Questionnaire - Specific Health Problem (WPAI-SHP):PsA will be used to study the impact of PsA on work and other daily activities during the past 7 days.

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

Serum samples will be used to evaluate the PK of guselkumab as well as the immunogenicity of guselkumab. Serum collected for PK and immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period.

BIOMARKERS

- Samples for the analysis of pharmacodynamic biomarkers will be collected from all subjects. The samples will be used to better understand the biology of PsA, to provide a biological assessment of the response of patients to treatment with guselkumab, to analyze differences between responders and non-responders, and to determine if the markers can be used to classify patients as potential responders prior to treatment.

  RNA from whole blood samples will be used for gene expression analysis to determine the molecular profile of PsA and to assess changes in gene expression post guselkumab treatment.

- Pharmacogenomics testing is optional. For subjects who provide consent, a whole blood sample will be utilized for pharmacogenomics evaluation. The analysis may include complete genome-wide testing and/or targeted sequencing. The testing will be done to search for links of specific genes to disease or response to drug.

SAFETY EVALUATIONS

The safety and tolerability of study agent (guselkumab and placebo) will be monitored by collecting information on adverse events (including injection site and allergic reactions), clinical laboratory tests, physical examinations, vital signs, suicidal ideation or behavior (using the electronic Columbia-Suicide Severity Rating Scale questionnaires), concomitant medication review, and early detection of tuberculosis.

Serum and/or plasma samples collected for pharmacokinetic or pharmacodynamic analyses may also be used to evaluate safety concerns that may arise during or after the study period.

Safety will be monitored through Week 112.

STATISTICAL METHODS

Simple descriptive summary statistics, such as n, mean, standard deviation, median, inter quantile range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data.

Sample Size Determination

The sample size selection was determined based on the primary endpoint of proportion of subjects who achieve ACR 20 response at Week 24 and the major secondary endpoint of change from baseline in vdH-S score at Week 24.

The table below provides the statistical power under various assumptions using a 2-sided chi-square test.

For this study, the sample size was also evaluated based on the following assumptions:

- 20% to 25% ACR 20 response rates at Week 24 in subjects treated with placebo
- 40% to 50% ACR 20 response rates at Week 24 in subjects treated with guselkumab

Statistical Power for Treatment Difference in ACR 20 Response at Week 24				
Sample size per arm	ACR 20 Response Rate			Power
	Placebo Group	Guselkumab Group	Difference (Δ)	
228	20%	40%	20%	>99%
228	20%	45%	25%	>99%
228	25%	45%	20%	99%
228	25%	50%	25%	>99%
228	30%	50%	20%	99%

The table below provides the statistical power under various assumptions. The statistical power was estimated based on 10000 simulations with treatment comparison performed at each simulation using an ANOVA test on the van der Waerden normal score.

For this study, the sample size was determined based on the following assumptions:

- The overall mean difference in change from baseline in vdH-S score at Week 24 between the placebo group and a guselkumab group ranges from 0.6 to 0.8.
  - 40% – 50% subjects in each treatment group have a change score of 0 from baseline in vdH-S score at Week 24 (ie, the subpopulation with a change score of 0).
  - For the other subjects (those from the normal distributions), the SD of the normal distributions is 2.5 for all treatment groups and the mean of the normal distribution is 1.80 for the placebo group.

If the SD of the normal distributions is 3.0, the power will go down to as low as approximately 80%.

Statistical Power for Treatment Difference in vdH-S Change from Baseline at Week 24									
Placebo Group				Guselkumab Group				Overall Mean Difference	Power
% subjects without change	Rest of subjects		Overall mean	% subjects without change	Rest of subjects		Overall mean		
	Mean	SD			Mean	SD			
45%	1.80	2.5	1.00	45%	0.71	2.5	0.40	0.60	89.0%
45%	1.80	2.5	1.00	45%	0.35	2.5	0.20	0.80	98.9%
50%	1.80	2.5	0.90	50%	0.60	2.5	0.30	0.60	91.7%
50%	1.80	2.5	0.90	50%	0.20	2.5	0.10	0.80	99.4%
50%	1.80	2.5	0.90	45%	0.55	2.5	0.30	0.60	91.1%
50%	1.80	2.5	0.90	45%	0.18	2.5	0.10	0.80	99.2%

Primary Endpoint Analysis

The primary endpoint to be analyzed for the primary analysis is the proportion of subjects who achieved an ACR 20 response at Week 24. Note that the intercurrent event of Treatment Failure prior to Week 24 (defined below) will be treated as non-response for the primary analysis, regardless of the observed ACR 20 response status.

Treatment Failure Criteria

Subjects who meet the following treatment failure criteria include subjects who:

1. Discontinued study agent injections due to lack of efficacy.
2. Terminate study participation for any reason
3. Initiated or increased the dose of non-biologic DMARDs (MTX, SSZ, HCQ, LEF) or oral corticosteroids over baseline for PsA.
4. Initiated protocol prohibited medications/therapies for PsA.

Subjects with missing data at Week 24 will be considered non-responders.

The treatment effect of each guselkumab group versus placebo will be tested using a Cochran-Mantel-Haenszel test stratified by baseline non-biologic DMARD (MTX, SSZ, HCQ, LEF) use (yes/no) and the most recent available CRP value prior to randomization (<2.0 mg/dL or ≥2.0 mg/dL). The magnitude of the effect will be estimated by the difference in ACR 20 response rates between the guselkumab and placebo groups with the 95% confidence interval calculated based on Wald statistics.

In order to control the overall Type 1 error rate, the primary analysis will be tested in a fixed sequence.

1. Guselkumab 100 mg q4w versus placebo in ACR 20 response at Week 24
2. Guselkumab 100 mg at Weeks 0, 4, and then q8w versus placebo in ACR 20 response at Week 24

With the above specified order, each of the hypotheses will be tested at a 2-sided α-level of 0.05 provided that significance is achieved for the preceding hypothesis in the specified order. If a given comparison is not significant at the 2-sided α-level of 0.05, the remaining treatment group comparisons will be considered as supportive analysis.

Major Secondary Analyses

The major secondary endpoints are listed above. The methods of analysis and the approach to control the Type I error for multiplicity, as well as the data-handling rules for the major secondary endpoints will be specified in the Statistical Analysis Plan.

Safety Analysis

Routine safety evaluations will be performed. Adverse events, serious adverse events, and infections will be summarized by treatment group. The following analyses will also be used to assess the safety of subjects in the study: incidence and type of adverse events, incidence and type of serious adverse events, incidence and type of infections, and incidence and type of injection site reactions.

Laboratory parameters, change from baseline in selected laboratory parameters (hematology and chemistry) and incidence of laboratory parameters that meet the criteria for Common Terminology Criteria for Adverse Events Grade 3 or Grade 4 will be summarized by treatment group.

All safety analyses will be based on the population of subjects who received at least 1 injection of study agent. Subjects will be summarized by the treatment they actually received

Interim Analysis

No interim analysis is planned for this study.

TIME AND EVENTS SCHEDULE

Table 1: TIME AND EVENTS SCHEDULE FROM SCREENING THROUGH WEEK 24

Phase	**Screening[a]**	**Placebo-controlled Treatment[b]**							
Week		**0[c]**	**2**	**4**	**8**	**12**	**16**	**20**	**24**
Study Procedures[d]									
Screening/Administrative									
Informed Consent (ICF/eICF[e])	X								
Pharmacogenomics (DNA) (optional)[f] ICF/eICF[e]	X								
Review of Inclusion/Exclusion Criteria	X	X							
Demography/Medical History	X								
Pre-planned Surgery/Procedure(s)	X								
Pre-study Therapy Review for Eligibility	X	X							
Study Agent Administration[g]									
Randomization		X							
Study Agent Administration		X		X	X	X	X	X	X
Early Escape									
Early Escape							X[h]		
Safety Assessments									
Physical Examination (including skin)	X								X
eC-SSRS[i]	X	X	X	X	X	X	X	X	X
Vital Signs[j]	X	X	X	X	X	X	X	X	X
Height		X							
Weight		X							X
Local 12-lead ECG		X[k]							
Tuberculosis Evaluation[l]	X	X	X	X	X	X	X	X	X
Chest Radiograph[m]	X								
Pregnancy Test[n]	X	X		X	X	X	X	X	X
Injection Site Reaction Evaluation		X		X	X	X	X	X	X

Table 1: TIME AND EVENTS SCHEDULE FROM SCREENING THROUGH WEEK 24

Phase	Screening[a]	Placebo-controlled Treatment[b]							
Week		**0[c]**	**2**	**4**	**8**	**12**	**16**	**20**	**24**
Efficacy Assessments									
PsA Evaluations for Arthritis[o]	X	X	X	X	X	X	X	X	X
HAQ-DI[p]		X	X	X	X	X	X	X	X
Patient's Global Assessment of Disease Activity (Arthritis and Psoriasis)[p]		X			X		X		X
Patient's Assessment of Skin Disease Activity (Skin VAS)[p]		X			X		X		X
Dactylitis assessments		X	X	X	X		X		X
Enthesitis assessments (LEI)		X	X	X	X		X		X
Radiographs of Hands and Feet[q,r]	X								X
BASDAI[p,s]		X			X		X		X
Pelvic x-ray[t]	X								
SF-36[p]		X			X		X		X
DLQI[p]		X			X		X		X
FACIT-fatigue[p]		X			X		X		X
WPAI:PsA[p]		X					X		X
EQ-5D[p]		X					X		X
BSA % Involvement of Psoriasis		X							
IGA-Psoriasis		X					X		X
PASI		X					X		X

Table 1: TIME AND EVENTS SCHEDULE FROM SCREENING THROUGH WEEK 24

Phase	Screening[a]	Placebo-controlled Treatment[b]							
Week		**0[c]**	**2**	**4**	**8**	**12**	**16**	**20**	**24**
Clinical Laboratory Assessments									
QuantiFERON-TB test[u]	X								
Hepatitis B and C Serologies[v]	X								
HIV Antibody Test[v]	X								
Hematology[v]	X	X		X	X	X	X	X	X
Chemistry[v]	X	X		X	X	X	X	X	X
Lipid Panel[v]		X							
C-reactive Protein[v]	X	X	X	X	X	X	X	X	X
Rheumatoid Factor[v,w]	X								
Follicle Stimulating Hormone[v,x]	X								
Pharmacokinetics/Immunogenicity[y]									
Serum Guselkumab Concentration		X	X	X	X	X	X	X	X
Population PK					X[z]				
Antibodies to Study Agent		X		X		X			X
Pharmacogenomics (DNA)									
DNA Collection (Whole Blood in EDTA)[f]		X		X					X
Other Biomarkers									
Serum Biomarkers		X		X					X
Whole Blood (RNA)		X		X					X
Ongoing Subject Review									
Concomitant Therapy	X----------X								
Adverse Events	X----------X								

Table 1: TIME AND EVENTS SCHEDULE FROM SCREENING THROUGH WEEK 24

a: The screening visit is to occur within 6 weeks before administration of study agent at Week 0. The screening visit may be completed in a single visit or may be divided into more than 1 visit. It is recommended that after obtaining informed consent, the investigator complete all laboratory tests at the first visit. The subject may then return for the remainder of the screening procedures only if the subject is eligible for the study as determined by the central laboratory test results.

b: Through Week 24, study visits will have a visit window of ±4 days.

c: Subjects must fast (ie, no food or beverages [except water]) for at least 8 hours before blood is drawn for the lipid panel (Week 0). All other visits can be nonfasting.

d: If a subject permanently discontinues study agent administration at Week 24, the final efficacy visit should occur at the time of discontinuation or as soon as possible and all assessments under the Week 100/final efficacy should be performed, including radiographs of hands and feet (see footnote "r" below), with the exception of study agent administration. Fasting is not required for the final efficacy visit. The subject should also return for a final safety visit approximately 12 weeks after the last study agent administration.

e: An eICF will be used at a limited number of sites to obtain informed consent to participate in the study, and to obtain informed consent to participate in the optional DNA research component of the study, as applicable.

f: To participate in the optional DNA research component of this study, subjects must sign the DNA research ICF (or eICF) indicating willingness to participate. Blood samples for pharmacogenomic and epigenetic research will be collected only from subjects who give informed consent for DNA research.

g: Study agent will be administered SC at the site by a health care professional during visits to the site until the subject (or caregiver) is trained for self-administration. Study agent will be administered by site personnel at Weeks 0 and 4. Beginning at Week 8, at the discretion of the investigator and subject, and after appropriate and documented training, subjects may self-administer study agent at the investigative site under the supervision of a health care professional. A caregiver may also be trained to administer study agent. Safety and efficacy assessments, including blood samples for clinical laboratory and pharmacokinetics/immunogenicity, should be performed before study agent administration.

h: At Week 16, all subjects who qualify for early escape will continue on the dosing regimen they were randomized to and will be allowed to initiate or increase the dose of one of the permitted concomitant medication interventions up to the maximum dose as specified in Table 4, at the discretion of the investigator. Titration to a stable dose of the medication should be completed for subjects qualifying for early escape by the Week 24 visit.

i: The eC-SSRS should be performed after the joint assessment at the screening visit (after signing informed consent). At Week 0/baseline and at all post-baseline visits, the eC-SSRS should be the first assessment/questionnaire that the subject completes prior to study agent administration (see Section 9.7.2 for details).

j: Vital signs include blood pressure and heart rate.

k: 12-lead ECG must be done prior to administration of study agent.

l: Subjects (as outlined in Inclusion Criterion 14) must undergo testing for TB (Attachment 2 or Attachment 3) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB.

m: The chest radiograph may be taken within 3 months prior to the first administration of study agent.

n: Females of childbearing potential must have a negative serum pregnancy test prior to randomization and a negative urine pregnancy test at all dosing visits prior to administration of study agent.

Table 1: TIME AND EVENTS SCHEDULE FROM SCREENING THROUGH WEEK 24

o: PsA evaluations for arthritis include joint assessments (swollen and tender joint counts), patient's assessment of pain, patient's global assessment of disease activity (arthritis), and physician's global assessment of disease activity on VAS. These procedures should be performed prior to study agent administration at each visit, as applicable.

p: All patient questionnaires should be completed before any other tests, procedures, or evaluations on the day of the visit for baseline and post-baseline visits.

q: To minimize unnecessary x-rays, it is recommended that subjects have the baseline radiographs of hands and feet taken after the inclusion and exclusion criteria have been checked and the subject appears eligible to enter the study. All eligible subjects should have radiographs taken approximately 2 weeks but not greater than 4 weeks prior to randomization.

r: Week 24 radiographs should be taken within ±2 weeks of the Week 24 visit. For subjects who discontinue study agent prior to Week 24, radiographs of the hands and feet should be performed at the time of study agent discontinuation. If discontinuation occurs prior to or at Week 16, the subject should also have radiographs performed at the Week 24 visit. If discontinuation occurs after Week 16, the radiographs do not need to be repeated at Week 24. For subjects who also discontinue study participation at any time during the study, radiographs should be performed at the time of study discontinuation unless another set of radiographs has been obtained within the past 6 weeks.

s: The BASDAI will be completed only in subjects with spondylitis with peripheral arthritis as their primary arthritic presentation of PsA.

t: For patients with spondylitis, confirmation of sacroiliitis should be performed at the screening visit by a locally performed pelvic x-ray (single anterior-posterior view) unless a pelvic or SI joint x-ray or pelvic MRI has been previously performed. Results must be documented.

u: A tuberculin skin test is additionally required if the QuantiFERON®-TB Gold test is not approved/registered in the country in which this study is being conducted, with the exception noted in Inclusion Criterion 14.

v: Laboratory tests are listed in Section 9.7.1.

w: This test is optional. It can be done if needed to confirm whether CASPAR criteria are met.

x: Prior to randomization, FSH is only required for female subjects with amenorrhea for less than 12 months. Two FSH measurements are needed to confirm amenorrhea in these subjects. This test should NOT be done for any female subject of childbearing potential or female subjects with amenorrhea for at least 12 months. Refer to Inclusion Criterion 10 for details.

y: All blood samples must be collected before study agent administration at visits when a study agent administration is scheduled. Blood collected from one venipuncture will be divided into multiple aliquots of serum for the measurement of guselkumab concentration, antibodies to guselkumab, and a back-up sample. Details will be provided in the Laboratory Manual.

Table 1: TIME AND EVENTS SCHEDULE FROM SCREENING THROUGH WEEK 24

z: An additional study visit, at which a venous blood sample (approximately 4 mL) for population PK analysis will be collected from all subjects, must occur on a random day between Week 4 to Week 12, but not on the same days of the scheduled Weeks 4, 8 or 12 visits. Additionally, this blood sample must be collected at least 24 hours prior to or after the actual time of study agent administration at Weeks 4, 8, or 12 (ie, it cannot be collected within 24 hours before or after study agent administration). The serum sample for population PK will be split into 2 aliquots (1 aliquot for serum guselkumab concentration and 1 aliquot as a back-up sample).

Abbreviations: BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BSA = body surface area; CASPAR = ClASsification criteria for Psoriatic Arthritis; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; EDTA = ethylenediaminetetraacetic acid; eICF = electronic informed consent form; EQ-5D = EuroQol five dimensions questionnaire; FACIT = Functional Assessment of Chronic Illness Therapy; FSH = follicle stimulating hormone; HAQ-DI = Disability Index of the Health Assessment Questionnaire; HIV = human immunodeficiency virus; ICF = informed consent form; IGA = Investigator's Global Assessment; LEI = Leeds Enthesitis Index; MRI = magnetic resonance imaging; PASI = Psoriatic Area and Severity Index; PsA = psoriatic arthritis; RNA = ribonucleic acid; SF-36 = 36-item Short Form Health Survey; SI =TB = tuberculosis; VAS = visual analog scale; WPAI = Work Productivity and Activity Impairment Questionnaire.

Table 2: TIME AND EVENTS SCHEDULE FROM WEEK 28 THROUGH WEEK 112

Phase	**Active Treatment[a]**																			**Safety Follow-up**
Week[b]	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**Final Efficacy Visit[c]/ 100**	**Final Safety Visit[a] /112**
Study Procedures[d]																				
Study Agent Administration[e]																				
Study Agent Administration	X	X	X	X	X	X	X	X[f]	X[f]	X[f]	X[g]	X[f]	X[g]	X[f]	X[g]	X[f]	X[f]	X[f]	X	
Safety Assessments																				
Physical Examination (including skin)							X													X
eC-SSRS[h]	X	X	X	X	X	X	X				X		X		X				X	X
Vital Signs[i]		X		X		X	X												X	X
Weight							X						X						X	
Tuberculosis Evaluation[j]	X	X	X	X	X	X	X				X		X		X				X	X
Pregnancy Test[k]	X	X	X	X	X	X	X				X[l]		X[l]		X[l]				X	X
Injection Site Reaction Evaluation	X	X	X	X	X	X	X				X[l]		X[l]		X[l]				X	

Table 2: TIME AND EVENTS SCHEDULE FROM WEEK 28 THROUGH WEEK 112

Phase	Active Treatment[a]																			Safety Follow-up
Week[b]	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**Final Efficacy Visit[c]/ 100**	**Final Safety Visit[a] /112**
Efficacy Assessments																				
PsA Evaluations for Arthritis[m]	X		X		X		X				X		X		X				X	
HAQ-DI[n]	X		X		X		X				X		X		X				X	
Patient's Global Assessment of Disease Activity (arthritis and psoriasis)[n]							X						X						X	
Patient's Assessment of Skin Disease Activity (Skin VAS)[n]							X						X						X	
Dactylitis Assessments							X						X						X	
Enthesitis Assessments (LEI)							X						X						X	
Radiographs of Hands and Feet[o]							X												X	
BASDAI[n,p]							X						X						X	
SF-36[n]							X						X						X	
DLQI[n]							X						X						X	
FACIT-fatigue[n]							X						X						X	
WPAI:PSA[n]							X						X						X	
EQ-5D[n]							X						X						X	
IGA-Psoriasis							X						X						X	
PASI							X						X						X	

Table 2: TIME AND EVENTS SCHEDULE FROM WEEK 28 THROUGH WEEK 112

Phase	Active Treatment[a]																			Safety Follow-up
Week[b]	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**Final Efficacy Visit[c]/ 100**	**Final Safety Visit[a] /112**
Clinical Laboratory Assessments																				
Hematology[q]	X	X	X		X		X				X		X		X				X	X
Chemistry[q]	X	X	X		X		X				X		X		X				X	X
CRP[q]	X		X		X		X				X		X		X				X	
Pharmacokinetics/Immunogenicity[r]																				
Serum Guselkumab Concentration	X		X		X		X						X						X	X
Antibodies to Study Agent	X						X						X						X	X
Pharmacogenomics (DNA)																				
DNA Collection (Whole Blood in EDTA)[s]							X												X	
Biomarkers																				
Serum Biomarkers							X												X	
Whole Blood (RNA)							X												X	
Ongoing Subject Review																				
Concomitant Therapy	X----------X																			
Adverse Events	X----------X																			

Table 2: TIME AND EVENTS SCHEDULE FROM WEEK 28 THROUGH WEEK 112

a: Through Week 100, study visits will have a visit window of ±7 days; Week 112 visit or the final safety visit (12 weeks after the last dose in subjects who discontinued study treatment) will have a visit window of ±14 days.
b: All visits can be nonfasting.
c: With the exception of study agent administration, all assessments performed at Week 100 will also be performed at the final efficacy visit.
d: If a subject discontinues study agent at or after Week 24, the final efficacy visit assessments should occur at the time of discontinuation or as soon as possible and all assessments under the final efficacy/Week 100 visit should be performed, including radiographs of hands and feet, with the exception of study agent administration. The subject should also return for a final safety visit approximately 12 weeks after the last study agent administration.
e: At the discretion of the investigator and subject, and after appropriate and documented training, subjects will continue to self-administer study agent at the investigative site under the supervision of a health care professional. Safety and efficacy assessments, including blood samples for clinical laboratory and pharmacokinetics/immunogenicity, should be performed before study agent administration.
f: The option to begin self-administration of study agent at home will begin at Week 56; subjects will record study agent administration on a diary card. Subjects who self-administer are not required to visit the study site at Weeks 56, 60, 64, 72, 80, 88, 92, and 96. Subjects unable to have injection(s) administered away from the study site will be required to return to the site at these study weeks for administration of study agent injection(s). An injection site evaluation and AE review will be done at the study site at the time of injection.
g: Dosing for all clinic visits (ie, Weeks 28, 32, 36, 40, 44, 48, 52, 68, 76, 84, and 100) should occur after all procedures at the clinic visit.
h: At all post-baseline visits, the eC-SSRS will be the first assessment/questionnaire that the subject must complete.
i: Vital signs include blood pressure and heart rate.
j: Subjects (as outlined in Inclusion Criterion 14) must undergo testing for TB (Attachment 2 or Attachment 3) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB.
k: Females of childbearing potential who are dosed at the clinic must have a negative urine pregnancy test at all dosing visits prior to administration of study agent. For subjects not dosed at the clinic (see footnote “f” above), a urine pregnancy test is not required prior to administration of study agent.
l: Only performed for subjects who are dosed at the site.
m: PsA evaluations for arthritis include joint assessments (swollen and tender joint counts), patient’s assessment of pain, patient’s global assessment of disease activity (arthritis), and physician’s global assessment of disease activity on VAS. These assessments should be performed prior to study agent administration at each visit, as applicable.
n: All patient questionnaires should be performed before any other tests, procedures, or evaluations on the day of the visit.

Table 2: TIME AND EVENTS SCHEDULE FROM WEEK 28 THROUGH WEEK 112

o: Single radiographs of the hands (posteroanterior) and feet (anteroposterior) should be performed within ±2 weeks of the Week 52 and Week 100 visits. For subjects who permanently discontinue study agent after Week 24 but prior to Week 100, radiographs of hands and feet should be performed at the time of discontinuation of study agent or as soon as possible unless another set of radiographs has been obtained within the past 6 weeks.

p: The BASDAI will be completed only in subjects with spondylitis with peripheral arthritis as their primary arthritic presentation of PsA.

q: Laboratory tests are listed in Section 9.7.1.

r: All blood samples must be collected before study agent administration at visits when a study agent administration is scheduled. Blood collected from one venipuncture will be divided into multiple aliquots of serum for the measurement of guselkumab concentration, antibodies to guselkumab and a back-up sample. Details will be provided in the Laboratory Manual.

s: Blood samples for pharmacogenomic and epigenetic research will be collected only from subjects who give informed consent for DNA research.

Abbreviations: BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CRP = C-reactive protein; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; EDTA = ethylenediaminetetraacetic acid; EQ-5D = EuroQol five dimensions questionnaire; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ-DI = Disability Index of the Health Assessment Questionnaire; IGA = Investigator's Global Assessment; LEI = Leeds Enthesitis Index; PASI = Psoriatic Area and Severity Index; PsA = psoriatic arthritis; RNA = ribonucleic acid; SF-36 = 36-item Short Form Health Survey; VAS = visual analog scale; WPAI = Work Productivity and Activity Impairment Questionnaire

ABBREVIATIONS

ACR	American College of Rheumatology
AMDF	Arithmetic Mean of the Desirability Function
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
ARC	Anticipated Event Review Committee
AST	aspartate aminotransferase
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BCG	bacillus Calmette-Guérin
BQL	below the lowest quantifiable sample concentration of the assay
BSA	body surface area
CASPAR	ClASsification criteria for Psoriatic Arthritis
CRF	case report form(s) (paper or electronic as appropriate for this study)
CRP	C-reactive protein
DAS28	Disease Activity Score 28
DBL	database lock
DLQI	Dermatology Life Quality Index
DMARDs	disease-modifying antirheumatic drugs
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
eDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
EQ-5D	EuroQol five dimensions questionnaire
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GRACE	GRAppa Composite score
GRAppa	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ	Health Assessment Questionnaire
HAQ-DI	Disability Index of the Health Assessment Questionnaire
HBV	hepatitis B virus
HCP	healthcare professional
HCQ	Hydroxychloroquine

HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IJA	independent joint assessor
IL	interleukin
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
JAK	Janus kinase
JSN	joint space narrowing
LEF	leflunomide
LEI	Leeds Enthesitis Index
mAb	monoclonal antibody
MCP	metacarpophalangeal
mCPDAI	modified Composite Psoriatic Disease Activity Index
MCS	Mental Component Summary
MDA	minimal disease activity
MI	multiple imputation
MRI	magnetic resonance imaging
MTX	methotrexate
NAb	neutralizing antibody
NSAID	nonsteroidal anti-inflammatory drug
PASDAS	Psoriatic ArthritiS Disease Activity Score
PASI	Psoriatic Area and Severity Index
PCS	Physical Component Summary
PD	pharmacodynamic(s)
PFS	prefilled syringe
PFS-U	prefilled syringe with an UltraSafe PLUS™ Passive Needle Guard
PGA	Physician's Global Assessment
PIP	proximal interphalangeal
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria

q4w	every 4 weeks
q8w	every 8 weeks
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SDC	smallest detectable change
SF-36	36-item Short Form Health Survey
SSZ	sulfasalazine
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
Th17	T helper 17
TNFα	tumor necrosis factor alpha
UV	ultraviolet
VAS	Visual Analogue Scale
vdH-S	van der Heijde-Sharp (score)
WPAI	Work Productivity and Activity Impairment Questionnaire

1. INTRODUCTION

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

Guselkumab has been extensively studied in 3 large Phase 3 studies in psoriasis. For the most comprehensive nonclinical and clinical information regarding guselkumab, refer to the latest version of the Investigator's Brochure for guselkumab.

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

1.1. Background

1.1.1. Disease Background

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy of the peripheral and axial joints associated with psoriasis.[46] The estimated prevalence of PsA in the general population varies from 0.02% to 1.0% across the world.[15,46] In patients with psoriasis, the prevalence of PsA ranges from 6% to 42%.[15] Psoriatic arthritis is a multi-faceted disease that impacts the joints, soft tissues, and skin, all of which affect quality of life.[18,45] The burden of disease can be severe, with some patients developing destructive arthritis leading to bony erosion and loss of joint architecture; some patients even require surgical intervention to alleviate pain and restore function of severely damaged joints.[57] Psoriatic arthritis not only results in functional disability and impaired quality of life, but patients with this disease have increased mortality.[16,47,49,56]

1.1.2. Treatment Options

Current treatment options for PsA include conventional therapies such as nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroid injections, low-dose systemic steroids, oral disease-modifying antirheumatic drugs (DMARDs; eg, methotrexate [MTX], sulfasalazine [SSZ], and leflunomide [LEF]), and immunosuppressive drugs (eg, cyclosporine A, tacrolimus). The addition of biologic treatments for PsA, including tumor necrosis factor alpha (TNFα) inhibitors (etanercept, infliximab, adalimumab, golimumab, certolizumab), ustekinumab, an IL-12/IL-23 inhibitor, and secukinumab (an IL-17 inhibitor) significantly improved skin and joint responses in patients when used on top of conventional DMARDS or alone. Apremilast, a new oral phosphodiesterase 4 inhibitor, is also available for the treatment of PsA; however, its use is associated with less degree of skin and joint improvements compared with biologic treatments.

Despite these recent advances in treatment options for PsA, there remains an unmet medical need for novel therapeutic agents that address the heterogeneous clinical manifestations of PsA and offer an improved benefit/risk profile for the individual patient.

1.1.3. Clinical Studies

Guselkumab is being developed as a potential treatment for psoriasis, PsA, and other immune-mediated diseases. As of 31 August 2016, 15 clinical studies with guselkumab have been completed or are ongoing.

Seven clinical studies have been completed:

- CNTO1959PSO1001, a Phase 1 study with 2 parts; Part 1 enrolled healthy subjects and Part 2 enrolled subjects with moderate to severe plaque psoriasis.
- CNTO1959PSO1002, a Phase 1 study of guselkumab in Japanese subjects with moderate to severe plaque psoriasis.
- CNTO1959PSO2001, a Phase 2, randomized, placebo- and active-comparator-controlled, parallel group, multicenter, dose-ranging study of guselkumab in subjects with moderate to severe plaque psoriasis.
- CNTO1275ARA2001, a Phase 2 study of guselkumab and ustekinumab (STELARA®) in subjects with active rheumatoid arthritis (RA) despite concomitant MTX therapy. Further development of guselkumab in the RA indication has been discontinued by the Sponsor.
- CNTO1959PPP2001, a Phase 2 study to assess the efficacy, safety, and tolerability of guselkumab following subcutaneous (SC) administration in Japanese subjects with palmoplantar pustulosis.
- CNTO1959NAP1001, a Phase 1 study to assess pharmacokinetic (PK) comparability of 2 formulations and to evaluate the PK comparability of guselkumab delivered by 2 different devices in healthy subjects.
- CNTO1959NAP1002, a Phase 1 study to characterize the elimination of guselkumab glycoform variants in healthy subjects.

Eight studies are ongoing:

- CNTO1959PSO1003, a Phase 1 study to assess the drug-drug interaction potential of guselkumab treatment in subjects with moderate to severe plaque psoriasis.
- CNTO1959PSA2001, a Phase 2 study to evaluate the efficacy and safety of guselkumab in subjects with active PsA.
- CNTO1959PSO3001, a Phase 3 study to evaluate the efficacy and safety of guselkumab in subjects with moderate to severe plaque psoriasis.
- CNTO1959PSO3002, a Phase 3 study to evaluate the efficacy and safety of guselkumab in subjects with moderate to severe plaque psoriasis with randomized withdrawal and retreatment.

- CNTO1959PSO3003, a Phase 3 study to evaluate the efficacy and safety of guselkumab in subjects with moderate to severe plaque psoriasis and an inadequate response to ustekinumab.
- CNTO1959PSO3004, a Phase 3 study to evaluate the efficacy and safety of guselkumab in subjects with moderate to severe plaque psoriasis in Japan.
- CNTO1959PSO3005, a Phase 3 study to evaluate the efficacy and safety of guselkumab in subjects with generalized pustular psoriasis or erythrodermic psoriasis in Japan.
- CNTO1959PPP3001, a Phase 3 study to evaluate the efficacy and safety of guselkumab in subjects with palmoplantar pustulosis in Japan.

Preliminary efficacy and safety results for the ongoing Phase 2 PsA study (CNTO1959PSA2001) are presented in Section 1.1.3.1. Preliminary efficacy and safety results for the 5 ongoing studies in psoriasis are presented in Section 1.1.3.2 (Phase 2 study) and Section 1.1.3.3 (Phase 3 studies).

In RA, 1 Phase 2 dose-ranging study has been completed; see Section 1.1.3.4.

Further details are provided in the guselkumab Investigator's Brochure.

1.1.3.1. Phase 2 Study in Psoriatic Arthritis (CNTO1959PSA2001)

Study Design

CNTO1959PSA2001 is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled, study evaluating the efficacy and safety of guselkumab in subjects with active PsA and ≥3% body surface area (BSA) of plaque psoriasis despite current or previous treatment with standard-of-care therapies, including those previously exposed to anti-TNFα agents. In this study, 149 subjects with active PsA were randomized in a 1:2 ratio to receive either placebo or guselkumab 100 mg SC at Weeks 0, 4, then every 8 weeks (q8w) through Week 44. At Week 16, subjects in both treatment groups who had <5% improvement from baseline in both tender and swollen joint counts qualified for early escape and switched to open-label therapy with ustekinumab. At Week 24, subjects remaining in the placebo group crossed over to receive guselkumab 100 mg at Week 24, 28, then q8w through Week 44. All subjects will have a final safety visit at Week 56.

Preliminary efficacy, safety and PK results through Week 24 are summarized below:

Efficacy Results

The study met its primary and all secondary endpoints. The primary endpoint was the proportion of subjects who achieved an American College of Rheumatology (ACR) 20 response at Week 24, and was significantly higher in the guselkumab group (58.0%) compared with the placebo group (18.4%, p<0.001).

In addition, significantly more guselkumab subjects achieved ACR 50 and ACR 70 responses, and PASI 50, PASI 75, and PASI 90 responses at Week 24 compared with the placebo group (Table 3). Significant treatment effect on ACR 20 response was observed as early as Week 4 (21% vs 0, p<0.001), and the effect increased over time reaching the maximum by Week 16

(60.0% vs. 16.3%, p<0.001) vs. placebo. Other secondary efficacy endpoints are summarized in Table 3. These results demonstrated that treatment with guselkumab significantly improved joint symptoms, physical function, psoriasis, enthesitis, dactylitis, and quality of life in this population.

Table 3: Summary of Efficacy Results at Week 24 (CNTO1959PSA2001)

Efficacy Endpoints	Placebo	Guselkumab	p-value
ACR 20	18.4%	58.0%	p<0.001
ACR 50	10.2%	34.0%	P=0.002
ACR 70	2.0%	14.0%	p=0.023 (post hoc)
PASI 75	12.5%	78.6%	p<0.001
PASI 90	6.3%	66.3%	p<0.001
PASI 100	6.3%	39.8%	P<0.001
Mean (SD) change from baseline in HAQ-DI score	-0.06 (0.530)	-0.42 (0.512)	p<0.001
Median percent change from baseline in Leeds Enthesitis Index (LEI)[a]	-33.33%	-100.00%	p=0.009
% of patients with unresolved enthesitis [a]	71.0%	43.4%	p=0.012
Median percent change from baseline in dactylitis[b]	-33.33%	-100.00%	p<0.001
% of patients with unresolved dactylitis[b]	82.6%	44.8%	p=0.001
Mean (SD) change from baseline in SF-36 physical component summary (PCS) score	0.46 (6.51)	6.59 (7.47)	p<0.001
Mean (SD) change from baseline in SF-36 mental component summary (MCS) score	0.42 (6.74)	4.95 (9.06)	p=0.002
% of patients achieving Minimal Disease Activity (MDA)	2.0%	23.0%	p=0.001

[a] Among the patients with enthesitis at baseline (Placebo: N=31; Guselkumab: N=76)

[b] Among the patients with dactylitis at baseline (Placebo: N=23; Guselkumab: N=58)

ACR = American College of Rheumatology; HAQ-DI = Disability Index of the Health Assessment Questionnaire; PASI = Psoriatic Area and Severity Index; SD = standard deviation

Safety Results

Treatment with guselkumab was generally well-tolerated through Week 24.

Through Week 24, the proportions of subjects with 1 or more adverse events (AEs) were comparable between placebo (32.7%) and guselkumab (36.0%) groups. The proportions of subjects with 1 or more AEs were similar in subjects with or without MTX at baseline. The most common AE in both treatment groups was nasopharyngitis, which was reported in 5 (10.2%) subjects in the placebo group and 6 (6.0%) subjects in the guselkumab group. No injection site reactions were reported in the guselkumab group. Two serious adverse events (SAEs) were

reported, one (2.0%) in the placebo group (joint injury) and one (1.0%) in guselkumab group (myocardial infarction). One (1.0%) subject in guselkumab group had AEs of leukopenia and neutropenia (both of mild severity) that subsequently resulted in discontinuation of study agent administration after the Week 24 visit. No deaths, malignancies, anaphylactic or serum sickness-like reactions were reported in the study through Week 24.

Infections (as assessed by the investigators) were comparable between the placebo (20.4%) and guselkumab (16.0%) groups. Infections reported by >1 subject in the guselkumab group included nasopharyngitis (6 [6.0%]), gingivitis (2 [2.0%]) and urinary tract infection (2 [2.0%]). No serious infections, tuberculosis (TB) or opportunistic infections were reported through Week 24. The proportions of subjects with 1 or more infections requiring oral or parenteral antimicrobial treatment were similar between the placebo (14.3%) and guselkumab (10.0%) groups.

Overall, there were no clinically important findings for hematology or chemistry laboratory parameters.

Pharmacokinetics and Immunogenicity Results

Steady state of serum guselkumab concentration was achieved by approximately Week 20 following SC administrations of 100 mg guselkumab at Week 0 and 4, and q8w thereafter. The median steady-state trough serum guselkumab concentration at Week 20 was 0.93 µg/mL, which is similar to those observed in Phase 3 studies in subjects with psoriasis. Only one subject (1%, 1/100) was positive for antibodies to guselkumab through Week 24 with low antibody titers (1:20).

Conclusions

In subjects with active PsA who had ≥3% BSA involvement of psoriasis, guselkumab demonstrated robust efficacy across all efficacy endpoints on joint signs and symptoms, physical function, skin disease, enthesitis, dactylitis, and health-related quality of life.

Efficacy was generally demonstrated both in subjects receiving MTX and in subjects not receiving MTX. Similarly, guselkumab 100 mg was well tolerated in the PsA population through Week 24 with no unexpected safety findings.

1.1.3.2. Phase 2 Study in Psoriasis (CNTO1959PSO2001, X-PLORE)

Study Design

In the X-PLORE study, 293 subjects with moderate to severe plaque-type psoriasis were randomized to receive 1 of 5 guselkumab SC dose regimens (5 mg at Weeks 0, 4, and then every 12 weeks [q12w], 15 mg q8w, 50 mg at Weeks 0, 4, and then q12w, 100 mg q8w, or 200 mg at Weeks 0, 4, and then q12w), placebo, or adalimumab (HUMIRA®) 80 mg at Week 0, 40 mg at Week 1, and then 40 mg every 2 weeks (q2w).

Efficacy Results

The proportions of subjects who achieved a Physician's Global Assessment (PGA) score of cleared (0) or minimal (1) were significantly higher at Week 16 in all guselkumab treatment groups compared with the placebo group. In addition, higher proportions of subjects in the guselkumab 50 mg q12w, 100 mg q8w, and 200 mg q12w groups achieved a PGA score of cleared (0) or minimal (1) compared with the adalimumab group at Week 16. A dose-response in efficacy was observed up to 100 mg q8w; the proportions of subjects who achieved a PGA of 0 or 1 were similar in the 100 mg q8w and 200 mg q12w dose groups. Results for improvements in Psoriasis Area and Severity Index (PASI) scores were generally similar to those observed for PGA.

Safety Results

Treatment with guselkumab was generally well-tolerated through Week 52. The proportions of subjects with 1 or more AEs were comparable across the combined guselkumab, placebo, and the adalimumab groups through Week 16, with no evidence of a dose-response in the occurrence of AEs across the guselkumab groups. Through Week 16, the proportion of subjects with 1 or more SAEs was low across all treatment groups. Two serious infections (appendicitis and lung abscess in the guselkumab 50 mg group), no malignancies, and no major cardiovascular events were reported. Similar patterns of AEs were observed through Week 52. Events of interest through Week 52 included the 2 serious infections noted through Week 16, 1 malignancy (cervical dysplasia, including carcinoma in situ) in the 200 mg q12w group, and 3 major cardiovascular events (1 fatal myocardial infarction in the 5 mg q12w group and 1 nonfatal myocardial infarction and 1 stroke, each in the 100 mg q8w group).

Pharmacokinetics and Immunogenicity Results

Approximate dose-proportionality in serum guselkumab concentrations through Week 52 was observed after multiple SC administrations at dose levels ranging from 15 mg to 200 mg. Steady state serum guselkumab concentrations were achieved by approximately Week 16 for both the q8w and q12w regimens. In each treatment group, mean or median trough serum guselkumab concentrations were maintained at steady state through Week 40 (q8w groups) or Week 52 (q12w groups). There was no evidence of accumulation in serum guselkumab concentrations over time with SC q8w or q12w administrations. Serum guselkumab concentrations appeared to be affected by subject body weight; higher-weight subjects (>90 kg) had lower mean steady-state trough serum guselkumab concentrations compared with lower-weight subjects (≤90 kg).

The overall incidence of antibodies to guselkumab across all guselkumab treatment groups through Week 52 was 3.8%, with generally low titers. None of the subjects who were positive for antibodies to guselkumab had antibodies that were able to neutralize the bioactivity of guselkumab in vitro. No consistent impact of antibodies to guselkumab on serum guselkumab concentrations was observed across the guselkumab treatment groups.

Conclusions

Treatment with guselkumab was well tolerated across a wide range of doses and led to substantial, clinically meaningful improvements in psoriasis, with several dose regimens yielding superior outcomes to those observed with adalimumab.

1.1.3.3. Phase 3 Studies in Psoriasis (CNTO1959PSO3001, CNTO1959PSO3002, and CNTO1959PSO3003)

1.1.3.3.1. Efficacy

A large global Phase 3 program consisting of 3 studies (CNTO1959PSO3001, CNTO1959PSO3002, and CNTO1959PSO3003) is ongoing to investigate the efficacy and safety of SC guselkumab in subjects with moderate to severe plaque psoriasis. Guselkumab treatment was compared with adalimumab treatment in both CNTO1959PSO3001 and CNTO1959PSO3002. Study CNTOPSO3003 was conducted in subjects with an inadequate response to ustekinumab.

Guselkumab administered as a 100 mg SC injection at Weeks 0 and 4 then q8w:

- Provided a rapid, substantial, and clinically meaningful improvement in skin disease as well as difficult to treat regional psoriasis resulting in improvements in patient-reported outcomes compared with placebo over 16 weeks and adalimumab up to 48 weeks. The superior efficacy of guselkumab was evident across all endpoints and thresholds assessed including measures of complete clearance of psoriasis as defined by an Investigator's Global Assessment (IGA) 0 or a PASI 100 response.
- Continuous q8w guselkumab maintenance treatment was significantly more effective at maintaining a high level skin response than withdrawal of treatment in study PSO3002.
- Guselkumab therapy provided a high level clinical response and treatment benefits among adalimumab PASI 90 non-responders in study PSO3002 and ustekinumab inadequate responders (IGA≥2) in study PSO3003.

1.1.3.3.2. Safety

In the Phase 3 pooled safety analysis set (subjects from CNTO1959PSO3002 and CNTO1959PSO3003), guselkumab at the dose regimen of 100 mg, administered SC at Weeks 0, 4 and then q8w, demonstrated a favorable safety profile consistent with that seen in the overall population from studies CNTO1959PSO3001 and CNTO1959PSO3002 and was well tolerated in adult patients with moderate to severe plaque psoriasis.

1.1.3.4. Phase 2 Study in Rheumatoid Arthritis (CNTO1275ARA2001)

Study Design

CNTO1275ARA2001 was a randomized, double-blind, multicenter, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ustekinumab and guselkumab administered SC in subjects with active RA despite MTX treatment. In this study, 274 subjects with active RA who were on a stable dose of MTX were randomized to receive 1 of 5 treatments:

placebo, ustekinumab 90 mg q8w, ustekinumab 90 mg q12w, guselkumab 50 mg q8w, or guselkumab 200 mg q8w through Week 28 with induction doses at Weeks 0 and 4. After the last study agent administration at Week 28, subjects were followed for safety through Week 48.

Conclusions

The primary efficacy endpoint (ACR 20 response at Week 28) was not met in the guselkumab groups and no significant improvements were observed in any of the major secondary endpoints for the combined guselkumab group. Further development of guselkumab for this indication has been discontinued.

Guselkumab was generally well tolerated.

1.2. Overall Rationale for the Study

1.2.1. Role of Interleukin-23 and TH17 Pathways in the Treatment of Psoriatic Arthritis

Interleukin (IL)-23 is a member of the IL-12 family of heterodimeric cytokines. IL-23 shares the p40 subunit with IL-12. However, in contrast to IL-12, which is formed from p40/p35 heterodimers, the p40 subunit is paired with a p19 subunit to form IL-23.[39] IL-23, alone or in combination with other cytokines (transforming growth factor-β and IL-6 or IL-1β), drives the expansion and/or maintenance of mouse and human CD4+ IL-17 producing T helper 17 (Th17) cells. Th17 cells produce downstream pro-inflammatory cytokines, IL-17A, IL-17F, IL-22, IL-6, and TNFα.[5,29,50]

Inhibition of upstream signaling by IL-23 blockade is expected to interrupt Th17 pathways that contribute to the chronic inflammation underlying the pathophysiology of many immune mediated diseases[41,48] including PsA, psoriasis, multiple sclerosis, inflammatory bowel disease, and axial spondyloarthritis. In addition, susceptibility to psoriasis, PsA, and inflammatory bowel disease has been shown to be associated with genetic polymorphisms in IL-23/IL-23R receptor (R) components.[2,7,30,38,40]

In addition to the robust efficacy demonstrated in the treatment of psoriasis, biologic treatments targeting Th17 pathways, including ustekinumab, secukinumab, and ixekizumab, have been shown to induce rapid and significant improvement of arthritis and psoriasis in subjects with active PsA. The efficacy and safety of ustekinumab, a fully human IgG1κ mAb that binds with high affinity and specificity to the shared p40 subunit of both human IL-12 and IL-23, in subjects with active PsA have been demonstrated in 3 adequate, placebo-controlled studies (1 Phase 2 study, C0743T10[20]; and 2 Phase 3 studies, CNTO1275PSA3001 [PSUMMIT1][26,31] and CNTO1275PSA3002 [PSUMMIT2][44]). In the Phase 3 PsA studies FUTURE 1,[32] FUTURE 2,[36] and SPIRIT-P1,[33] both secukinumab and ixekizumab, the 2 anti-IL17 agents, demonstrated significant reduction on signs and symptoms of PsA, improvement of physical function and inhibition of structural damage. The robust efficacy of the treatments targeting Th17 pathways observed in both psoriasis and PsA, including that demonstrated by guselkumab across all efficacy endpoints in the Phase 2 PsA study (CNTO1959PSA2001) (see Section 1.1.3.1),

highlights the central role that IL-23/IL-17 axis has in the pathogenesis of both psoriasis and PsA.

1.2.2. Study Rationale

Psoriatic arthritis is a multi-faceted disease that impacts the joints, soft tissues, and skin, all of which affect quality of life. Up to 42% of patients with moderate to severe psoriasis have PsA. There is often a medical need to have a single therapeutic agent to control both skin and joint psoriatic symptoms, as well as to control enthesitis, dactylitis, and to prevent joint damage.

Investigation of guselkumab in the current Phase 3 PsA clinical study is supported by the following:

- Robust efficacy results and a favorable safety profile from a Phase 2 study of guselkumab in PsA (Section 1.1.3.1), in which the primary and all secondary endpoints were met.
- Efficacy and safety results of guselkumab observed in Phase 2 and Phase 3 studies in psoriasis (Sections 1.1.3.2 and 1.1.3.3, respectively).

The purpose of this study is to further define the clinical efficacy of guselkumab in the reduction of signs and symptoms, and structural damage inhibition and to evaluate the safety profile of guselkumab in the treatment of PsA.

1.2.3. Dose Rationale

Based upon guselkumab clinical efficacy, safety, pharmacokinetics data, and exposure-response modeling analysis using data from the Phase 2 study (CNTO1959PSA2001) in subjects with PsA, 2 dose regimens have been chosen for evaluation in the guselkumab Phase 3 PsA program:

- 100 mg at Weeks 0 and 4 then every 8 weeks (q8w)
- 100 mg every 4 weeks (q4w)

The rationale for these dose regimens of guselkumab is presented below in Section 1.2.3.1 (100 mg at Weeks 0 and 4 then q8w) and Section 1.2.3.2 (100 mg q4w).

1.2.3.1. Rationale for Guselkumab 100 mg at Weeks 0 and 4 then Every 8 Weeks Dose Regimen

- This dose regimen was evaluated in the Phase 2 PsA study (CNTO1959PSA2001) and in the 3 global Phase 3 studies in psoriasis. In the CNTO1959PSA2001 study, robust efficacy and clinically meaningful improvement was observed with this dose regimen in all important domains of PsA including joint signs and symptoms, physical function, psoriasis, enthesitis, dactylitis, and quality of life in patients with active PsA and ≥3% BSA of psoriasis (Section 1.1.3.1). Additionally, significant benefit was also observed with this dose regimen on plaque psoriasis in patients with moderate-to-severe psoriasis in the Phase 3 psoriasis studies (Section 1.1.3.3).

- PsA is a chronic inflammatory arthropathy which can result in irreversible structural damage of joints, therefore, rapid control of the disease is desired. An additional dose is being included at Week 4 to ensure that trough guselkumab levels do not fall below those obtained at steady-state levels. This additional Week 4 dose results in a slightly higher C_{max} and C_{trough} in the first 12 weeks than those at steady state (~21% and ~18%, respectively) and may result in a more rapid onset of response. However, this dosing regimen is not expected to result in substantially higher levels of efficacy at Week 24 than would be achieved by q8w dosing during maintenance, ie, from Week 24 and onwards.
- The safety of this dosing regimen has been established in a large psoriasis development program. Furthermore, the safety profile in the Phase 2 studies in patients with PsA and RA is consistent with that seen in the psoriasis program.
- In summary, the efficacy and safety data in both the PsA and psoriasis studies support further evaluation of this dose regimen in the Phase 3 PsA studies, including evaluation of its effect on the inhibition of structural damage.

1.2.3.2. Rationale for Guselkumab 100 mg Every 4 Weeks Dose Regimen

- A dose regimen of 100 mg q4w is being included in this study in order to determine if more frequent dosing may achieve higher efficacy in PsA, including the inhibition of structural damage.
- Modeling analyses based on data from CNTO1959PSA2001 suggest that a higher or more frequent dose regimen may achieve better efficacy in PsA:
  - Based on population pharmacokinetic modeling and simulation, the 100 mg q4w dose regimen was predicted to result in an approximately 4-fold higher median steady-state trough concentration (3.95 µg/mL) compared to 100 mg q8w (0.99 µg/mL), and higher trough concentrations, may provide an opportunity to maximize efficacy, including inhibition of structural damage, in PsA.
  - An exposure-response modeling and simulation analysis based on the data from CNTO1959PSA2001 predicted that the 100 mg q4w dose regimen could achieve higher efficacy (ie, ACR responses) in PsA patients at Week 16 compared with the q8w dose regimen. Conversely, this analysis showed that a lower dose regimen (50 mg q8w) could result in lower efficacy (ie, ACR responses).
- Treatment with the 100 mg q4w dose regimen is expected to result in acceptable safety based on the exposure-safety analysis in the Phase 3 psoriasis program:
  - No consistent pattern suggesting an association between systemic guselkumab exposure quartiles and the rates of occurrence of SAEs or AEs leading to discontinuation was evident, with a possible exception of non-serious infections. Moreover, the clinical relevance of this finding appears to be limited, given that the vast majority of these non-serious infections were mild to moderate in intensity and that the frequency of the infections requiring treatment was generally similar across all 4 exposure quartiles.
- Guselkumab has been shown to have an acceptable safety profile in multiple patient populations, including with a higher dose regimen that was studied in a Phase 2 RA study (200 mg q8w). Therefore, guselkumab 100 mg q4w is expected to be well tolerated in the Phase 3 PsA population.

Overall, the two dose regimens of guselkumab (100 mg Weeks 0 and 4 then q8w and 100 mg q4w) selected for the Phase 3 PsA program will allow for an adequate assessment of the optimal benefit/risk profile of guselkumab in PsA.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

The primary objective of this study is to evaluate the efficacy of guselkumab treatment in subjects with active PsA by assessing the reduction in signs and symptoms of PsA.

Secondary Objectives

The secondary objectives are to assess the following for guselkumab treatment:

- Efficacy in improving psoriatic skin lesions
- Improvement in physical function
- Inhibition of progression of structural damage
- Efficacy in improving general and disease specific health-related quality of life and patient-reported health outcomes
- Safety
- Pharmacokinetics, pharmacodynamics (PD), and immunogenicity

2.1.2. Endpoints

Note: Refer to Section 9 for evaluations related to endpoints.

Primary Endpoint

The primary endpoint is proportion of subjects who achieve an ACR 20 response at Week 24.

Major Secondary Endpoints

1. Change from baseline in HAQ-DI score at Week 24.
2. Proportion of subjects who achieve an ACR 50 response at Week 24.
3. Proportion of subjects with a psoriasis response of an IGA (ie, an IGA psoriasis score of 0 [cleared] or 1 [minimal] AND ≥2-grade reduction from baseline) at Week 24 among the subjects with ≥3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline.
4. Proportion of subjects who achieve an ACR 20 response at Week 16.
5. Change from baseline in modified van der Heijde-Sharp (vdH-S) score at Week 24.

6. Proportion of subjects with resolution of enthesitis at Week 24 among the subjects with enthesitis at baseline.

7. Proportion of subjects with resolution of dactylitis at Week 24 among the subjects with dactylitis at baseline.

8. Change from baseline in enthesitis score (based on Leeds Enthesitis Index [LEI]) at Week 24 among the subjects with enthesitis at baseline.

9. Change from baseline in dactylitis score at Week 24 among the subjects with dactylitis at baseline.

10. Change from baseline in 36-item Short Form Health Survey (SF-36) Physical Component Summary (PCS) at Week 24.

11. Change from baseline in Disease Activity Score 28 (DAS28) C-reactive protein (CRP) at Week 24.

12. Change from baseline in SF-36 Mental Component Summary (MCS) at Week 24.

13. Proportion of subjects who achieve an ACR 50 response at Week 16.

14. Proportion of subjects who achieve an ACR 70 response at Week 24.

Other Secondary Endpoints

Endpoints Related to Reduction of Signs and Symptoms and Physical Function

1. Proportions of subjects who achieve an ACR 20, ACR 50, and ACR 70 responses by visit over time through Week 100.

2. Percent change from baseline in ACR components by visit over time through Week 100.

3. Change from baseline in HAQ-DI score by visit over time through Week 100.

4. Proportion of subjects who achieve a clinically meaningful improvement (a ≥0.35 improvement from baseline) in HAQ-DI score by visit over time through Week 100 among those subjects with HAQ-DI score ≥ 0.35 at baseline.

5. Proportion of subjects who achieve a DAS28 (CRP) response by visit over time through Week 100.
6. Proportion of subjects who achieve a DAS28 (CRP) remission by visit over time through Week 100.
7. Change from baseline in DAS28 (CRP) by visit over time through Week 100.

8. Proportion of subjects who achieve a response based on modified Psoriatic Arthritis Response Criteria (PsARC) by visit over time through Week 100.

9. Proportion of subjects with resolution of enthesitis by visit by visit over time through Week 100 among the subjects with enthesitis at baseline.

10. Proportion of subjects with resolution of dactylitis by visit by visit over time through Week 100 among the subjects with dactylitis at baseline.

11. Change from baseline in enthesitis score (based on LEI) by visit over time through Week 100 among the subjects with enthesitis at baseline.

12. Change from baseline in dactylitis score by visit over time through Week 100 among the subjects with dactylitis at baseline.

13. Change from baseline in Psoriatic ArthritiS Disease Activity Score (PASDAS) by visit over time through Week 100.

14. Change from baseline in Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAppa) Composite score (GRACE) Index by visit over time through Week 100.

15. Change from baseline in Work Productivity and Activity Impairment Questionnaire (WPAI) scores by visit over time through Week 100.

16. Change from baseline in modified Composite Psoriatic Disease Activity Index (mCPDAI) score by visit over time through Week 100.

17. Change from baseline in Disease Activity Index for Psoriatic Arthritis score by visit over time through Week 100.

18. Proportion of subjects who maintain an ACR 20 response at Week 52 and Week 100 among the subjects who achieved an ACR 20 response at Week 24.

19. Proportion of subjects who maintain an ACR 50 response at Week 52 and Week 100 among the subjects who achieved an ACR 50 response at Week 24.

20. Proportion of subjects who maintain an ACR 70 response at Week 52 and Week 100 among the subjects who achieved an ACR 70 response at Week 24.

21. Proportion of subjects who maintain a HAQ-DI response (ie, ≥0.35 improvement from baseline in HAQ-DI score) at Week 52 and Week 100 among the subjects who achieved a HAQ-DI response at Week 24.

22. Proportion of subjects who achieve minimal disease activity (MDA) by visit over time through Week 100.

23. Proportions of subjects who achieve a ≥20%, ≥50%, ≥70%, and ≥90% improvement from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score by visit over time through Week 100 among the subjects with spondylitis and peripheral joint involvement as their primary arthritic presentation of PsA.

Endpoints Related to Skin Disease

1. Proportions of subjects who achieve ≥75%, ≥90%, and 100% improvement in Psoriatic Area and Severity Index (PASI) score from baseline by visit over time through Week 100 among the subjects with ≥3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline.

2. Proportion of subjects with an IGA score of 0 (cleared) by visit over time through Week 100 among the subjects with ≥3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline.

3. Change from baseline in PASI score by visit over time through Week 100 among the subjects with ≥3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline.

4. Proportion of subjects who achieve a Dermatology Life Quality Index (DLQI) score of 0 or 1 by visit over time through Week 100 among the subjects with baseline DLQI score >1 and with ≥ 3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline.

5. Proportion of subjects who achieve ≥ 5-point improvement from baseline in DLQI score by visit over time through Week 100 among the subjects with baseline DLQI score ≥ 5 and with ≥ 3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline.

6. Change from baseline in DLQI score by visit over time through Week 100 among the subjects with ≥ 3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline.

7. Proportion of subjects who achieve both PASI 75 and ACR 20 responses by visit over time through Week 100 among the subjects with ≥3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline.

8. Proportion of subjects who achieve both PASI 75 and modified PsARC response by visit over time through Week 100 among the subjects with ≥3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline.

Endpoints Related to Joint Structural Damage

1. Change from baseline in modified vdH-S score by visit over time through Week 100.

2. Change in total modified vdH-S score from Week 24 to Week 52, from Week 24 to Week 100, and from Week 52 to Week 100.

3. Change from baseline in modified vdH-S erosion score by visit over time through Week 100.

4. Change in modified vdH-S erosion score from Week 24 to Week 52, from Week 24 to Week 100, and from Week 52 to Week 100.

5. Change from baseline in modified vdH-S joint space narrowing (JSN) score by visit over time through Week 100.

6. Change in modified vdH-S JSN score from Week 24 to Week 52, from Week 24 to Week 100, and from Week 52 to Week 100.

7. Change from baseline in modified vdH-S score by region and type of damage (ie, hand erosion, hand JSN, foot erosion, foot JSN subscores) by visit over time through Week 100.

8. Proportion of subjects with a change of ≤0 from baseline and proportion of subjects with a change of ≤ 0.5 from baseline in modified vdH-S score by visit over time through Week 100.

9. Proportion of subjects with a change of ≤0 from baseline and proportion of subjects with a change of ≤ 0.5 from baseline in modified vdH-S erosion score at by visit over time through Week 100.

10. Proportion of subjects with a change of ≤0 from baseline and proportion of subjects with a change of ≤ 0.5 from baseline in modified vdH-S JSN score by visit over time through Week 100.

11. Proportion of subjects with radiographic progression (based on the smallest detectable change [SDC]) from baseline by visit over time through Week 100.

12. Proportion of subjects with radiographic joint erosion progression (based on SDC) from baseline by visit over time through Week 100.

13. Proportion of subjects with radiographic JSN progression (based on the SDC) from baseline by visit over time through Week 100.

14. Proportion of subjects with pencil in cup or gross osteolysis deformities by visit over time through Week 100.

Endpoints Related to Health Related Quality of Life

1. Change from baseline in PCS score of the SF-36 by visit over time through Week 100.

2. Change from baseline in MCS score of the SF-36 by visit over time through Week 100.

3. Change from baseline in domain scales scores of SF-36 by visit over time through Week 100.

4. Proportion of subjects who achieve ≥ 5-point improvement from baseline in SF-36 MCS score by visit over time through Week 100.

5. Proportion of subjects who achieve ≥ 5-point improvement from baseline in SF-36 PCS score by visit over time through Week 100.

6. Change from baseline in Functional Assessment of Chronic Illness Therapy-fatigue (FACIT-Fatigue) by visit over time through Week 100.

7. Proportion of subjects who achieve ≥ 4-point improvement from baseline in FACIT-Fatigue score improvement by visit over time through Week 100.

8. Change from baseline in EuroQol five-dimension questionnaire (EQ-5D) Visual Analogue Scale (VAS) and in EQ-5D index scores by visit over time through Week 100.

2.2. Hypothesis

The primary hypothesis is that the guselkumab 100 mg q4w treatment group is superior to placebo as assessed by the proportion of subjects achieving an ACR 20 response at Week 24.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a Phase 3 randomized, double-blind, placebo-controlled, multicenter, 3-arm study of guselkumab in subjects with active PsA who are biologic naïve and have had inadequate response to standard therapies (eg, non-biologic DMARDs, apremilast, NSAIDs). The study will include approximately 684 subjects. Stable doses of concomitant NSAIDs, oral corticosteroids, and selected non-biologic DMARDs (limited to MTX, SSZ, hydroxychloroquine [HCQ], LEF) will be allowed (see Table 4) but are not required.

The study consists of the following phases:

- a screening phase of up to 6 weeks
- a blinded treatment phase of approximately 2 years (ie, 100 weeks), including a placebo-controlled period from Week 0 to Week 24 and an active treatment period from Week 24 to Week 100
- a safety follow-up phase of 12 weeks after the last administration of study agent.

An overview of the study design is provided in Figure 1.

At Week 0, approximately 684 subjects who satisfy all inclusion and exclusion criteria will be randomly assigned to one of the following 3 treatment groups in a 1:1:1 ratio using permuted block randomization stratified by baseline non-biologic DMARD (MTX, SSZ, HCQ, LEF) use (yes/no) and the most recent available CRP value prior to randomization (<2.0 mg/dL vs ≥2.0 mg/dL):

- **Group I** (n=228): Subjects will receive SC guselkumab 100 mg q4w from Week 0 through Week 100.
- **Group II** (n=228): Subjects will receive SC guselkumab 100 mg at Weeks 0 and 4 then q8w (Weeks 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, and 100) and placebo injections at other visits (Weeks 8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, and 96) to maintain the blind.
- **Group III** (n=228): Subjects will receive SC placebo q4w from Week 0 to Week 20 and will cross over at Week 24 to receive SC guselkumab 100 mg q4w from Week 24 through Week 100.

At Week 16, all subjects in Groups I, II and III with <5% improvement from baseline in both tender and swollen joint counts will be considered as meeting early escape criteria. These subjects will remain on the dosing regimen they were to randomized at Week 0. At Week 16, subjects who meet early escape criteria will be allowed to initiate or increase the dose of one of the permitted concomitant medications up to the maximum allowed dose as specified in Table 4, as selected by the investigator. Titration to a stable dose of the medication should be completed for subjects qualifying for early escape by the Week 24 visit.

At Week 24, all subjects in the placebo group (Group III) will cross over to receive guselkumab 100 mg SC q4w through Week 100; this will allow for collection of additional safety data for the 100 mg SC q4w dose. Subjects in the guselkumab groups (Groups I and II) will remain on the dosing regimen they were randomized to at Week 0, through Week 100.

Subjects will be followed for AEs and SAEs up to 12 weeks following the last study agent administration. The end of the study is defined as the time the last subject completes the last study visit. For subjects who complete the Week 100 visit, the last study visit is the Week 112 visit. For subjects who discontinue study agent prior to Week 100, the last study visit is the final safety visit.

Database locks (DBLs) are scheduled at Weeks 24, 52, and End of Study (Week 112). The first DBL will occur when all randomized subjects have either completed the Week 24 assessments or terminated study participation prior to the Week 24 visit (referred to as Week 24 DBL). The second DBL will occur when all randomized subjects have either completed the Week 52 assessments or terminated study participation prior to the Week 52 visit (referred to as Week 52 DBL). The third DBL will occur when all randomized subjects have either completed their final safety visit or have terminated study participation (referred to as Final DBL).

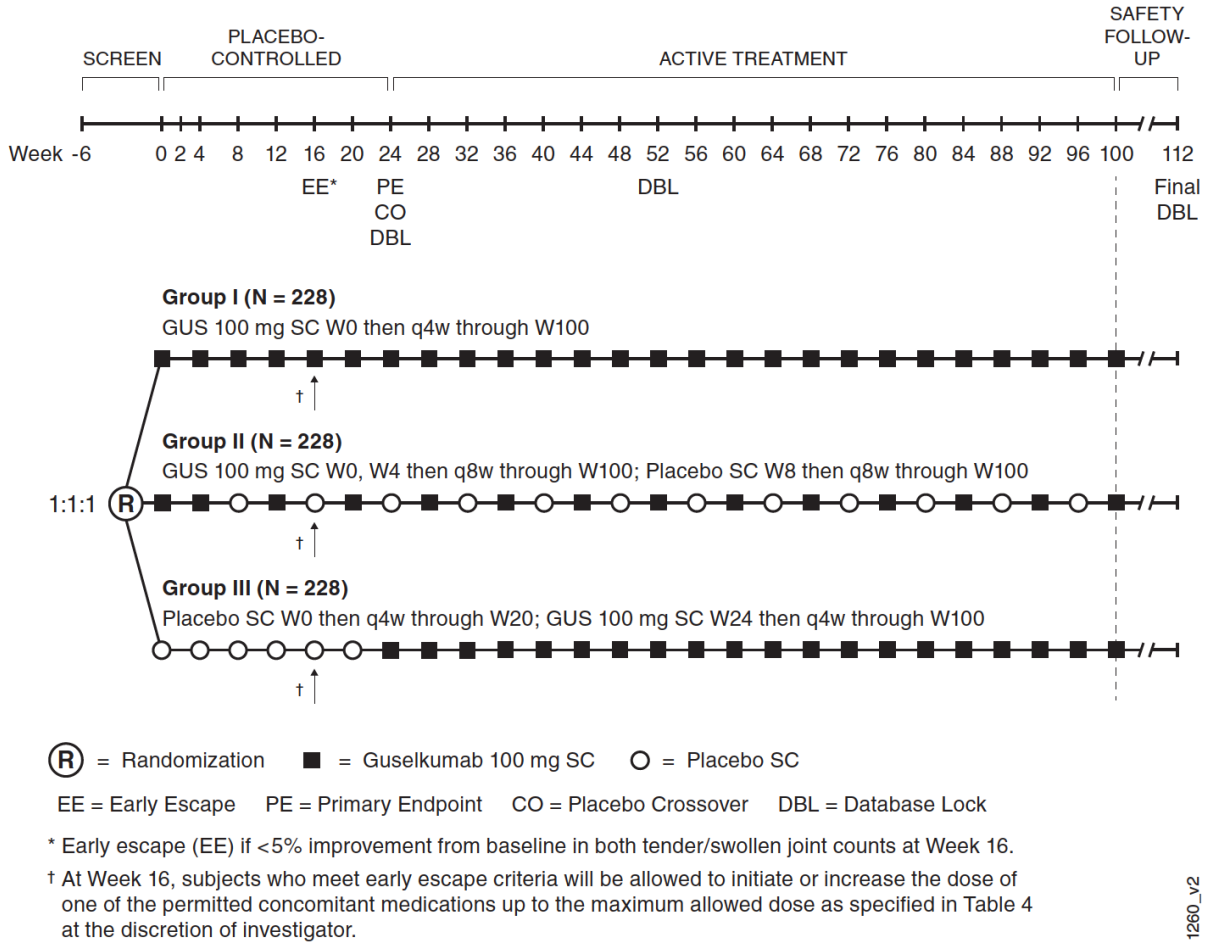
An independent Data Monitoring Committee (DMC) will be established to monitor unblinded data on an ongoing basis through at least the Week 24 DBL to ensure the continuing safety of the subjects enrolled in this study. Refer to Section 11.12 for further detail.

Samples for the analysis of pharmacodynamic biomarkers will be collected from all subjects.

A pharmacogenomic blood sample will be collected from subjects who consent separately to this component of the study where local regulations permit. Subject participation in pharmacogenomic research is optional.

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

Figure 1: Schematic Overview of the Study Through End of Study



3.2. Study Design Rationale

3.2.1. Study Population

The target study population is subjects with active PsA who are biologic naïve and have had inadequate response to standard therapies (eg, non-biologic DMARDs, apremilast, and/or NSAIDs). This population is considered appropriate to provide relevant efficacy and safety information for the intended use of guselkumab in PsA. Additionally, a biologic naïve population with a CRP ≥0.6 mg/dL is required to enrich the population for radiographic progression and increase the power for detection of treatment effect on radiographic endpoints.

3.2.2. Study Control, Randomization, and Blinding

A placebo control will be used to establish the frequency and magnitude of changes in endpoints that may occur in the absence of active treatment.

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

3.2.3. Study Phases and Duration of Treatment

There will be 4 phases in this study: Screening, double-blind placebo-controlled, active treatment, and safety follow-up.

- The screening phase of up to 6 weeks will allow for sufficient time to perform screening study evaluations and determine study eligibility.
- The second phase of the study will be the double-blind, placebo-controlled phase from Week 0 to Week 24. The primary endpoint is evaluated at Week 24 as guselkumab is expected to achieve maximal efficacy between Weeks 20 and 24 of treatment based on the findings in the guselkumab Phase 2 study (CNTO1959PSA2001) in PsA.
- The third phase of the study will be the double-blind, active treatment phase from Week 24 through Week 100. This duration will provide adequate time to evaluate the maintenance of the efficacy and long-term safety of guselkumab in PsA over a 2-year exposure period.
- The fourth phase of the study will be the safety follow-up phase and will be 12 weeks from the last administration of study agent to the final safety visit. The safety follow-up allows for monitoring of the subjects for a period equivalent to approximately 5 times the half-life of guselkumab.

The placebo-controlled period is limited to 24 weeks. An early escape option is included in the study design to provide additional treatment options for subjects who have <5% improvement in swollen and tender joint counts at Week 16.

3.2.4. Study Evaluations

Efficacy evaluations chosen for this study were established in previous studies of therapeutic biologic agents for the treatment of PsA. Patient reported outcomes (PROs) chosen for this study are also consistent with clinically relevant measurements that are accepted in the medical literature for other studies in PsA and applicable United States/European Union regulatory guidance documents.

Subjects will be monitored closely for safety with visits at the clinical site as described in the Time and Events Schedule (Table 1 and Table 2) while on therapy. Safety monitoring will include collecting information on AEs, review of concomitant medications, vital signs, laboratory assessments, physical exams, and early detection of TB as described in Section 9.7. Safety data will be reviewed by the Sponsor's Medical Monitor on an ongoing basis. An independent DMC composed of clinicians and statisticians not associated with the conduct of the study will review unblinded study data for safety purposes on a periodic basis through at least the Week 24 DBL.

Serum samples will be collected to evaluate the PK of guselkumab, as well as the immunogenicity of guselkumab (antibodies to guselkumab) as described in the Time and Events Schedule (Table 1 and Table 2).

DNA and Biomarker Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the pharmacogenomic component is to collect deoxyribonucleic acid (DNA) to allow the identification of genetic factors that may influence efficacy of guselkumab and to identify genetic factors associated with PsA.

Biomarker samples will be collected to better understand the biology of PsA, to provide a biological assessment of the response of patients to treatment with guselkumab, to analyze differences between responders and non-responders, and to determine if the markers can be used to classify patients as potential responders prior to treatment. The goal of the biomarker analyses is to evaluate the pharmacodynamics of guselkumab and aid in evaluating the drug-clinical response relationship.

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

4. SUBJECT POPULATION

Adult subjects age 18 and older with active PsA are eligible for the study.

Screening for eligible subjects will be performed within 6 weeks before the first administration of the study agent.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate Sponsor representative or delegate and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

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

4.1. Inclusion Criteria

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

1. Be a man or a woman at least 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place).
2. Have a diagnosis of PsA for at least 6 months before the first administration of study agent and meet ClASsification criteria for Psoriatic ARthritis (CASPAR) at screening (Attachment 1).

3. Have active PsA as defined by:

   a. At least 5 swollen joints and at least 5 tender joints at screening and at baseline

   -AND-

   b. CRP ≥0.6 mg/dL at screening from the central laboratory.

   NOTE: A one-time repeat assessment of CRP level is allowed during the 6-week screening phase and the Investigator may consider the subject eligible if the test result is within acceptable range on repeat testing in the central laboratory.

4. Have at least 1 of the PsA subsets: distal interphalangeal joint involvement, polyarticular arthritis with absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis (confirmation of sacroiliitis should be performed at the screening visit by a locally performed pelvic x-ray [single anterior-posterior view] unless a pelvic or SI joint x-ray or pelvic magnetic resonance imaging (MRI) has been previously performed. Results must be documented).
5. Have active plaque psoriasis, with at least one psoriatic plaque of ≥2cm diameter or nail changes consistent with psoriasis or documented history of plaque psoriasis.
6. Have active PsA despite previous non-biologic DMARD, apremilast, and/or NSAID therapy.
   - Non-biologic DMARD therapy is defined as taking a non-biologic DMARD for at least 3 months or evidence of intolerance.
   - Apremilast therapy is defined as taking apremilast at the marketed dose approved in the country where the study is being conducted for at least 4 months or evidence of intolerance.
   - NSAID therapy is defined as taking an NSAID for at least 4 weeks or evidence of intolerance.
7. If currently using non-biologic DMARDs (limited to MTX, SSZ, HCQ, or LEF), subjects should have started treatment at least 3 months and the dose must be stable for at least 4 weeks before first administration of study agent and should have no serious toxic side effects attributable to the non-biologic DMARD. If currently not using MTX, SSZ, or HCQ, must not have received for at least 4 weeks before first administration of study agent. If currently not using LEF, must not have received for at least 12 weeks before first administration of study agent.

   a. If using MTX, the route of administration and dose must be stable and the dose must be ≤25 mg/week.

   b. If receiving SSZ, the dose must be ≤3g/day.

   c. If receiving HCQ, the dose must be ≤400 mg/day.

   d. If receiving LEF, the dose must be ≤20 mg/day.
8. If currently using NSAIDs or other analgesics for PsA, subjects must be on a stable dose for at least 2 weeks before first administration of study agent. If currently not using NSAIDs or other analgesics for PsA, must not have received NSAIDs or other analgesics for PsA within 2 weeks before first administration of study agent.

9. If currently using oral corticosteroids for PsA, subjects must be on a stable dose equivalent to ≤10 mg of prednisone/day for at least 2 weeks before first administration of study agent. If currently not using oral corticosteroids, the subject must not have received oral corticosteroids within 2 weeks before first administration of study agent.

10. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies.

    Before randomization, a woman must be either:

    - Not of childbearing potential defined as:
      - Premenarchal: A premenarchal state is one in which menarche has not yet occurred.
      - Postmenopausal: A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
      - Permanently sterile: Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.
    - Of childbearing potential and practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly). Examples of highly effective contraceptives include:
      - User-independent methods: implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject).
      - User-dependent methods: combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable.

        Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.
      - Agree to remain on a highly effective method throughout the study and for at least 12 weeks after the last dose of study agent.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active,) a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

11. A woman of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at Week 0.
12. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction from first administration of study agent through at least 12 weeks after receiving the last administration of study agent.
13. A man who is sexually active with a woman of childbearing potential and who has not had a vasectomy must agree to use a barrier method of birth control (eg, either a condom [with spermicidal foam/gel/film/cream/suppository if available in their locale] or a partner with an occlusive cap [diaphragm or cervical/vault caps] plus spermicidal foam/gel/film/cream/suppository if available in their locale), during the study and for at least 12 weeks after receiving the last administration of guselkumab. All men must also agree to not donate sperm during the study and for at least 12 weeks after receiving the last administration of guselkumab.
14. Are considered eligible according to the following TB screening criteria:
    - Have no history of latent or active TB prior to screening. An exception is made for subjects who have a history of latent TB and are currently receiving treatment for latent TB, will initiate treatment for latent TB prior to first administration of study agent, or have documentation of having completed appropriate treatment for latent TB within 5 years prior to the first administration of study agent. It is the responsibility of the investigator to verify the adequacy of previous anti-TB treatment and provide appropriate documentation.
    - Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
    - Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB prior to the first administration of study agent.
    - Within 8 weeks prior to the first administration of study agent, have a negative QuantiFERON®-TB Gold test result (Attachment 2), or have a newly identified positive QuantiFERON®-TB Gold test result in which active TB has been ruled out and for which appropriate treatment for latent TB (Section 9.1.3) has been initiated prior to the first administration of study agent. Within 8 weeks prior to the first administration of study agent, a negative tuberculin skin test (Attachment 3), or a newly identified positive tuberculin skin test in which active TB has been ruled out and for which appropriate treatment for latent TB (Section 9.1.3) has been initiated prior to the first administration of study agent, is additionally required if the QuantiFERON®-TB Gold test is not approved/registered in that country* or the tuberculin skin test is mandated by local health authorities.

- Indeterminate results should be handled as outlined in Section 9.1.3. Subjects with persistently indeterminate QuantiFERON®-TB Gold test results may be enrolled without treatment for latent TB, if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB), and the subject has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the Sponsor's medical monitor and recorded in the subject's source documents and initialed by the investigator.

  NOTE: The QuantiFERON®-TB Gold test and the tuberculin skin test (is/are) not required to be performed at screening for subjects with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment as described above; subjects with documentation of having completed adequate treatment as described above are not required to initiate additional treatment for latent TB.

- Have a chest radiograph (posterior-anterior view) taken within 3 months prior to the first administration of study agent and read by a qualified radiologist, with no evidence of current, active TB or old, inactive TB.

15. Agree not to receive a live virus or live bacterial vaccination during the study, or within 12 weeks after the last administration of study agent.
16. Agree not to receive a bacillus Calmette-Guérin (BCG) vaccination during the study, and within 12 months after the last administration of study agent.
17. Have screening laboratory test results within the following parameters:

a.	Hemoglobin	≥8.5 g/dL	(SI: ≥85 g/L)
b.	White blood cells	≥3.5 x 10^3/µL	(SI: ≥3.5 GI/L)
c.	Neutrophils	≥1.5 x 10^3/µL	(SI: ≥1.5 GI/L)
d.	Platelets	≥100 x 10^3/µL	(SI: ≥100 GI/L)
e.	Serum creatinine	≤1.5 mg/dL	(SI: ≤133 µmol/L)

    f. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase levels must be ≤1.5 times the upper limit of normal range for the central laboratory conducting the test.

    NOTE: A one-time repeat of these screening laboratory tests is allowed during the 6-week screening phase and the Investigator may consider the subject eligible if the previously abnormal laboratory test result is within acceptable the range on repeat testing in the central laboratory.

18. Agree to avoid prolonged sun exposure and agree not to use tanning booths or other ultraviolet (UV) light sources from the first administration of study agent through 12 weeks after the final dose of study agent (for patients with skin lesions or with documented history of psoriasis).

19. Are willing to refrain from the use of complementary therapies for PsA or psoriasis including ayurvedic medicine, traditional Taiwanese, Korean, or Chinese medication(s) and acupuncture within 2 weeks before the first study agent administration and through Week 52.
20. Be willing and able to adhere to the prohibitions and restrictions specified in this protocol.
21. Sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.
22. Sign a separate ICF if he or she agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to provide consent for the optional DNA research sample does not exclude a subject from study participation.

4.2. Exclusion Criteria

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

1. Has other inflammatory diseases that might confound the evaluations or benefit of guselkumab therapy, including but not limited to RA, axial spondyloarthritis (this does not include a primary diagnosis of PsA with spondylitis), systemic lupus erythematosus, or Lyme disease.
2. Has previously received any biologic treatment including, but not limited to, guselkumab, ustekinumab, secukinumab (AIN457), anti-TNFα agents (such as adalimumab, etanercept, infliximab, golimumab SC or intravenous [IV], certolizumab pegol, or their respective biosimilars), tildrakizumab (MK3222), ixekizumab (LY2439821), brodalumab (AMG827), risankizumab (BI-655066), or other investigative biologic treatment for PsA or psoriasis.
3. Has ever received tofacitinib, baricitinib, filgotinib, peficitinib (ASP015K), decernotinib (VX-509), or any other Janus kinase (JAK) inhibitor.
4. Has received any systemic immunosuppressants (eg, azathioprine, cyclosporine, 6 thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, tacrolimus) within 4 weeks of the first administration of study agent.
5. Is currently receiving 2 or more non-biologic DMARDs specified in Table 4.
6. Has received non-biologic DMARDs (other than MTX, SSZ, HCQ, LEF) including, but not limited to chloroquine, gold preparations, and penicillamine within 4 weeks before the first administration of study agent.
7. Has received apremilast within 4 weeks prior to the first administration of study agent.
8. Has received phototherapy or any systemic medications/treatments that could affect psoriasis evaluations (including, but not limited to, retinoids, 1,25-dihydroxy vitamin D3 and analogues, psoralens, fumaric acid derivatives, with the exception of those in Table 4) within 4 weeks of the first administration of study agent.
9. Has used topical medications/treatments that could affect psoriasis evaluations (including, but not limited to, topical or intralesional injection of corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, pimecrolimus, tacrolimus, or topical traditional Taiwanese, Korean, or Chinese medicines) within 2 weeks of the first administration of any study agent.

10. Has received epidural, intra-articular, intramuscular, or IV corticosteroids, including adrenocorticotropic hormone during the 4 weeks before first administration of study agent.
11. Has received lithium within 4 weeks of the first administration of any study agent.
12. Has received an experimental antibody or biologic therapy within 6 months prior to the first administration of study agent, or received any other experimental therapy, including an investigational medical device, or new investigational agent within 90 days or 5 half-lives (whichever is longer) prior to the first administration of study agent or is currently enrolled in another study using an investigational agent or procedure.
13. Has unstable suicidal ideation or suicidal behavior in the last 6 months, that may be defined as an eC-SSRS rating at screening of:
    - Ideation level 4: Some intent to act, no plan; OR
    - Ideation level 5: Specific plan and intent; OR
    - Any of the following suicidal behaviors:
      - actual suicide attempts
      - interrupted attempts
      - aborted attempts
      - preparatory actions

    AND is confirmed to be at risk by the investigator based on an evaluation by a mental health professional. The final decision on excluding a subject will be made at the judgment of the investigator.
14. Has a history or current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic (with the exception of PsA), psychiatric, genitourinary, or metabolic disturbances.
15. Has unstable cardiovascular disease, defined as a recent clinical deterioration (eg, unstable angina, rapid atrial fibrillation, or transient ischemic attack) in the last 3 months prior to screening or a cardiac hospitalization within the last 3 months prior to screening.
16. Currently has a malignancy or has a history of malignancy within 5 years before screening (with the exception of a nonmelanoma skin cancer that has been adequately treated with no evidence of recurrence for at least 3 months before the first study agent administration or cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 3 months before the first study agent administration).
17. Has a history of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance; or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly.
18. Has a history of chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection (eg, bronchiectasis), recurrent urinary tract infection (eg, recurrent pyelonephritis or chronic nonremitting cystitis), fungal infection (eg, mucocutaneous candidiasis), or open, draining, or infected skin wounds or ulcers.
19. Has a transplanted organ (with exception of a corneal transplant >3 months before the first administration of study agent).

20. Has a history of an infected joint prosthesis, or has ever received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.
21. Has or has had a serious infection (eg, sepsis, pneumonia, or pyelonephritis) or has been hospitalized or received IV antibiotics for an infection within 2 months before screening.
22. Has or has had a herpes zoster infection within 2 months before screening.
23. Is currently pregnant, breastfeeding, or planning a pregnancy (both men and women) within 12 weeks after receiving the last administration of study agent.
24. Has a nonplaque form of psoriasis (eg, erythrodermic, guttate, or pustular).
25. Has current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium).
26. Has received, or is expected to receive, any live virus or bacterial vaccination within 3 months before the first administration of study agent.
27. Has had a BCG vaccination within 12 months of screening.
28. Has known intolerance or hypersensitivity to any biologic medication, or known allergies or clinically significant reactions to murine, chimeric, or human proteins, mAbs, or antibody fragments.
29. Subject has known allergies, hypersensitivity, or intolerance to guselkumab or its excipients (refer to Investigator's Brochure).
30. Has a history of active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening. Refer to Inclusion Criterion 14 for information regarding eligibility with a history of latent TB.
31. Has a chest radiograph within 3 months prior to the first administration of study agent that shows an abnormality suggestive of a malignancy, significant cardiovascular or pulmonary disease or current active infection, including TB.
32. Has ever had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystosis, aspergillosis).
33. Is infected with human immunodeficiency virus (HIV, a confirmed positive serology for HIV antibody).
34. Tests positive for hepatitis B virus (HBV) infection (Attachment 4) at screening.
35. Is seropositive for antibodies to hepatitis C virus (HCV) at screening, unless the subject had 2 negative HCV ribonucleic acid (RNA) test results at least 6 months apart prior to screening <u>and</u> have a third negative HCV RNA test result at screening.
36. Has had major surgery (eg, requiring general anesthesia and hospitalization) within 8 weeks before screening, or will not have fully recovered from such surgery, or has such major surgery planned during the time the subject is expected to participate in the study (112 weeks).

    Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate.
37. Is known to have had a substance abuse (drug or alcohol) problem within the previous 12 months prior to the first administration of study agent.

38. Is unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.
39. Lives in an institution on court or authority order.
40. Has any condition that, in the opinion of the investigator, would make participation not be in the best interest (eg, compromise the well-being) of the subject or that could prevent, limit, or confound the protocol-specified assessments.
41. Is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.
42. Is an employee of the Sponsor.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening and at baseline before randomization. If a subject's status changes (including laboratory results or receipt of additional medical records) before randomization such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4 describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

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

1. A woman of childbearing potential who is heterosexually active must remain on a highly effective method of birth control (Inclusion Criterion 10) from the first administration of study agent through at least 12 weeks after receiving the last administration of study agent.
2. A woman must not currently be pregnant or breastfeeding and should agree to plan to not become pregnant.
3. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction from the first administration of study agent through at least 12 weeks after receiving the last administration of study agent.
4. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control (ie, male condom, female diaphragm or cervical cap, or condom, Inclusion Criterion 13) from the first administration of study agent through at least 12 weeks after receiving the last administration of study agent. Additionally, he should agree to not plan a pregnancy.
5. All men must agree to not donate sperm from the first administration of study agent through at least 12 weeks after receiving the last administration of study agent.
6. Subjects must not receive a live virus or bacterial vaccination during the study and for 12 weeks after the last administration of study agent, with the exception of a BCG vaccination, which is prohibited for 12 months after the last administration of study agent; see Prohibition 7.
7. Subjects must not receive a BCG vaccination during the study and for 12 months after the last administration of study agent.

8. Subjects must comply with restrictions on concomitant medications and therapies during the study as specified in Section 8.
9. Subjects must avoid prolonged sun exposure and not to use tanning booths or other UV light sources during the study (for patients with skin lesions or with documented history of psoriasis).

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Central randomization will be implemented in this study. At Week 0, subjects will be randomly assigned (1:1:1) to 1 of 3 treatment groups (guselkumab 100 mg q4w, guselkumab 100 mg at Weeks 0 and 4 then q8w, or placebo) based on a computer-generated randomization schedule prepared before the study by or under the supervision of the Sponsor. Permuted block randomization with stratification by the most recent available CRP value prior to randomization (<2.0 mg/dL vs ≥2.0 mg/dL) and baseline non-biologic DMARD (MTX, SSZ, HCQ, or LEF) use (yes/no) will be used. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study agent kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant subject details to uniquely identify the subject.

Blinding

To maintain the study blind, the study agent container will have a multipart label containing the appropriate regulatory requirements for clinical supplies. Each unit will be uniquely identifiable through a medication number. A tear-off label is designed to be torn off, separated from the study agent container, and attached to the subject's source documents. The label will not identify the study agent in the container. However, if it is necessary for a subject's safety, the study blind may be broken and the identity of the study agent ascertained. The study agent number will be entered in the case report form (CRF) when the study agent is administered. The study agents will be identical in appearance and will be packaged in identical containers.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject. In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed.

Under normal circumstances, the blind should not be broken for individual subjects until the End of Study DBL of the study. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In the event of an emergency, the investigator may determine the identity of the treatment from IWRS. It is recommended that the investigator contact the Sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the Sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the Sponsor must be informed as soon as possible. The date and reason for the unblinding must

be documented by site personnel in the appropriate section of the CRF and in the source document. The investigator is also advised not to reveal the study treatment assignment to the study site or Sponsor personnel.

Subjects who have had their treatment assignment unblinded are expected to continue to return for scheduled evaluations. Further study agent administrations should be discussed with the study responsible physician. At the Week 24 DBL, the data will be unblinded for analysis to some Sponsor personnel while subjects are still participating in the study. Identification of Sponsor personnel who will have access to the unblinded subject-level data will be documented prior to unblinding. Investigative study sites and subjects will remain blinded to initial treatment assignment until after the final database is locked.

Data that may potentially unblind the treatment assignment (ie, study agent serum concentrations, antibodies to study agent, treatment allocation) will be handled with special care so that, prior to unblinding, such data will only be available to data management staff for purposes of data cleaning and, if applicable, clinical pharmacology representatives for the purposes of performing PK and antibodies to guselkumab analyses and quality assurance representatives for the purposes of conducting independent drug audits.

A given subject's treatment assignment may be unblinded to the Sponsor, Institutional Review Board/Independent Ethics Committee (IRB/IEC), and site personnel to fulfill regulatory reporting requirements.

6. DOSAGE AND ADMINISTRATION

Guselkumab 100 mg and matching liquid placebo for guselkumab will be provided in a single-use prefilled syringe (PFS) assembled with the UltraSafe PLUS™ Passive Needle Guard (PFS-U).

Study agent will be administered at the site by a health care professional (HCP) until the subject (or caregiver) is trained for self-administration. Study agent will be administered by site personnel at Week 0 and Week 4. Beginning at Week 8, at the discretion of the investigator and subject, and after appropriate and documented training, subjects may self-administer study agent at the investigative site under the supervision of an HCP. A caregiver may also be trained to administer study agent. Subjects unable or unwilling to self-administer will continue to have study agent injections performed by an HCP.

The option to begin self-administration of study agent at home will begin after Week 52. After Week 52, subjects (or a caregiver) who are able to self-administer will be supplied study agent for self-administration away from the site (ie, at home). Subjects will be instructed to contact the investigator promptly in the event of any signs of an allergic reaction, infection, or bleeding. Subjects unable to have injection(s) administered away from the site will be required to return to the site for administration of study agent injection(s) by a health care professional. After Week 52, subjects will have study visits and assessments at Weeks 68, 76, 84, 100, and 112.

Through Week 24, study agent administration at the site should be ± 4 days from the scheduled day of study agent administration; after Week 24, all administrations should be ± 7 days from scheduled study agent administration day. Study agent administrations must always be at least 14 days apart.

The dose regimens are as follows:

- **Group I** (n=228): Subjects will receive SC guselkumab 100 mg q4w from Week 0 through Week 100;
- **Group II** (n=228): Subjects will receive SC guselkumab 100 mg at Weeks 0 and 4 then q8w (Weeks 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, and 100) and placebo injections at other visits (Weeks 8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, and 96) to maintain the blind.
- **Group III** (n=228): Subjects will receive SC placebo q4w from Week 0 to Week 20, and will cross over at Week 24 to receive SC guselkumab 100 mg q4w from Week 24 through Week 100.

At Week 16, all subjects in Groups I, II and III with <5% improvement from baseline in both tender and swollen joint counts will be considered as meeting early escape criteria. These subjects will remain on the dosing regimen they were randomized to at Week 0. At Week 16, subjects who meet early escape criteria will be allowed to initiate or increase the dose of one of the permitted concomitant medications up to the maximum allowed dose as specified in Table 4, as selected by the investigator. Titration to a stable dose of the medication should be completed for subjects qualifying for early escape by the Week 24 visit.

7. TREATMENT COMPLIANCE

Study agent will be administered at the investigational site through Week 52 and study personnel will maintain a log of all study agent administrations. Study agent supplies for each subject will be inventoried and accounted for. All ongoing therapies administered at the time of screening must be recorded.

Subjects will receive instructions on compliance with study treatment when they begin self-administration of study agent at home. When subjects begin self administration at home, the investigator or designated study personnel will maintain a log of all study agent dispensed and returned.

When study agent is self administered by subjects at home, subjects will record all study drug administrations on a diary card.

During the course of the study, the investigator or designated study research personnel will be responsible for providing additional instruction to reeducate any subject who is not compliant with taking the study agent.

Compliance with the treatment schedule is strongly encouraged. It is understood that treatment may be interrupted for health-related or safety reasons. Therefore, if for any reason a subject cannot receive a dose of study agent at the scheduled visit, the subject must make every effort to

still come in for the scheduled assessments for that visit. The dose should be administered within 2 weeks of that scheduled visit. The subject should then resume the normal study schedule relative to the baseline visit (Week 0). In the case when a subject does not come in to the investigational site for a scheduled visit, the site will follow-up with that subject. Due diligence could include telephone calls, certified letters, and email requests. Measures taken to obtain follow-up information must be documented.

Study-site personnel will keep a log of all study drug dispensed and will compare the amount of study drug dispensed with the amount returned. Additional details may be provided in the Site Investigational Product Manual that is provided separately and noted in Section 15.

All post-baseline visits up to and including Week 24 will have a visit window of ±4 days counting from Week 0 as Day 1. After Week 24, all visits will have a visit window of ±7 days. The Week 112 visit or the final safety visit (12 weeks after the last dose in subjects who discontinued study treatment) will have a visit window of ±14 days. If a study visit occurs outside this window, the Sponsor should be consulted about how the subject should resume his or her normal dose schedule.

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

8. PRESTUDY AND CONCOMITANT THERAPY

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

Every effort should be made to keep subjects' concomitant medications for PsA stable through Week 24 or as specified in the following sections. The concomitant medication dose may be reduced or temporarily discontinued because of abnormal laboratory values, adverse effects or intolerance, concurrent illness, or the performance of a surgical procedure but the change and reason for the change should be clearly documented in the subject's medical record.

Subjects may not be receiving more than one non-biologic DMARD from baseline (see Exclusion Criterion 5) through Week 52. After Week 52 and through the end of the study, subjects may receive another non-biologic DMARD.

Permitted concomitant medications for PsA and the maximum allowed doses during the study as specified in the following sections are summarized in Table 4.

Table 4: Permitted Concomitant Medications for PsA and the Maximum Allowed Doses During the Study

Permitted Concomitant Medications for PsA[a,b]	Maximum Allowed Dose
NSAIDs and other analgesics	Marketed dose approved in in the country where the study is being conducted
Oral corticosteroids	Equivalent to 10 mg/day of prednisone
Non-biologic DMARDs:	
Methotrexate (MTX)[c]	25 mg/week
Sulfasalazine (SSZ)	3 g/day
Hydroxychloroquine (HCQ)	400 mg/day
Leflunomide (LEF)	20 mg/day

[a] Permitted concomitant medications are not supplied by the Sponsor.
[b] Subjects may not be receiving more than one non-biologic DMARD from baseline (see Exclusion Criterion 5) through Week 52. After Week 52 and through the end of the study, subjects may receive another non-biologic DMARD.
[c] It is recommended that all subjects taking MTX in this study receive at least 5 mg oral folate or 5 mg folinic acid weekly. Guidelines for dose adjustment in the event of MTX toxicity are included in the Trial Center File.

Subjects should not initiate any new treatment for PsA through Week 52, except at Week 16 for those subjects who have < 5% improvement from baseline in both tender and swollen joint counts (early escape criteria). Subjects who meet early escape criteria will be allowed to initiate or increase the dose of one of the permitted concomitant medications up to the maximum allowed dose as specified in Table 4, as selected by the investigator. Titration to a stable dose of the medication should be completed for subjects qualifying for early escape by the Week 24 visit.

Beginning at Week 52, the treatment options in Table 4 are allowed to be initiated or dose increased up to the maximum allowed dose specified in Table 4 for subjects with ongoing PsA disease activity at the investigator's judgment; the rationale should be clearly documented in the subject's medical record.

Concomitant medication review will occur at study visits identified in the Time and Events Schedule.

8.1. Non-biologic DMARDs

8.1.1. Permitted Non-biologic DMARDs

Subjects are permitted to enter the study on a stable dose of one non-biologic DMARD (limited to MTX, SSZ, HCQ, or LEF) up to the maximum allowed dose specified in Table 4. Only 1 of these non-biologic DMARDs is allowed from baseline through Week 52; subjects receiving 2 or

more non-biologic DMARDs at baseline are excluded from study participation. After Week 52 and through the end of the study, subjects may receive another non-biologic DMARD.

At any time during the study, the dose of the permitted non-biologic DMARD may be reduced or temporarily discontinued due to abnormal laboratory values, side effects, concurrent illness, or the performance of a surgical procedure.

Refer to Table 5 for protocol requirements of the permitted non-biologic DMARDs.

Table 5: Protocol Requirements of the Permitted Non-biologic DMARDs

Permitted Non-biologic DMARDs	Baseline Usage	Prior to Week 0	Week 0 through Week 52	Week 52 through Week 112
Methotrexate (MTX)	Used	Treatment should have started at least 3 months prior to the first administration of study agent. MTX routes of administration and doses should be stable for at least 4 weeks prior to the first administration of the study agent and must be ≤ 25mg/week.	Stable dose and route of administration (oral, intramuscular, or SC permitted) required unless early escape or unacceptable side effects	Dose changes allowed up to the maximum dose specified in Table 4 or change of the route of administration, at the investigator's discretion
	Not Used	Discontinued at least 4 weeks prior to the first administration of study agent	Not allowed unless early escape (see Section 6)	Allowed up to the maximum dose specified in Table 4 at investigator's discretion
Sulfasalazine (SSZ) or Hydroxychloroquine (HCQ)	Used	Treatment should have started at least 3 months prior to the first administration of study agent. Dose should be stable for at least 4 weeks prior to the first administration of the study agent and must be ≤ 3 g/day (SSZ) or ≤ 400mg/day (HCQ).	Stable dose required unless early escape or unacceptable side effects	Dose changes allowed up to the maximum dose specified in Table 4, at the investigator's discretion
	Not Used	Discontinued at least 4 weeks prior to the first administration of study agent	Not allowed unless early escape (see Section 6)	Allowed up to the maximum dose specified in Table 4 at investigator's discretion
Leflunomide (LEF)	Used	Treatment should have started at least 3 months prior to the first administration of study agent. Dose should be stable for at least 4 weeks prior to the first administration of the study agent and must be ≤ 20mg/day.	Stable dose required unless early escape or unacceptable side effects	Dose changes allowed up to the maximum dose specified in Table 4 at the investigator's discretion
	Not Used	Discontinued at least 12 weeks prior to the first administration of study agent.	Not allowed unless early escape (see Section 6)	Allowed up to the maximum dose specified in Table 4 at investigator's discretion

8.1.2. Prohibited Non-biologic DMARDs and Apremilast

All other non-biologic DMARDs (including, but not limited to chloroquine, gold preparations, penicillamine) and apremilast must be discontinued at least 4 weeks prior to the first administration of study agent and remain prohibited through Week 112.

8.1.3. Systemic Immunosuppressive Drugs

Systemic immunosuppressants (including, but not limited to azathioprine, cyclosporine, 6 thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, or tacrolimus) must be discontinued at least 4 weeks prior to the first administration of study agent and remain prohibited through Week 112. If any of these systemic immunosuppressants is initiated during the study, study agent must be permanently discontinued.

Systemic immunosuppressants do not refer to corticosteroids; see Section 8.2 for restrictions regarding the use of corticosteroids.

8.2. Corticosteroids

8.2.1. Oral Corticosteroids

Subjects using oral corticosteroids at baseline for PsA must be on a stable dose equivalent to ≤10 mg prednisone per day for at least 2 weeks prior to the first administration of study agent and continue on this dose through Week 52 unless early escape at Week 16 (see Section 3).

After Week 24 and through Week 52, a one-time dose decrease in oral corticosteroids is allowed.

Starting at Week 52, the dose and type of oral corticosteroid may be adjusted, at the discretion of the investigator, for subjects with ongoing PsA disease activity.

Otherwise, throughout the study, the dose and type of oral corticosteroid may be changed at the discretion of the investigator only if the subject develops unacceptable side effects.

Subjects not using oral corticosteroids at baseline for PsA must have discontinued oral corticosteroids at least 2 weeks prior to the first administration of study agent and must not receive oral corticosteroids through Week 52 of the study for PsA. An exception is made for subjects who qualify for early escape at Week 16 (see Section 3).

8.2.2. Corticosteroids – Intravenous, Intramuscular, or Epidural Administration

Intravenous, intramuscular, or epidural administration of corticosteroids for the treatment of PsA are not allowed through Week 112.

Long-term, (>2 weeks), oral or IV corticosteroid use for indications other than PsA or psoriasis is not allowed through Week 112. Short-term (≤2 weeks) oral, IV, intramuscular, or epidural corticosteroid used for indications other than PsA should be limited to situations where, in the opinion of the investigator, there are no adequate alternatives.

8.2.3. Corticosteroids – Intra-articular Injection

Attempts should be made to avoid intra-articular corticosteroid injections for PsA, especially during the first 24 weeks of the study. However, if necessary, subjects may receive up to 2 intra-articular, tendon sheath, or bursal corticosteroid injections in no more than 2 affected sites within any 24-week period of the study. In the case of severe tenderness or swelling in a single joint, it is suggested that the subject be evaluated for infection prior to receiving an intra-articular corticosteroid injection.

8.2.4. Corticosteroids – Other Routes of Administration

Inhaled, otic, ophthalmic, intranasal, and other routes of mucosal delivery of corticosteroids for indications other than PsA and psoriasis are allowed throughout the course of the study.

8.3. Nonsteroidal Anti-inflammatory Drugs and Other Analgesics

For subjects receiving NSAIDs, including aspirin and selective cyclooxygenase 2 inhibitors, or other analgesics for PsA at baseline, treatment with a stable dose of NSAIDs or other analgesics should have been initiated at least 2 weeks prior to the first administration of study agent and continue through Week 52 unless early escape at Week 16 (see Section 3). The dose administered should be the usual marketed dose approved in the country where the study is being conducted.

The use of topical analgesics including capsaicin and diclofenac is allowed and should be recorded in the CRF. For topical and analgesic patches, the dose should be stable through Week 52 and may be changed only if the subject develops unacceptable side effects.

Subjects not receiving NSAIDs or other analgesics for PsA at baseline must have discontinued NSAIDs or other analgesics at least 2 weeks prior to the first administration of study agent and must not receive NSAIDs or other analgesics for PsA through Week 52 of the study. An exception is made for subjects who qualify for early escape at Week 16 (see Section 3).

Starting at Week 52, subjects with ongoing PsA disease activity can initiate or increase the dose of NSAIDs or other analgesics based on the investigator's clinical judgment.

At any time during the study, the dose of NSAIDs or other analgesics may be reduced or temporarily discontinued due to abnormal laboratory values, side effects, concurrent illness, or the performance of a surgical procedure.

Use of NSAIDs and other analgesics for indications other than PsA are permitted throughout the study.

8.4. Biologic Agents, Cytotoxic Drugs, JAK Inhibitors, or Investigational Agents

The concomitant use of biologic agents, cytotoxic agents, JAK inhibitors, and investigational drugs is not allowed. Biologic agents include, but are not limited to golimumab, anakinra, etanercept, adalimumab, infliximab, ustekinumab, alefacept, efalizumab, rituximab, natalizumab,

certolizumab pegol, tildrakizumab (MK3222), secukinumab (AIN457), ixekizumab (LY2439821), brodalumab (AMG827), and respective biosimilars as applicable. Cytotoxic agents include, but are not limited to chlorambucil, cyclophosphamide, nitrogen mustard, and other alkylating agents. JAK inhibitors include, but are not limited to tofacitinib, baricitinib, filgotinib, peficitinib (ASP015K), and decernotinib (VX-509). If any of these medications are used, study agent must be permanently discontinued.

8.5. Complementary Therapies

The use of complementary therapies, including ayurvedic medicine, traditional Chinese medications or non-medicinal therapy such as acupuncture for PsA or psoriasis, is not allowed from 2 weeks prior to the first administration of study agent through Week 52.

8.6. Topical Therapy and Ultraviolet B Light

Concurrent use of topical medications/treatments for psoriasis (eg, topical or intralesional corticosteroids, keratolytics (with the exception of salicylic acid shampoos, which are allowed throughout the study), coal tar (with the exception of coal tar shampoos, which are allowed throughout the study), anthralin, vitamin D3 analogues, or topical tacrolimus, and retinoids) are not permitted through Week 24.

Use of salicylic acid- and tar-containing shampoos is not permitted on the morning prior to a study visit; non-medicated shampoos may be used on the day of a study visit.

Low and mid-potency topical or intralesional corticosteroids (Class III-VII) may be used after Week 24 for psoriasis. High and ultra-high potency corticosteroids (Class I and II) are prohibited through Week 112.

Phototherapy including UVB or tanning beds are not permitted during the study through Week 112. Subjects should be encouraged to avoid prolonged sun exposure during the study.

8.7. Systemic Therapy for Psoriasis

Concurrent use of systemic therapy for psoriasis (eg, psoralen with ultraviolet light A, systemic retinoids, cyclosporine or tacrolimus, with the exception of those in Table 4) must be discontinued at least 4 weeks prior to the first administration of study agent and is not permitted through Week 112; if a systemic antipsoriatic treatment (except those in Table 4) is initiated during the study, study agent must be permanently discontinued.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule (Table 1 and Table 2) summarizes the frequency and timing of efficacy, PK, immunogenicity, biomarker, and safety measurements applicable to this study.

For women of childbearing potential only, additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study. Also additional TB tests may be performed as determined necessary by the investigator or required by local regulation.

Except at the screening visit, all PRO assessments should be conducted/completed before any tests, procedures, or other consultations at all other visits as specified in the Time and Events Schedule to prevent influencing subject perceptions. For additional details and the order for which that are to be performed, refer to the PRO user manuals.

To minimize unnecessary x-rays, it is recommended that subjects have the baseline radiographs of hands and feet taken after the inclusion and exclusion criteria have been checked and the subject appears eligible to enter the study. All eligible subjects should have radiographs taken approximately 2 weeks but not greater than 4 weeks prior to randomization.

During screening, each subject will be provided with an electronic device to enter study-related data as applicable. Study-site personnel will train the subjects on how to use the electronic device, including instructions to capture the data according to the study design.

9.1.2. Blood Sample Collection

Blood samples should be collected at the visits indicated in the Time and Events Schedule. The date and time of collection will be recorded. When blood samples are to be collected for safety, PK, efficacy, biomarkers, and pharmacogenomics/epigenetic evaluations at the same time point, the order of blood draws will be samples for: CRP, chemistry/lipids, hematology, PK/Immunogenicity, serum biomarkers, pharmacogenomics, epigenetics, and RNA expression.

The total blood volume to be collected in this study from each subject will be approximately 313.5 mL. Subjects who consent to participate in the optional pharmacogenomics will have an additional blood volume collected of approximately 50 mL, for a total of approximately 363.5 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.3. Screening Phase

Screening procedures will be performed as indicated in the Time and Events Schedule.

After written informed consent has been obtained and within a period of 6 weeks before randomization, all screening evaluations will be performed. The screening visit may be completed in a single visit or may be divided into more than 1 visit.

It is recommended that after obtaining informed consent, the investigator complete all laboratory tests at the first visit. The subject may then return for the remainder of the screening procedures only if the subject is eligible for the study as determined by the central laboratory test results.

Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled in the study. Subjects who chose to participate in the optional pharmacogenomics research component of the study must provide consent on a separate ICF.

The recording of AEs and concomitant medications will start after the signing of the informed consent and will continue until the last study-related procedure has been completed.

If the screening is a single visit, the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) (*Lifetime* version) should be performed after the joint assessment (after signing informed consent). If the screening visit is divided into more than 1 visit, the eC-SSRS should be performed after the joint assessment and after the subject is determined to be eligible by the central laboratory test results.

Females of childbearing potential must have a negative serum pregnancy test prior to randomization and a negative urine pregnancy test at all dosing visits prior to administration of study agent. Females of childbearing potential and males capable of fathering a child must consent to use a highly effective method of contraception and continue to use contraception for the duration of the study and for at least 12 weeks after receiving the last administration of blinded study agent. The method(s) of contraception used by each subject must be documented. For details, see Section 4.1.

A 12-lead electrocardiogram (ECG) will be performed locally at baseline prior to administration of study agent to ensure that, should the subject require an ECG during the study for any reason, an ECG before first study agent administration is available for comparison to detect changes.

A chest radiograph (posterior-anterior view) will be performed at screening to ensure that the subject does not have any abnormality suggestive current, active TB or old, inactive TB. Chest radiographs taken up to 3 months before the first administration of study agent may be used.

The BASDAI will be completed only in subjects with spondylitis with peripheral arthritis as their primary arthritic presentation of PsA (confirmation of sacroiliitis should be performed at the screening visit by a locally performed pelvic x-ray [single anterior-posterior view] unless a pelvic or SI joint x-ray or pelvic MRI has been previously performed. Results must be documented).

Subjects as outlined in Inclusion Criterion 14 must undergo testing for TB (Attachment 2 or Attachment 3) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The subject should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing. Investigators have the option to use both the QuantiFERON®-TB Gold test and the tuberculin skin test to screen for latent TB if they believe, based on their judgment, that the use of both tests is clinically indicated in order to evaluate a subject who has high risk of having latent TB. If either the QuantiFERON®-TB Gold test or the tuberculin skin test is positive, the subject is considered to have latent TB infection for the purposes of eligibility for this study.

Subjects with a negative QuantiFERON®-TB Gold test result (and a negative tuberculin skin test result in countries in which the QuantiFERON®-TB Gold test is not approved/registered* or the tuberculin skin test is mandated by local health authorities) are eligible to continue with prerandomization procedures. Subjects with a newly identified positive QuantiFERON®-TB Gold or tuberculin skin test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, United States guidelines must be followed, or the subject will be excluded from the study.

* Exceptions are made for those countries where the tuberculin skin test is not feasible due to various reasons (eg, shortage of test reagents) with the permission of respective health authorities, as applicable.

A subject whose first QuantiFERON®-TB Gold test result is indeterminate should have the test repeated. In the event that the second QuantiFERON®-TB Gold test result is also indeterminate, the subject may be enrolled without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB), and the subject has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the Sponsor's medical monitor and recorded in the subject's source documents and initialed by the investigator.

Subjects will undergo screening for HBV (Attachment 4) and antibodies to HCV and HIV.

The baseline radiographs of the hands and feet must be taken prior to randomization. To minimize unnecessary x-rays, it is recommended that subjects have the baseline radiographs of hands and feet taken after the inclusion and exclusion criteria have been checked and the subject appears eligible to enter the study. All eligible subjects should have radiographs taken approximately 2 weeks but not greater than 4 weeks prior to randomization.

Retesting

The re-testing of abnormal screening laboratory blood tests and CRP levels, which are exclusionary, is allowed only once using an unscheduled visit during the screening period (to reassess eligibility).

Repeat Screening

If a subject was a screen failure in the past but currently the subject is expected to be able to meet the subject eligibility criteria, the subject may be screened again on one occasion only after consultation with the Sponsor (ie, study responsible physician, scientists, or designee). For the second screening, the subject will be assigned a new subject number, and must undergo the informed consent process and all other screening procedures again as in the Time and Events Schedule.

Chest x-rays and radiographs of hands and feet, if done within the specified allowed time, are not required to be repeated.

If the QuantiFERON®-TB Gold test and/or the tuberculin skin test was positive in the first screening, these tests should not be repeated. Also, if the QuantiFERON®-TB Gold test and tuberculin skin test were done within the specified allowed time, they should not be repeated.

9.1.4. Treatment Phase

The treatment phase includes the placebo-controlled and active treatment phases. At Week 0, eligible subjects will be randomly assigned to receive 1 of 3 treatments: guselkumab SC 100 mg q4w, guselkumab SC 100 mg at Weeks 0 and 4 then q8w, or placebo SC. For additional details, see Section 6. Safety and efficacy assessments must be performed before study agent administration as noted in the Time and Events Schedule.

Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at scheduled visits (refer to Time and Events Schedule) or by telephone contact approximately every 8 to 12 weeks if a subject misses scheduled visits. The following series of questions is suggested for use during the evaluation:

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

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

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

Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON®-TB Gold test, a repeat tuberculin skin test in countries in which the QuantiFERON®-TB Gold test is not approved/registered or the tuberculin skin test is mandated by local health authorities, and, if possible, referral to a physician specializing in TB to determine the subject's risk of developing

active TB and whether treatment for latent TB is warranted. If the QuantiFERON®-TB Gold test result is indeterminate, the test should be repeated as outlined in Section 9.1.3.

Subjects should be encouraged to return for all subsequent scheduled study visits according to the protocol.

Columbia-Suicide Severity Rating Scale

At all visits except during screening, the eC-SSRS (*Since Last Contact* version) should be the first assessment/questionnaire that the subject must complete.

9.1.5. Post Treatment Phase (Follow-Up)

All subjects who complete the Week 100 visit assessments will be asked to return for a final safety visit at Week 112.

Subjects Who Discontinue Study Agent

Prior to Week 24

If a subject discontinues study agent before the Week 24 visit, the subject should return for all visits through Week 24. The final safety visit assessments will be conducted at the next scheduled visit that occurs approximately 12 weeks after the last administration of study agent. If a subject discontinues before the Week 24 visit and after the Week 12 study agent administration, the subject should return for the Week 24 visit and also 12 weeks after the last administration of study agent for a final safety visit (refer to the Week 112 visit in Table 1 and Table 2).

For subjects who discontinue study agent prior to Week 24, radiographs of the hands and feet should be performed at the time of study agent discontinuation. If the discontinuation occurs prior to or at Week 16, the subject should also have radiographs performed at the Week 24 visit. If the discontinuation occurs after Week 16, the radiographs do not need to be repeated at Week 24.

At or After Week 24 and Prior to Week 100

If a subject discontinues study agent at or after Week 24 and before the Week 100 visit, the final efficacy visit (refer to the Week 100 visit in Table 2) should be performed as soon as possible. The subject should return 12 weeks after their last dose for their final safety visit (refer to the Week 112 visit in Table 2).

For subjects who permanently discontinue study agent after Week 24 but prior to Week 100, radiographs of hands and feet should be performed at the time of discontinuation of study agent or as soon as possible unless another set of radiographs has been obtained within the past 6 weeks.

Subjects Who Discontinue Study Participation

For subjects who discontinue study participation at any time during the study, radiographs of the hands and feet should be performed at the time of study discontinuation unless another set of radiographs has been obtained within the past 6 weeks.

No procedures and evaluations should be conducted after a subject withdraws consent.

9.2. Efficacy Evaluations

Efficacy assessments will be performed at the site by applicable site personnel trained by the Sponsor as indicated in the Time and Events Schedule.

9.2.1. Psoriatic Arthritis Response Evaluations

9.2.1.1. Joint Assessment

Each of 68 joints will be evaluated for tenderness, and each of 66 joints will be evaluated for swelling (hips are excluded for swelling).

An independent joint assessor (IJA) with adequate training and experience in performing joint assessments will be designated at each study site to perform all joint assessments. The IJA should preferably be a rheumatologist but if a rheumatologist is not available, it should be a health care provider with at least 1 year of experience in performing joint assessments. Health care providers with less than 1 year of experience may serve as an IJA based upon the discretion and approval of the Sponsor. It is strongly recommended that the designated IJA identify an appropriate back-up IJA for coverage in the event of absences of the designated IJA. It is strongly recommended that the same IJA who performs the baseline joint assessments for a subject should also perform the joint assessments for that subject at every subsequent visit through Week 52.

Through Week 112, the IJA should have no other contact with the subject once the subject is randomized, should not be the treating physician, should not discuss the subject's clinical status with the subject or other site personnel during the joint assessment, and will not be permitted to review the subject's medical records or the CRFs, or any of the previous joint assessments. The IJA should maintain a neutral attitude during joint assessment and should limit interactions with the subject only to activities associated with performing joint assessment or enthesitis or dactylitis assessments.

The IJA will perform only joint assessments and enthesitis and dactylitis assessments; this individual will not perform or assist in any other assessments in this study such as but not limited to administering patient and/or physician global assessments or administering study agent.

The Sponsor will provide training for each site's designated IJA prior to the screening of the first subject at each site. A back-up IJA must complete training before performing a joint assessment for a subject's study visit.

If an IJA was trained by the Sponsor (with joint assessments) in a previous clinical study within the last 3 years and there is adequate documentation of this training (certification), that training will be considered adequate for this study; however, repeat training prior to start of the study is encouraged. Training documentation of each IJA should be maintained at the study site.

All IJA performing the joint evaluation at a site must be listed on the Delegation Log at the study site.

9.2.1.2. Nonevaluable Joints

While it may be reasonable in clinical practice to identify as nonevaluable any joint which in the past or during study participation has been surgically altered (ie, prosthesis placement) or medically treated (ie, intra-articular injection), the designation of nonevaluable joints for the purposes of this study is slightly different.

Joints should only be designated as "non-evaluable" by the IJA if it is physically impossible to assess the joint (ie, joint inaccessible due to a cast, joint not present due to an amputation, or a recent wound near or at the joint so as to make it impossible to assess). In all other cases, the IJA should assess each joint for tenderness and swelling (hips are excluded for swelling). This should be completed regardless of any visual indications of prior surgeries (eg, scars) or knowledge they may have of a subject's prior joint procedures/injections (eg, if the subject was the IJA's patient prior to study participation).

9.2.1.3. American College of Rheumatology Response

American College of Rheumatology responses are presented as the numerical measurement of improvement in multiple disease assessment criteria. For example, an ACR 20 response[10] is defined as:

1. ≥20% improvement from baseline in both swollen joint count (66 joints) and tender joint count (68 joints),

AND

2. ≥20% improvement from baseline in 3 of the following 5 assessments:
   - Patient's assessment of pain (VAS)
   - Patient's Global Assessment of Disease Activity (arthritis, VAS)
   - Physician's Global Assessment of Disease Activity (VAS)
   - Patient's assessment of physical function as measured by HAQ-DI
   - CRP

ACR 50 and ACR 70 similarly defined except improvement threshold from baseline is 50% and 70%, respectively.

9.2.1.4. Dactylitis Assessment

Presence and severity of dactylitis will be assessed by the IJA in both hands and feet using a scoring system from 0 to 3 (0 – no dactylitis, 1 – mild dactylitis, 2 – moderate dactylitis, and 3 – severe dactylitis)[17,19].

The Sponsor will provide dactylitis assessment training. Documentation of this training will be maintained in the study site's training files. Previous dactylitis assessment training by the Sponsor within the last 3 years with adequate documentation (eg, training certification) will be considered adequate for this study; however, repeat training prior to start of the study is encouraged.

It is strongly recommended that the same person who performs the baseline dactylitis assessments for a subject should also perform the dactylitis assessments for that subject at every subsequent visit through Week 100.

9.2.1.5. Enthesitis Assessment

Enthesitis will be assessed by the IJA using the LEI.[21] The LEI was developed to assess enthesitis in subjects with PsA, and evaluates the presence or absence of pain by applying local pressure to the following entheses:

- Lateral epicondyle humerus, left and right
- Medial femoral condyle, left and right
- Achilles tendon insertion, left and right

The Sponsor will provide enthesitis assessment training. Documentation of this training will be maintained in the study site's training files. Previous enthesitis assessment (LEI) training by the Sponsor within the last 3 years with adequate documentation (eg, training certification) will be considered adequate for this study; however, repeat training prior to start of the study is encouraged.

It is strongly recommended that the same person who performs the baseline enthesitis assessments for a subject should also perform the enthesitis assessments for that subject at every subsequent visit through Week 100.

9.2.1.6. Imaging Evaluation

Single radiographs of the hands (posteroanterior) and feet (anteroposterior) will be performed at visits as specified in the Time and Events Schedule. To minimize unnecessary x-rays, it is recommended that subjects have the baseline radiographs of hands and feet taken after the inclusion and exclusion criteria have been checked and the subject appears eligible to enter the study. All eligible subjects should have radiographs taken approximately 2 weeks but not greater than 4 weeks prior to randomization; and at Week 24, Week 52, and Week 100 within ± 2 weeks of the scheduled visit.

Subjects Who Discontinue Study Agent

For subjects who discontinue study agent prior to Week 24, radiographs of the hands and feet should be performed at the time of study agent discontinuation. If the discontinuation occurs prior to or at Week 16, the subject should also have radiographs performed at the Week 24 visit. If the discontinuation occurs after Week 16, the radiographs do not need to be repeated at Week 24.

For subjects who permanently discontinue study agent after Week 24 but prior to Week 100, radiographs of hands and feet should be performed at the time of discontinuation of study agent or as soon as possible unless another set of radiographs has been obtained within the past 6 weeks.

Subjects Who Discontinue Study Participation

For subjects who discontinue study participation at any time during the study radiographs of the hands and feet should be performed at the time of study discontinuation unless another set of radiographs has been obtained within the past 6 weeks.

The radiographs will be evaluated by central independent readers and scored using total modified vdH-S score. Total modified vdH-S is an original vdH-S score[51], modified for the purpose of PsA radiological damage assessment, by addition of distal interphalangeal joints of the hands and assessment of pencil in cup and gross osteolysis deformities. The total modified vdH-S score includes the joint erosion score and the JSN score. The joint erosion score is a summary of erosion severity in 40 joints of the hands and 12 joints in the feet. Each hand joint is scored, according to surface area involved, from 0 indicating no erosion through 5 indicating extensive loss of bone from more than one half of the articulating bone. Because each side of the foot joint is graded on this scale, the maximum erosion score for a foot joint is 10. Thus, the maximal erosion score is 320. The JSN score summarizes the severity of JSN in 40 joints in the hands and 12 joints of the feet. Assessment of JSN is scored from 0 through 4, with 0 indicating no JSN and with 4 indicating complete loss of joint space, bony ankylosis, or complete luxation. Thus, the maximal JSN score is 208 and 528 is the worst possible total modified vdH-S score for PsA.

Detailed information on the acquisition of radiographs will be provided in an Imaging Manual and the Central Read Campaigns will be defined in the Imaging Charter.

9.2.1.7. Disability Index of the Health Assessment Questionnaire

The functional status of the subject will be assessed by the HAQ-DI.[13] This 20-question instrument assesses the degree of difficulty a person has in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living). Responses in each functional area are scored from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area (ie, lower scores are indicative of better functioning). Properties of the assessment have been evaluated and its validity in PsA has been determined.[25] It has also been shown to be responsive to changes in a subject's disease.[34] In PsA, a decrease in score of 0.35 has been determined to indicate a meaningful improvement.[35]

9.2.1.8. Minimal Disease Activity

The PsA MDA criteria are a composite of 7 outcome measures used in PsA. Subjects are classified as achieving MDA if they fulfilled 5 of 7 outcome measures: tender joint count ≤1; swollen joint count ≤1; psoriasis activity and severity index ≤1; patient pain VAS score of ≤15; patient global disease activity VAS (arthritis and psoriasis) score of ≤20; Health Assessment Questionnaire (HAQ) score ≤0.5; and tender entheseal points ≤1.[6]

9.2.1.9. Psoriatic Arthritis Disease Activity Score

The PASDAS is calculated using the following variables: patient global VAS (arthritis and psoriasis, to 0–100), physician global VAS (range 0–100), swollen joint count (0-66), tender joint count (0-68), CRP level (mg/L), enthesitis (measured by the LEI), tender dactylitis count (scoring each digit from 0–3 and recoding to 0–1, where any score >0 equaled 1), and, finally, the PCS scale of the SF-36 health survey.[24,23]

PASDAS = {[(0.18 × √Physician global VAS) + (0.159 × √Patient global VAS) – (0.253 × √SF36 – PCS) + (0.101 × LN (Swollen joint count + 1)) + (0.048 × LN (Tender joint count + 1)) + (0.23 × LN (Leeds Enthesitis Count + 1)) + (0.377 × LN (Dactylitis count + 1)) + (0.102 × LN (CRP + 1))] +2} ×1.5

The cutoffs for disease activity are 3.2 (low) to 5.4 (high).[22]

9.2.1.10. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAppa) Composite Score (GRACE)

The GRAPPA Composite score (GRACE) is a composite score of Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), derived as **GRACE Index = (1 - AMDF) x 10**, where, AMDF is the Arithmetic Mean of the Desirability Function (AMDF).[22-24]

The AMDF is calculated by transforming the following variables, using predefined algorithms and expressing the total score as a mean with a score range of 0–1, where 1 indicates a better state than 0: [22, 23]

- Tender joint count (0-68)
- Swollen joint count (0-66)
- HAQ-DI score (0-3)
- Patient's global assessment of disease activity (arthritis and psoriasis, 0-100 VAS)
- Patient's assessment of skin disease activity (0-100 VAS)
- Patient's global assessment of disease activity (arthritis) (0-100 VAS)
- PASI score (0-72)

- Psoriatic arthritis Quality of Life Index (PsAQoL) which is derived as follows:

  PsAQoL = 25.355 + (2.367 × HAQ-DI) – (0.234 × SF-PCS) – (0.244 × SF-MCS), *where,*

  - HAQ-DI: HAQ-DI score (0-3)
  - SF-PCS: PCS score of SF-36 Health Survey
  - SF-MCS: MCS score of SF-36 Health Survey.

9.2.1.11. Disease Activity Index Score 28

The DAS28 using CRP is a statistically derived index combining tender joints (28 joints), swollen joints (28 joints), CRP, and Patient's Global Assessment of Disease Activity (GH).[52] The set of 28 joint count is based on evaluation of the shoulder, elbow, wrist, metacarpophalangeal (MCP) 1, MCP2, MCP3, MCP4, MCP5, proximal interphalangeal (PIP1), PIP2, PIP3, PIP4, PIP5 joints of both the upper right extremity and the upper left extremity as well as the knee joints of lower right and lower left extremities. The DAS28 using CRP is a continuous parameter and is defined as follows:

- DAS28(CRP) = 0.56 × SQRT(TEN28) + 0.28 × SQRT(SW28) + 0.36 × ln (CRP+1) + 0.014 × GH + 0.96; where:
- TEN28 is 28 joint count for tenderness
- SW28 is 28 joint count for swelling
- Ln (CRP+1) is natural logarithm of (CRP value [mg/L] + 1)
- SQRT(TEN28) is square root of TEN28
- SQRT(SW28) is square root of SW28
- GH is Patient's Global Assessment of Disease Activity (arthritis).

DAS Response

To be classified as a DAS28 responder, subjects should have a good or moderate response. The DAS28 response criteria are defined in Table 6.[53]

Table 6: DAS Response

	Improvement in DAS28 score		
Present DAS28 score	**> 1.2**	**> 0.6 to ≤ 1.2**	**≤ 0.6**
≤ 3.2	Good response	Moderate response	No response
> 3.2 to ≤ 5.1	Moderate response	Moderate response	No response
> 5.1	Moderate response	No response	No response

9.2.1.12. Modified Composite Psoriatic Disease Activity Index

The mCPDAI assesses 4 domains (joints, skin, entheses, and dactylitis). The mCPDAI scores are calculated using the following assessments: joints (66 swollen and 68 tender joint counts), HAQ-DI score, PASI, dactylitis, and enthesitis. Within each domain a score (range 0–3) is assigned according to predefined cutoffs[23], as below. The scores for each domain are then added together to give a final score range of 0 to 12.

	Not involved (0)	Mild (1)	Moderate (2)	Severe (3)
Peripheral Arthritis		≤4 joints (swollen or tender); normal function (HAQ ≤0.5)*	≤4 joints but function impaired; or >4 joints, normal function	>4 joints and function impaired
Skin Disease		PASI≤10 and DLQI≤10	PASI≤ 10 but DLQI >10; or PASI >10 but DLQI ≤10	PASI > 10 and DLQI > 10
Enthesitis		≤ 3 sites; normal function (HAQ ≤0.5)*	≤3 sites but function impaired; or >3 sites but normal function	>3 sites and function impaired
Dactylitis		≤3 digits; normal function (HAQ ≤0.5)*	≤3 digits but function impaired; or >3 digits but normal function	>3 digits and has function impaired

* HAQ only counted if clinical involvement of domain (joint/enthesis/dactylitis) present

9.2.1.13. Disease Activity Index for Psoriatic Arthritis

Disease Activity Index for Psoriatic Arthritis is calculated as the sum of the following components: tender joint count (0–68), swollen joint count (0–66), CRP level (mg/dL), patient assessment of pain for pain (0–10 VAS), and patient global assessment of disease activity (arthritis, 0 –10 VAS).[23] The cutoffs for disease activity are 18.5 (low) to 45.1 (high).[22]

9.2.1.14. Modified Psoriatic Arthritis Responder Criteria

Subjects will be assessed using the modified PsARC. A subject is considered a responder if they have improvement in at least 2 of the following criteria, including at least one of the joint criteria and with no deterioration in the other criteria[42]:

- ≥ 30% decrease in the swollen joint count (66 joints);
- ≥ 30% decrease in the tender joint count (68 joints);
  - ≥ 20% improvement in the patient's overall assessment of disease (arthritis) on a VAS; and
  - ≥ 20% improvement in the physician's overall assessment of disease on a VAS.

9.2.1.15. Bath Ankylosing Spondylitis Disease Activity Index

The BASDAI was developed as a subject self-assessment for ankylosing spondylitis that consists of 6 questions relating to the 5 major symptoms of ankylosing spondylitis.[14] Only subjects with spondylitis with peripheral arthritis as their primary arthritic presentation of PsA will complete the BASDAI using a 10-unit VAS to indicate the degree of their symptoms over the past week on the following criteria:

A. Fatigue
B. Spinal pain
C. Joint pain
D. Enthesitis
E. Qualitative morning stiffness
F. Quantitative morning stiffness

The BASDAI score = 0.2 (A + B + C + D + 0.5[E + F]). Higher scores indicate greater disease severity and a score decrease of 50% or 2 points is considered clinically meaningful (49).[58]

9.2.2. Psoriasis Response Evaluations

9.2.2.1. Investigator's Global Assessment of Psoriasis

The IGA documents the investigator's assessment of the subject's psoriasis at a given time point. Overall lesions are graded for induration, erythema, and scaling using 0 (no evidence), 1 (minimal), 2 (mild), 3 (moderate) and 4 (severe) scale. The IGA score of psoriasis is based upon the average of induration, erythema and scaling scores. The patient's psoriasis is assessed as cleared (0), minimal (1), mild (2), moderate (3), or severe (4).

Every effort should be made to ensure that the physician or designee who performed the IGA evaluations for a subject at baseline should also perform the IGA evaluations for the subject at all subsequent visits through Week 52. The Sponsor will provide IGA training. Documentation of this training will be maintained in the site's training files. Previous IGA training by the Sponsor within the last 3 years with adequate documentation (eg, training certification) will be considered adequate for this study; however, repeat training prior to start of the study is encouraged.

9.2.2.2. Psoriasis Area and Severity Index

The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy.[12] The PASI produces a numeric score that can range from 0 to 72. A PASI 75 response is defined as ≥75% improvement in PASI score from baseline; PASI 90 and PASI 100 are similarly defined.

Every effort should be made to ensure that the physician or designee who performed the PASI evaluations for a subject at baseline should also perform the PASI evaluations for the subject at all subsequent visits through Week 52. The Sponsor will provide PASI training. Documentation of this training will be maintained in the site's training files. Previous PASI training by the Sponsor within the last 3 years with adequate documentation (eg, training certification) will be considered adequate for this study; however, repeat training prior to start of the study is encouraged.

9.2.2.3. Dermatology Life Quality Index

The DLQI questionnaire is frequently used to assess the patient's perspective on the impact of skin disorders on daily living. The development of the instrument included a wide variety of dermatologic conditions.[11] The content validity and other psychometric properties were further assessed in a subsequent study in patients with psoriasis[9]and other conditions[1]. The DLQI, a

10 item instrument, has 4 item response options, and has a recall period of 1 week. The total score of DLQI range from 0-30 with lower scores indicating lesser impact of psoriasis on the patients' daily lives. In dermatologic disease, a change of 5 points has been determined to be meaningful.[27]

9.2.3. Other Patient Reported Outcomes

9.2.3.1. 36-Item Short-form Health Survey

The SF-36 questionnaire was developed as part of the Rand Health Insurance Experiment and consists of 8 multi-item domain scales:

- Limitations in physical functioning due to health problems;
- Limitations in usual role activities due to physical health problems;
- Bodily pain;
- General mental health (psychological distress and well-being);
- Limitations in usual role activities due to personal or emotional problems;
- Limitations in social functioning due to physical or mental health problems;
- Vitality (energy and fatigue);
- General health perception.

These scales are scored from 0 to 100 with higher scores indicating better health. Another algorithm yields 2 summary scores, the PCS and the MCS. These summary scores are also scaled with higher scores indicating better health but are scored using a norm-based system where linear transformations are performed to transform scores to a mean of 50 and standard deviations of 10, based upon general US population norms.[54] It has been demonstrated in a study of patients with RA that a change of 4.4 in PCS and 4.7 in MCS was the minimally important change.[28] There is no specific cut-off for a clinically meaningful change in patients with PsA and a conservative threshold of ≥5 points change in both PCS and MCS have been used in the clinical studies to define clinically meaningful improvement for various diseases. The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments.[55]

9.2.3.2. EQ-5D Questionnaire

The EQ-5D is a standardized measure of health status developed by the EuroQoL Group to provide a simple, generic measure of health for clinical and economic appraisal.[8] The EQ-5D is applicable to a wide range of health conditions and treatments. EQ-5D essentially consists of 2 elements: The EQ-5D descriptive system and the EQ VAS. The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected

for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state, which can be converted into a single summary index (EQ-5D index) by applying a formula that attaches values (also called weights) to each of the levels in each dimension. The EQ VAS records the respondent's self-rated health on a vertical line, VAS where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state'. The EQ VAS can be used as a quantitative measure of health outcome as judged by the individual respondents.

9.2.3.3. Functional Assessment of Chronic Illness Therapy - Fatigue

Fatigue has been identified as an important symptom and a unique concept in addition to the core disease measures of patients with PsA.[4] The FACIT-Fatigue questionnaire consists of 13 questions that assess a subject's level of fatigue and tiredness over the last 7 days. Each question is graded on a 5-point scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much); accordingly, scores can range from 0 to 52. Lower scores reflect more severe fatigue. Although not developed for PsA, FACIT-Fatigue has demonstrated strong internal consistency and test-test reliability. It distinguishes between healthy and PsA patients and is correlated with swollen joint count and actively inflamed joint count. In rheumatology, a change of 4 points is considered meaningful and has been used in the PsA population.[3]

9.3. Health Economics

The Work Productivity and Activity Impairment Questionnaire - Specific Health Problem (WPAI-SHP) is a validated instrument that has been used to study the impact of various diseases on patients' ability to work and perform daily activities (http://www.reillyassociates.net/WPAI_General.html). The WPAI:PsA assesses the impact of PsA on work and other daily activities during the past 7 days. The WPAI: PsA consists of six questions to determine employment status, hours missed from work due to PsA, hours missed from work for other reasons, hours actually worked, the degree to which AS affected work productivity while at work and the degree to which PsA affected activities outside of work. Four scores are derived: percentage of absenteeism, percentage of presenteeism (reduced productivity while at work), an overall work impairment score that combines absenteeism and presenteeism and percentage of impairment in activities performed outside of work. Greater scores indicate greater impairment.

9.4. Pharmacokinetics and Immunogenicity

Serum samples will be used to evaluate the PK of guselkumab as well as the immunogenicity of guselkumab (antibodies to guselkumab). Serum collected for PK and immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

9.4.1. Serum Collection and Handling

Venous blood samples will be collected at the time points shown in the Time and Events Schedule for the determination of serum guselkumab concentrations and antibodies to

guselkumab. Serum samples will also be collected at the final visit from subjects who terminate study participation early. At visits where PK and immunogenicity will be evaluated, 1 blood draw of sufficient volume can be used. Each sample will be split into 3 aliquots (1 aliquot for serum guselkumab concentration, 1 aliquot for antibodies to study agent, and 1 aliquot as a back-up). Samples must be collected before study agent administration at visits when a study agent administration is scheduled. The exact dates and times of blood sample collection must be recorded in the laboratory requisition form.

A random venous blood sample for population PK analysis will be collected from all subjects on any day between Weeks 4 to 12, except on the days of the scheduled study visit at Weeks 4, 8, and 12. Additionally, this blood sample must be collected at least 24 hours prior to or after the actual time of study agent administration at Weeks 4, 8, or 12 (ie, it cannot be collected within 24 hours before or after study agent administration). Each population PK serum sample will be split into 2 aliquots (1 aliquot for serum guselkumab concentration and 1 aliquot as a back-up sample).

Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

9.4.2. Analytical Procedures

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

9.4.3. Pharmacokinetic Parameters

If feasible, the apparent total systemic clearance and apparent volume of distribution of guselkumab will be estimated using a nonlinear mixed-effects modeling approach.

9.4.4. Immunogenicity Assessments

Antibodies to guselkumab will be detected using a validated immunoassay method in serum samples collected from all subjects according to the Time and Events Schedule. Serum samples that test positive for antibodies to guselkumab will be further characterized to determine if antibodies to guselkumab could neutralize the biological effects of guselkumab in vitro (ie, neutralizing antibodies [NAbs] to guselkumab). All samples will be tested by the Sponsor or Sponsor's designee.

9.5. Biomarkers

Samples for serum biomarkers will be collected for all subjects as indicated in the Time and Events Schedule.

Samples for the analysis of pharmacodynamic biomarkers will be collected from all subjects. The samples will be used to better understand the biology of PsA, to provide a biological assessment of the response of patients to treatment with guselkumab, to analyze differences

between responders and non-responders, and to determine if the markers can be used to classify patients as potential responders prior to treatment. They may also be used to develop tests/assays related to guselkumab and PsA. Serum samples will be used to analyze inflammation and spondyloarthropathy related proteins. Markers related to the biology of PsA, including (but not limited to) Th17, IL-17A, IL-17F, IL-21, IL-22 and IL-23, metabolomics and bone homeostasis pathways will also be measured. Ribonucleic acid from whole blood samples will be used for gene expression analysis to determine the molecular profile of PsA and to assess changes in gene expression post guselkumab treatment.

9.6. Pharmacogenomics (DNA) Evaluations

A whole blood sample will be utilized for pharmacogenomics evaluation. The analysis may include complete genome-wide testing and/or targeted sequencing. The testing will be done to search for links of specific genes to disease or response to drug. Genes of interest may include (but are not limited to) HLA-B27 and HLAcw6. DNA methylation testing may also be performed. Only DNA research related to guselkumab or to the diseases for which this drug is developed will be performed. Pharmacogenetics testing as well as methylation testing will be undertaken in this study in consenting subjects. Subjects participating in this portion of the study must sign a separate informed consent. Further, a subject may withdraw such consent at any time without affecting their overall participation in the study.

9.7. Safety Evaluations

Safety assessments will be collected for all subjects as indicated in the Time and Events Schedule.

The safety and tolerability of study agent (guselkumab and placebo) will be monitored by collecting information on AEs (including injection site and allergic reactions), clinical laboratory tests, physical examinations, vital signs, suicidal ideation or behavior (using the eC-SSRS questionnaires), concomitant medication review, and early detection of TB, as specified in the Time and Events Schedule. Serum and/or plasma samples collected for PK or PD analyses may also be used to evaluate safety concerns that may arise during or after the study period.

Details regarding the independent DMC are provided in the DMC Charter.

Safety will be monitored through Week 112. Any clinically relevant changes occurring during the study must be recorded on the AE section of the CRF.

Clinically important abnormalities persisting at the end of the study/early withdrawal may be followed by the investigator until resolution or until a clinically stable endpoint is reached.

9.7.1. Evaluations of Safety and Tolerability

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule:

Adverse Events

Adverse events will be reported by the subject for the duration of the study. Adverse events will be followed by the investigator.

At each of the visits, subjects will be questioned about the occurrence of new AEs since the previous visit, or the outcome of any AEs reported at previous visits.

Allergic Reactions

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

Injection-Site Reactions

An injection site reaction is any unfavorable or unintended sign that occurs at the study agent injection site. Any adverse reaction (eg, pain, erythema, and/or induration) should be noted on the AE page of the CRF.

Through Week 52, all subjects will be carefully observed at the study site for at least 30 minutes after the SC injection of study agent for symptoms of an injection-site reaction. If an injection site reaction is observed, the subject should be treated at the investigator's discretion. Subjects self-administering study agent away from the study site will be trained in the recognition and documentation of injection site reactions.

Clinical Laboratory Tests

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

All abnormal laboratory values will be evaluated for clinical significance by the investigator. If clinically significant abnormal laboratory values (in the opinion of the investigator) are detected, the test(s) should be repeated as necessary and in discussion with the study responsible physician.

Instructions for the collection, handling, and shipping of blood samples are provided in the Laboratory Manual.

The following tests will be performed by the central laboratory:

- Hematology Panel

-hemoglobin	-neutrophils
-hematocrit	-bands
-red blood cell count	-eosinophils
-white blood cell count	-basophils

-lymphocytes
-monocytes
-platelets

- Serum Chemistry Panel

-sodium
-potassium
-chloride
-alkaline phosphatase
- blood urea nitrogen (BUN)
-creatinine
-glucose
-AST
-calcium
-albumin
-total protein
-ALT
-bicarbonate
-total bilirubin, with fractionation if hyperbilirubinemia
-uric acid

- Lipid Panel

-total cholesterol
-low density lipoprotein cholesterol
-high density lipoprotein cholesterol
-triglycerides

- Serology: HBV, including HBV serology and HBV DNA (when indicated), antibody to HCV and HCV RNA (when indicated), and antibody to HIV.
- Rheumatoid Factor test (optional, if needed for checking CASPAR criteria at screening)
- High sensitivity CRP
- FSH is optional. It is only needed for determining childbearing potential of a female subject of any age with amenorrhea for less than 12 months. In the absence of 12 months of amenorrhea, 2 FSH measurements are needed. FSH is not needed for female subjects with amenorrhea for at least 12 months or any female subject of childbearing potential. Refer to Inclusion Criterion 10 for detail.

Pregnancy Testing

Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline before randomization. Additionally, urine pregnancy testing is required for all women of childbearing potential at every study agent administration visit. Pregnancy tests must be completed and the result must be negative before the administration of any agent for that visit. All pregnancy test results must be recorded in study source documents.

Electrocardiogram (ECG)

A supine 12-lead ECG will be performed locally at Week 0 prior to administration of study agent, as specified in the Time and Events Schedule. A full 12-lead ECG will be recorded and

the ECG data, including a copy of tracing as well as interpretation, should be stored in the subject's source document.

Physical Examination

Physical examinations will be performed by the investigator or designated physician as specified in the Time and Events Schedule. Any abnormalities or changes in severity noted during the review of body systems should be documented in the source document.

Height and Weight

Height and weight will be measured as specified in the Time and Events Schedule.

Vital Signs

Blood pressure and heart rate measurements will be assessed at the time points specified in the Time and Events Schedule.

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

9.7.2. Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)

No signal of suicidal ideation and behavior has been observed in the clinical trials of guselkumab to date.

However, in light of the recent reports concerning suicidal ideation and behavior in patients with plaque psoriasis treated with an IL-17R antagonist (brodalumab), the eC-SSRS will be used as a screening tool to prospectively evaluate the potential of guselkumab to induce suicidal ideation and behavior. The eC-SSRS measures five possible levels of suicidal ideation and four possible suicidal behaviors, as well as non-suicidal self-injurious behavior. The assessment is a fully-structured, subject self-report eC-SSRS questionnaire, including standardized questions, follow-up prompts, error handling routines, and scoring conventions.[37,43] Two versions of the eC-SSRS will be used in this study, the *Lifetime* version and the *Since Last Contact* version. The *Lifetime* version will be conducted during the screening visit and the *Since Last Contact* version will be conducted at all other visits through Week 112.

Subjects will complete the eC-SSRS questionnaire using the Sponsor-provided electronic tablets (or through an Interactive Voice Response System [IVRS], if available). Study site personnel will train the subjects on how to use the electronic device and/or a telephone system. The eCSSRS will be provided in the local languages in accordance with local guidelines.

The eC-SSRS will be performed during each evaluation visit according to the Time and Events schedule. During a visit, subjects will be directed to a private, quiet place with the electronic device and/or a telephone to complete the assessment. Subjects who do not have suicidal behavior or ideation will answer a limited number of questions and will usually complete the assessment in about 3 minutes. Subjects with significant suicidal ideation and behavior may require up to 10 minutes to answer all relevant questions. The eC-SSRS should be performed

after the joint assessment at the screening visit (after signing informed consent). At Week 0/baseline and at all post-baseline visits, the eC-SSRS will be the first assessment/questionnaire that the subject completes prior to study agent administration.

At the conclusion of each assessment, the site will receive an eC-SSRS Findings Report. At screening (In the last 6 months") and Week 0, subjects with an *Ideation level (1-5)* or any suicidal behaviors or with a response of "YES" for *non-suicidal, self-injurious behavior* must be determined to be not at risk by the investigator based on an evaluation by a mental health professional in order to be randomized. Subjects with an *Ideation level (1-5)* on the eC-SSRS or any suicidal behaviors or with a response of "YES" for *non-suicidal, self-injurious behavior* at any post-baseline visit will also be referred to an appropriate mental health professional for evaluation. If a subject's psychiatric disorder can be adequately treated with psychotherapy and/or pharmacotherapy then the subject, at the discretion of the investigator, should be continued with treatment. Ultimately, the determination of suicidality and risk is up to the investigator's clinical judgment following evaluation by a mental health professional (eg, psychiatrist, psychologist, or appropriately trained social worker or nurse).

Positive reports are generated from the eC-SSRS vendor for ANY of the following findings:

- Ideation level 4: Some intent to act, no plan
- Ideation level 5: Specific plan and intent
- Behaviors: Actual suicide attempts
- Behaviors: Interrupted attempts
- Behaviors: Aborted attempts
- Behaviors: Preparatory actions.

Negative suicidality indication reports are generated from the eC-SSRS vendor when there are NO indications of the above.

The subject should not be released from the site until the eC-SSRS Findings Report (both for negative and positive reports) is reviewed by the investigator and the subject's risk has been assessed and follow-up determined, as appropriate.

For each Ideation Level and Behavior, the following actions and associated alerts will be generated, if applicable:

- No ideation with No Behaviors: No further action is needed.
- Ideation Levels (1-5) or suicidal behavior: Subject risk assessed and referral to a mental health professional.
  - Ideation Level of a 1, 2, or 3 with No Behaviors: Negative findings report will be generated.

  - Ideation Level of a 4 or 5 or any suicidal behavior: Positive findings report will be generated. When the system reports that the subject has a positive suicidal indication (including for an incomplete-positive assessment), the site will be immediately notified by fax/email and a telephone call from the eC-SSRS vendor.

- Non-suicidal, self-injurious behavior = YES: Subject risk assessed and referral to a mental health professional. Negative findings report will be generated.

Interruption or the discontinuation of study treatment should be considered for any subject who reports suicidal Ideation Level 4 (some intent to act, no plan), Ideation Level 5 (specific plan and intent), or any suicidal behavior (actual suicide attempts, interrupted attempts, aborted attempts, or preparatory actions) on a post-baseline (after Week 0) eC-SSRS assessment and who is deemed to be at risk by the investigator based upon evaluation by a mental health professional. Discussion of such subjects with the medical monitor or designee is required (See Section 10.2). The final decision on suitability for continuing in the study will be made by the investigator.

Any eC-SSRS findings, which in the opinion of the investigator are new or considered to be a worsening and clinically significant, should be reported on the AE eCRF (see Section 12).

9.7.3. Anticipated Events

Anticipated events will be recorded and reported in this study.

An anticipated event is an AE (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

- Worsening of psoriasis
- Worsening of PsA

These events will be captured on the CRF and in the database, and will be reported to the Sponsor as described in All Adverse Events (Section 12.3.1). Any event that meets SAE criteria will be reported to the Sponsor within the appropriate timeline as described in Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study agent, the Sponsor will report these events in an expedited manner.

An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the Sponsor's organization that is independent of the Sponsor's study team. The ARC will meet to aid in the recommendation to the Sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study agent.

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan.

9.8. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the laboratory requisition form. Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

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

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she has completed assessments at Week 112 of the study. Subjects who prematurely discontinue study treatment for any reason before completion of the final safety visit at Week 112 will not be considered to have completed the study.

10.2. Discontinuation of Study Treatment

A subject will not be automatically withdrawn from the study if he or she has to discontinue treatment before the end of the treatment regimen.

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment.
- The subject becomes pregnant or plans to become pregnant.
- The subject is diagnosed with a malignancy, with the exception of no more than 2 localized basal cell skin cancers that are treated with no evidence of recurrence or residual disease.
- The subject is deemed ineligible according to the following TB screening criteria:
  - A diagnosis of active TB is made.
  - A subject has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination, or has had recent close contact with a person with active TB, and cannot or will not continue to undergo additional evaluation.
  - A subject undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON®-TB Gold test result (or a positive tuberculin skin test result in countries in which the QuantiFERON®-TB Gold test is not approved/registered or the tuberculin skin test is mandated by local health authorities),

unless active TB can be ruled out and appropriate treatment for latent TB can be initiated before the next administration of study agent and continued to completion. Indeterminate QuantiFERON®-TB Gold test results should be handled as described in Section 9.1.3. Subjects with persistently indeterminate QuantiFERON®-TB Gold test results may continue without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the subject has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the Sponsor's medical monitor and recorded in the subject's source documents and initialed by the investigator.

– A subject receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.

- The subject initiates the following protocol-prohibited medications: apremilast, systemic immunosuppressive drugs (Section 8.1.3), biologic agents, cytotoxic drugs, JAK inhibitors, or investigational agents (Section 8.4), and systemic therapy for psoriasis (Section 8.7).
- The subject withdraws consent for administration of study agent.
- The subject is unable to adhere to the study visit schedule or comply with protocol requirements.
- The subject develops an allergic reaction such as bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension that occurs following a study agent administration.
- The subject has a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an injection of study agent. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.

Discontinuation of study treatment should be considered for subjects who report suicidal Ideation Level 4 (some intent to act, no plan), Ideation Level 5 (specific plan and intent), or any suicidal behavior (actual suicide attempts, interrupted attempts, aborted attempts, or preparatory actions) on a post-baseline (after Week 0) eC-SSRS assessment. Discussion of such subjects with the medical monitor or designee is required.

Discontinuation of study agent should be considered and discussed with the study responsible physician or designee for subjects who develop a serious or opportunistic infection.

Subjects who decide to discontinue study agent administration must be interviewed by the investigator to determine if a specific reason for discontinuing study agent can be identified. Subjects should be explicitly asked about the contribution of possible AEs or lack of efficacy to their decision to discontinue study agent; investigators should confirm that any AE information elicited or lack of efficacy has been documented. If a subject elects to discontinue study agent due to an AE or lack of efficacy, the event or lack of efficacy should be recorded as the reason for study agent discontinuation, even if the investigator's assessment is that the AE or the patient's PsA condition would not require study agent discontinuation. The reason for study

agent discontinuation must be documented in the CRF and in source documents. Study agent assigned to a subject who discontinues may not be assigned to another subject.

If a subject discontinues study agent administrations before the Week 100 visit, he/she should be encouraged to return for all visits as outlined in the Time and Events Schedule (see Section 9.1.5).

If a subject permanently discontinues study agent at or after Week 24, the final efficacy visit should occur at the time of discontinuation or as soon as possible and all assessments under the final efficacy/Week 100 visit should be performed, including radiograph of hands and feet, with the exception of study agent administration. The subject should also return for a final safety visit approximately 12 weeks after the last study agent administration.

10.3. Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent
- Death

To ensure access for subject follow-up, study sites should try to obtain both primary and secondary telephone contact numbers from subjects (eg, home, work, and mobile phones), as well as other contact information such as email addresses, and emphasize the importance of follow-up information to the subject, before randomization.

If a subject fails to return for study visits, study site personnel must make all reasonable efforts to contact the subject to determine the subject's reason for discontinuation/withdrawal before considering the subject to be lost to follow-up. Due diligence should include repeated telephone calls, certified letters, and email requests. Measures taken to obtain follow-up information must be documented.

Withdrawal of consent should be a very unusual occurrence in a clinical trial; the investigator should make every effort to maintain good subject relationships to avoid withdrawals of consent. For subjects who truly request withdrawal of consent, it is recommended that the subject withdraw consent in writing and provide a reason, if possible; if the subject or the subject's representative refuses to do so or is physically unavailable, the study site should document the reason for the subject's failure to withdraw consent in writing, sign the documentation, and maintain it with the subject's source records.

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

10.4. Withdrawal From the Use of Research Samples

A subject who withdraws from the study will have the following options regarding the optional research sample(s):

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

Withdrawal From the Optional Research Samples While Remaining in the Main Study

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

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for future research (refer to Section 16.2.5). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for future research are presented in the main ICF and in the separate ICF for optional research samples.

11. STATISTICAL METHODS

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

In general, efficacy and subject information analyses will be based on Full Analysis Set (FAS) and include all randomized subjects who received at least 1 dose (complete or partial) of study treatment and will be analyzed based on the randomized treatment groups, regardless of the treatment they actually received.

Safety analyses will include all subjects who received at least 1 dose (complete or partial) of study treatment and subjects will be analyzed based on the treatment groups they actually received, regardless of the treatment groups they were assigned to.

Pharmacokinetics (PK) analysis for guselkumab will include subjects who receive at least one complete dose of guselkumab and have at least one post-dose sample collection. Antibodies to guselkumab will be analyzed for subjects who receive at least one dose of guselkumab and have at least one post-dose sample collection.

Simple descriptive summary statistics, such as n, mean, standard deviation (SD), median, inter quantile (IQ) range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data.

In general, for response efficacy endpoints, treatment comparisons will be performed using a Cochran-Mantel-Haenszel (CMH) test stratified by baseline non-biologic DMARD (MTX, SSZ, HCQ, LEF) use (yes/no) and the most recent available CRP value prior to randomization (<2.0 mg/dL or ≥2.0 mg/dL).

In general, for continuous endpoints of efficacy data, treatment comparisons will be performed using either a Mixed-Effect Model Repeated Measure model or an analysis of covariance model. All the models will have treatment group, the baseline non-biologic DMARD (MTX, SSZ, HCQ, LEF) use (yes/no), the most recent available CRP value prior to randomization (<2.0 mg/dL or ≥2.0 mg/dL), and baseline value as explanatory factors

In general, for continuous endpoints of radiographic data, treatment comparisons will be performed using an ANOVA test on the van der Waerden normal score.

In general, all statistical tests will be performed at a 2-sided significance level of α=0.05.

In addition, graphical data displays (eg, line plots) and subject listings may also be used to summarize/present the data.

11.1. Subject Information

Descriptive statistics by the randomized treatment group will be provided for demographics, baseline disease characteristics, and prior and concomitant medications.

11.2. Sample Size Determination

The sample size selection was determined based on the primary endpoint of proportion of subjects who achieve ACR 20 response at Week 24 and the major secondary endpoint of change from baseline in vdH-S score at Week 24.

Primary Endpoint – ACR 20 Response at Week 24

In the Phase 3 CNTO1275PSA3001 study with ustekinumab, the ACR 20 response rates at Week 24 were 22.8%, 42.4% and 49.5%, respectively, for the placebo, ustekinumab 45 mg, and ustekinumab 90 mg treatment groups. In the Phase 2 CNTO1959PSA2001 study with guselkumab, the ACR 20 response rates at Week 24 were 18.4% and 58.0%, respectively, for the placebo and guselkumab 100 mg treatment groups.

Assuming a 45% ACR 20 response rate in the guselkumab group and a 25% ACR 20 response rate in the placebo group, a sample size of 228 subjects per treatment group (684 in total) will provide a power of approximately 99% to detect a significant treatment difference at a 2-sided significance level of 0.05. Table 7 provides the statistical power under various assumptions using a 2-sided chi-square test.

For this study, the sample size was also evaluated based on the following assumptions:

- 20% to 25% ACR 20 response rates at Week 24 in subjects treated with placebo
- 40% to 50% ACR 20 response rates at Week 24 in subjects treated with guselkumab

Table 7: Statistical Power for Treatment Difference in ACR 20 Response at Week 24

Sample size per arm	ACR 20 Response Rate			Power
	Placebo Group	Guselkumab Group	Difference (Δ)	
228	20%	40%	20%	>99%
228	20%	45%	25%	>99%
228	25%	45%	20%	99%
228	25%	50%	25%	>99%
228	30%	50%	20%	99%

Major Secondary Endpoint – Change from Baseline in vdH-S Score at Week 24

For change from baseline in vdH-S score, subjects in each treatment group can be considered a mixture of 2 subpopulations: 1 subpopulation with a change score of 0 and 1 subpopulation with a change score sampled from a normal distribution. Therefore, the distribution of the vdH-S change scores is determined by 3 parameters: the probability that a subject has a change score of 0, mean of the normal distribution, and SD of the normal distribution. The overall mean (ie, crude mean) of the change scores for a treatment group is the overall average of the change scores among all subjects (including both subpopulations 1 and 2) in that treatment group.

In the Phase 3 CNTO1275PSA3001 study with ustekinumab, the following statistics were observed on change from baseline in vdH-S score at Week 24:

- The overall mean (SD) of change from baseline in vdH-S score at Week 24 (after excluding one extreme outlier, eg, the subject with a change score of 58) was 0.92 (2.15), 0.28 (1.94), and 0.17 (1.45) in the placebo, ustekinumab 45 mg and 90 mg treatment groups, respectively.
  - Approximately 49%, 47%, and 46% subjects had a change score of 0 in the placebo, ustekinumab 45 mg and 90 mg treatment groups, respectively.
  - Approximately 40% of 0's in each group was true 0's (that is, the difference in the reader-level vdH-S score between the 2 readers selected was ≤ 2 and the average of the reader-level vdH-S score between the 2 readers selected was 0).
  - Excluding the above subjects with a true 0 change score, the mean (SD) change score (after one excluding extreme outlier) was 1.59 (2.60), 0.47 (2.50), and 0.32 (1.96) in the placebo, ustekinumab 45 mg and 90 mg treatment groups, respectively. Excluding all 0's, the mean (SD) change score for the 3 groups was 1.82 (2.75), 0.52 (2.64), and 0.32 (1.96).

Assuming an overall mean change of 0.9 from baseline in vdH-S score in the placebo group, and an overall mean change of 0.3 in the guselkumab group, and an SD of 2.5 for each treatment group, a sample size of 228 subjects per treatment group (684 in total) will provide a power of approximately 90% to detect a significant treatment difference at a 2-sided significance level of 0.05. Table 8 provides the statistical power under various assumptions. The statistical power was estimated based on 10000 simulations with treatment comparison performed at each simulation using an ANOVA test on the van der Waerden normal score.

For this study, the sample size was determined based on the following assumptions:

- The overall mean difference in change from baseline in vdH-S score at Week 24 between the placebo group and a guselkumab group ranges from 0.6 to 0.8.
  - 40% – 50% subjects in each treatment group have a change score of 0 from baseline in vdH-S score at Week 24 (ie, the subpopulation with a change score of 0).
  - For the other subjects (those from the normal distributions), the SD of the normal distributions is 2.5 for all treatment groups and the mean of the normal distribution is 1.80 for the placebo group.

If the SD of the normal distributions is 3.0, the power will go down to as low as approximately 80%.

Table 8: Statistical Power for Treatment Difference in vdH-S Change from Baseline at Week 24

Placebo Group				Guselkumab Group				Overall Mean Difference	Power
% subjects without change	Rest of subjects		Overall mean	% subjects without change	Rest of subjects		Overall mean		
	Mean	SD			Mean	SD			
45%	1.80	2.5	1.00	45%	0.71	2.5	0.40	0.60	89.0%
45%	1.80	2.5	1.00	45%	0.35	2.5	0.20	0.80	98.9%
50%	1.80	2.5	0.90	50%	0.60	2.5	0.30	0.60	91.7%
50%	1.80	2.5	0.90	50%	0.20	2.5	0.10	0.80	99.4%
50%	1.80	2.5	0.90	45%	0.55	2.5	0.30	0.60	91.1%
50%	1.80	2.5	0.90	45%	0.18	2.5	0.10	0.80	99.2%

11.3. Efficacy Analyses

11.3.1. Primary Endpoint Analyses

The primary endpoint to be analyzed for the primary analysis is proportion of subjects who achieved an ACR 20 response at Week 24. Note that the intercurrent event of Treatment Failure prior to Week 24 (defined below) will be treated as non-response for the primary analysis, regardless of the observed ACR 20 response status.

Subjects who meet the following treatment failure criteria include subjects who:

1. Discontinued study agent injections due to lack of efficacy.
2. Terminate study participation for any reason.
3. Initiated or increased the dose of non-biologic DMARDs (MTX, SSZ, HCQ, LEF) or oral corticosteroids over baseline for PsA.
4. Initiated protocol prohibited medications/therapies for PsA.

Subjects with missing data at Week 24 will be considered non-responders.

The treatment effect of each guselkumab group versus placebo will be tested using a CMH test stratified by baseline non-biologic DMARD (MTX, SSZ, HCQ, LEF) use (yes/no) and the most recent available CRP value prior to randomization (<2.0 mg/dL or ≥2.0 mg/dL). The magnitude of the effect will be estimated by the difference in ACR 20 response rates between the guselkumab and placebo groups with the 95% confidence interval calculated based on Wald statistics.

In order to control the overall Type 1 error rate, the primary analysis will be tested in a fixed sequence.

1. Guselkumab 100 mg q4w versus placebo in ACR 20 response at Week 24
2. Guselkumab 100 mg at Weeks 0, 4, and then q8w versus placebo in ACR 20 response at Week 24

With the above specified order, each of the hypotheses will be tested at a 2-sided α-level of 0.05 provided that significance is achieved for the preceding hypothesis in the specified order. If a given comparison is not significant at the 2-sided α-level of 0.05, the remaining treatment group comparisons will be considered as supportive analysis.

To evaluate the robustness of the primary endpoint analysis results, the exhaustive scenario tipping point sensitivity analyses will be performed by varying the amount of non-responder imputation for missing data.

Additional sensitivity/supplemental analyses which vary how intercurrent events (eg, treatment failures) are handled, how observed data are used, and how missing data are treated will be specified in the SAP to further address the robustness of treatment effect of ACR 20 at Week 24 for the primary and alternative estimands (which will also be defined in the SAP).

Subgroup Analyses

Subgroup analysis will be performed to evaluate consistency in the primary efficacy endpoint by demographic characteristics, baseline disease characteristics, and baseline medications. Interaction test between the subgroups and treatment group will also be provided if appropriate.

11.3.2. Major Secondary Analyses

The major secondary endpoints are provided in Section 2.1.2.

The methods of analysis and the approach to control the Type I error for multiplicity, as well as the data-handling rules for the major secondary endpoints will be specified in the SAP.

11.3.3. Other Planned Secondary Analyses

In addition to the primary analyses and major secondary analyses, all other secondary endpoints (Section 2.1.2) will be descriptively summarized over time by treatment groups. Treatment comparisons will be performed by visit through Week 24. The methods of analysis and the data-handling rules will be provided in the SAP.

11.4. Pharmacokinetic Analyses

Serum guselkumab concentrations over time will be summarized for each treatment group using descriptive statistics. All concentrations below the lowest quantifiable sample concentration of the assay (BQL) or missing data will be labeled as such in the concentration data listing or statistical analysis system dataset. The BQL concentrations will be treated as zero in the summary statistics.

If feasible, a population PK analysis using a nonlinear mixed effects modeling approach will be used to characterize the disposition characteristics of guselkumab. The apparent total systemic clearance and apparent volume of distribution values will be estimated. The influence of important variables (such as body weight, antibodies to guselkumab, and concomitant medications) on the population PK parameter estimates may be evaluated. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate technical report.

11.5. Immunogenicity Analyses

The incidence and titers of antibodies to guselkumab will be summarized for all subjects who receive at least 1 dose of guselkumab and have appropriate samples for detection of antibodies to guselkumab (ie, subjects with at least 1 sample obtained after their first dose of guselkumab). The incidence of NAbs to guselkumab will be summarized for subjects who are positive for antibodies to guselkumab and have samples evaluable for NAbs.

11.6. Biomarkers Analyses

Results will be presented in a separate biomarker technical report.

11.7. Pharmacokinetic/Pharmacodynamic Analyses

If data permit, the relationships between serum guselkumab concentration and efficacy may be analyzed graphically. If a relationship is observed, a suitable PK/PD model may be developed to describe the exposure-response relationship and will be presented in a separate technical report.

11.8. Pharmacogenomic Analyses

Results will be presented in a separate pharmacogenomics technical report.

11.9. Health Economics Analysis

The change from baseline in impact of disease on work productivity and daily activity via WPAI:PsA will be descriptively summarized by treatment group over time and compared between treatment groups at Week 24.

11.10. Safety Analyses

Routine safety evaluations will be performed. Adverse events, serious AEs (SAEs), and infections will be summarized by treatment group.

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

- The incidence and type of AEs.
- The incidence and type of SAEs.
- The incidence and type of infections.
- The incidence and type of injection site reactions.
- The laboratory parameters and change from baseline in selected laboratory parameters (hematology and chemistry).
- The incidence of Common Terminology Criteria for Adverse Events Grade 3 or Grade 4 abnormal laboratory parameters (hematology and chemistry).

Listings of serious infections and anaphylactic reaction/serum sickness reactions will also be provided. All safety analyses will be based on the population of subjects who received at least 1 injection of study agent; subjects will be summarized by the treatment they actually received.

11.11. Interim Analysis

No interim analysis is planned for this study.

11.12. Data Monitoring Committee

An independent DMC will be established to monitor unblinded data on an ongoing basis through at least the Week 24 database lock (DBL) to ensure the continuing safety of the subjects enrolled in the study.

The DMC will have 3 to 6 members who are independent of the Sponsor. None of the members will be participating in the current study. The DMC will consist of at least 1 medical expert in the relevant therapeutic area and at least 1 statistician. The members of the committee will be specified prior to study initiation. The major function of this committee will be to monitor the safety of the study agent and to provide recommendations for placing the study on hold or stopping the study in the event that any unanticipated serious events occur.

The committee will meet periodically to review interim data. After the review, the DMC will make recommendations regarding the continuation of the study.

SAE reports will be provided to the DMC members on an ongoing monthly basis. Periodic safety reviews will occur every 4 months. The DMC may change the frequency or number of reviews based on interim safety findings and may request additional data. The safety reviews will focus on particular AEs, SAEs, and mortality.

In addition, during the study, the Sponsor's study responsible physician (or designee) will regularly review blinded safety data from the sites and notify the DMC and appropriate Sponsor personnel of any issues.

The content of the safety summaries, the DMC role and responsibilities and the general procedures (including communications) and their recommendations on the study conduct will be defined and documented in the DMC charter prior to the first DMC review.

12. ADVERSE EVENT REPORTING

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

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

Solicited Adverse Events

Solicited AEs are predefined local and systemic events for which the subject is specifically questioned (see Section 9.1.1).

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the subject is specifically not questioned.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a

medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

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

Note: The Sponsor collects AEs starting with the signing of the ICF (refer to Section 12.3.1 for time of last AE recording).

Serious Adverse Event

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

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

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

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study agent and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

Adverse Event Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely (Section 12.1.2).

12.1.2. Attribution Definitions

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

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

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

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

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

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

12.2. Special Reporting Situations

Safety events of interest on a Sponsor study agent that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a Sponsor study agent
- Suspected abuse/misuse of a Sponsor study agent
- Accidental or occupational exposure to a Sponsor study agent
- Medication error involving a Sponsor product (with or without subject/patient exposure to the Sponsor study agent, eg, name confusion)
- Exposure to a Sponsor study agent from breastfeeding

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

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. Serious AEs, including those spontaneously reported to the investigator within 12 weeks after the last dose of study agent, must be reported using the Serious Adverse Event Form. The Sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 5.

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

The Sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The Sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or Sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR

will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

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

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

12.3.2. Serious Adverse Events

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

Information regarding SAEs will be transmitted to the Sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the Sponsor **within 24 hours**. The initial and follow-up reports of an SAE should be made by facsimile (fax).

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

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

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

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the CRF).

  Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.

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

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the Sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the study agent on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

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

12.3.4. Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first administration of study agent in subjects participating in this clinical study must be reported by the investigator according to the procedures in Section 12.2. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE.

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may

have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

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

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

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY AGENT INFORMATION

14.1. Physical Description of Study Agents

The guselkumab supplied for this study is a sterile liquid for SC injection in a single-use PFS assembled in a PFS-U. Each single-use PFS-U contains 100 mg (1 mL fill of liquid) in a 1 mL glass syringe with a 27 gauge, 1/2 inch fixed needle and a latex-free rigid needle shield. No preservatives are present. The guselkumab solution should be essentially free of visible particulate matter. The PFS-U is a passive safety needle guard that is permanently assembled on the syringe and incorporates a spring driven shield that automatically extends beyond the PFS needle following complete injection of the guselkumab PFS contents. Guselkumab will be manufactured and provided under the responsibility of the Sponsor. Refer to the Investigator's Brochure for a list of excipients.

Placebo for guselkumab is supplied as a sterile liquid for SC injection at a nominal volume of 1.0 mL in a single-use PFS assembled with the PFS-U.

Concomitant medications, including those in Table 4, will not be supplied by the Sponsor but rather must be acquired from a commercial pharmacy.

14.2. Packaging

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

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

All study agent must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C) and protected from light. Vigorous shaking of the product should be avoided. The sterile product does not contain preservatives and is designed for single use only. Protection from light is not required during administration.

After Week 52, subjects who are able and who have been appropriately trained in the self-administration of study agent may self-administer study agent at home, as per the Time and Events Schedule. Study personnel will instruct subjects on how to transport, store, and administer study agent for at-home use as indicated for this protocol.

Further details regarding the storage of guselkumab and placebo will be provided in the Site Investigational Product Manual.

14.5. Drug Accountability

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

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

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

Study agents should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study agents will be supplied only to subjects participating in the study. Study agents may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study agent from, nor store it at, any site other than the study sites agreed upon with the Sponsor.

Subjects who will be self-administering study agent at home will receive detailed instructions for study drug storage and disposal of used syringes and handling of unused study material. These subjects will receive a sharps container to dispose of used syringes and will be instructed to return the sharps container and/or unused cartons with syringes. Subjects who self administer at home will record study drug administrations with time and date information on a diary card.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure
- Study site investigational product and procedures manual
- Laboratory manual and laboratory supplies
- ePRO device and user manual
- Interactive voice response system/IWRS manual
- Electronic data capture (eDC) manual
- Sample ICF
- Imaging manual
- iPad® and site user guide, if the study site is participating in electronic informed consent

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The primary ethical concern is that subjects with active disease may receive placebo for 24 weeks. However, the placebo control is necessary to capture the change in clinical endpoints that may occur in the absence of active treatment and is recommended by regulatory authorities. The disease activity of each subject will be closely monitored during the study and early escape has been incorporated in the study design to allow subjects receive additional concomitant medications for PsA at the investigator's discretion if the early escape criterion is met. The duration of the placebo exposure is limited to 24 weeks and is considered acceptable by ICH (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E10/Step4/E10_Guideline.pdf).

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

Subjects will be exposed to radiation during radiography of hands/feet collected at Weeks 0, 24, 52, and 100. A total of 0.012 mSV radiation exposure is expected from these procedures, which is comparable to ~3 days of exposure to natural background radiation. Additionally 1 Chest X-ray may be performed at screening if the subject does not have a chest X-ray within 12 weeks prior to the first administration of study agent. The exposure from 1 standard chest X-ray is 0.1 mSV, comparable to 10 days of exposure to natural background radiation.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Independent Ethics Committee or Institutional Review Board

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

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

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

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the Sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study agent
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

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

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the Sponsor and by the

reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

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

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

Subjects will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the subject will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the subject.

The subject must be able to read and write and should personally sign the ICF. An impartial witness or legally acceptable representative should not sign the ICF on the subject’s behalf.

A limited number of study sites may be asked by the Sponsor to obtain informed consent using a validated electronic system instead of a paper-based process. If both parties (Sponsor and the study site) agree, and if participation is allowed by local regulations and IEC/IRB requirements, the means to facilitate such a process will be provided to the sites by Sponsor. The actual mechanism of consenting will be facilitated by the use of an eTablet device (eg, iPad®), but overall the consent process will remain the same, as described in this section. At these study sites, subjects will still be required to review the entire informed consent as a written document on the eTablet and then to apply their handwritten signature electronically by the use of a stylus directly onto the eTablet. Alternately, the site will also have the option to print the electronic version of the ICF and apply a handwritten signature.

16.2.4. Privacy of Personal Data

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

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

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

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

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

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years, starting from last patient, last visit (or according to local regulations) for additional research. Samples will only be used to understand guselkumab, to understand PsA, to understand differential drug responders, and to develop tests/assays related to guselkumab and PsA. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the Sponsor will modify this protocol without a formal amendment by the Sponsor. All protocol amendments must be issued by the Sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the Sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

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

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

The following documents must be provided to the Sponsor before shipment of study agent to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be

obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.

- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

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

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

17.3. Subject Identification, Enrollment, and Screening Logs

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

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

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

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; prior and concomitant medication; drug receipt/dispensing/return records; study agent administration information; and date of study

completion and reason for early discontinuation of study agent or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following subject- and investigator-completed PsA scales and assessments designated by the Sponsor will be recorded directly into an electronic device and will be considered source data: Joint Assessment, Subject's Assessment of Pain, Subject's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, Dactylitis and Enthesitis Assessments, HAQ-DI, SF-36, FACIT-Fatigue, BASDAI, PASI, DLQI, BSA, EQ-5D, eC-SSRS. If available, subjects may also use the telephone as an alternative method to complete the eC-SSRS assessment.

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

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

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

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the Sponsor. If the electronic source system is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

During at-home administration (Weeks 56, 60, 64, 72, 80, 88, 92, and 96), subjects will enter information on their study agent administration on a patient diary.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the Sponsor for each subject in electronic format. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the Sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or Sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

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

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study

The Sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the Sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

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

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

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

17.8. Monitoring

The Sponsor will use a combination of monitoring techniques (central, remote, on-site monitoring) to monitor this study.

The Sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the Sponsor and study-site personnel and are accessible for verification by the Sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

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

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

Central monitoring will take place for data identified by the Sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

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

17.9.2. Study Termination

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

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

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

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

17.10. On-Site Audits

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

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

17.11. Use of Information and Publication

All information, including but not limited to information regarding guselkumab or the Sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the Sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker

research data, generated as a result of this study, are considered confidential and remain the sole property of the Sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the Sponsor's prior written consent.

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

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

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

Registration of Clinical Studies and Disclosure of Results

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

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Attachment 1: The CASPAR Criteria

To meet the CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis.

- Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.†
- A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider.
- A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report.

2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination.

3. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range.

4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist.

5. Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

† Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.

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Attachment 2: QuantiFERON® TB Gold Testing

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

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

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

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

Performing the QuantiFERON®-TB Gold Test

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

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

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

In the rare instance that the site is not able to perform the QuantiFERON®-TB Gold test handling process prior to sending to Covance, this test may be performed locally by another laboratory, as approved by the Sponsor.

Adherence to Local Guidelines

Local country guidelines **for immunocompromised patients** should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

In countries in which the QuantiFERON®-TB Gold test is not considered approved/registered, a tuberculin skin test is additionally required.

References

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Attachment 3: Tuberculin Skin Testing

Administering the Mantoux Tuberculin Skin Test

The Mantoux tuberculin skin test (CDC, 2000) is the standard method of identifying persons infected with *Mycobacterium tuberculosis*. Multiple puncture tests (Tine and Heaf) should not be used to determine whether a person is infected because the amount of tuberculin injected intradermally cannot be precisely controlled. Tuberculin skin testing is both safe and reliable throughout the course of pregnancy. The Mantoux tuberculin test is performed by placing an intradermal injection of 0.1 mL of tuberculin into the inner surface of the forearm. The test must be performed with tuberculin that has at least the same strength as either 5 tuberculin units (TU) of standard purified protein derivative (PPD)-S or 2 TU of PPD-RT 23, Statens Seruminstitut, as recommended by the World Health Organization. PPD strengths of 1 TU or 250 TU are not acceptable (Menzies, 2000). Using a disposable tuberculin syringe with the needle bevel facing upward, the injection should be made just beneath the surface of the skin. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable needles and syringes should be placed in puncture-resistant containers for disposal. Institutional guidelines regarding universal precautions for infection control (eg, the use of gloves) should be followed. A trained health care worker, preferably the investigator, should read the reaction to the Mantoux test 48 to 72 hours after the injection. Subjects should never be allowed to read their own tuberculin skin test results. If a subject fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a subject who fails to return within 72 hours has a negative test, tuberculin testing should be repeated. The area of induration (palpable raised hardened area) around the site of injection is the reaction to tuberculin. For standardization, the diameter of the induration should be measured transversely (perpendicular) to the long axis of the forearm. Erythema (redness) should not be measured. All reactions should be recorded in millimeters, even those classified as negative.

Interpreting the Tuberculin Skin Test Results

In the US and many other countries, the most conservative definition of positivity for the tuberculin skin test is reserved for immunocompromised patients, and this definition is to be applied in this study to maximize the likelihood of detecting latent TB, even though the subjects may not be immunocompromised at baseline.

In the US and Canada, an induration of 5 mm or greater in response to the intradermal tuberculin skin test is considered to be a positive result and evidence for either latent or active TB.

In countries outside the US and Canada, country-specific guidelines **for immunocompromised patients** should be consulted for the interpretation of tuberculin skin test results. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

Treatment of Latent Tuberculosis

Local country guidelines **for immunocompromised patients** should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

References

Centers for Disease Control and Prevention. Core curriculum on tuberculosis: What the clinician should know (Fourth Edition). Atlanta, GA: Department of Health and Human Services; Centers for Disease Control and Prevention; National Center for HIV, STD, and TB Prevention; Division of Tuberculosis Elimination; 2000:25-86.

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Attachment 4: Hepatitis B Virus (HBV) Screening with HBV DNA

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

- Subjects who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this study.
- Subjects who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this study.
- Subjects who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this study.
- Subjects who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this study, regardless of the results of other hepatitis B tests.
- Subjects who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of hepatitis B virus deoxyribonucleic acid (HBV DNA test). If the HBV DNA test is **positive**, the subject ***is NOT eligible*** for this study. If the HBV DNA test is **negative**, the subject ***is eligible*** for this study. In the event the HBV DNA test cannot be performed, the subject ***is NOT eligible*** for this study.

For subjects who **are not eligible for this study due to HBV test results**, consultation with a physician with expertise in the treatment of hepatitis B virus infection is recommended.

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

Attachment 5: Anticipated Events

Anticipated Event

Anticipated events will be recorded and reported in this study.

An anticipated event is an AE (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

- Worsening of psoriasis
- Worsening of PsA

Reporting of Anticipated Events

These events will be captured on the CRF and in the database, and will be reported to the Sponsor as described in All Adverse Events. Any event that meets SAE criteria will be reported to the Sponsor within the appropriate timeline as described in Serious Adverse Events (Section 12.3.2). These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study agent, the Sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the Sponsor's organization that is independent of the Sponsor's study team. The ARC will meet to aid in the recommendation to the Sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study agent.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan.

INVESTIGATOR AGREEMENT

CNTO 1959 (guselkumab)
Protocol CNTO1959PSA3002 Amendment 1

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Elizabeth Hsia, MD MSCE, Head of Rheumatology Clinical Development

Institution: Janssen Research & Development

Signature: [redacted] Date: 23 January 2018
(Day Month Year)

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

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Approved, Date: 23 January 2018