Janssen Research & Development *

Clinical Protocol

Protocol Title

A Phase 2a, Multicenter, Randomized, Double-blind Study Evaluating the Efficacy and Safety of Subcutaneously Administered Guselkumab and Golimumab Combination Therapy in Participants with Active Psoriatic Arthritis

AFFINITY

Short Title

Subcutaneously Administered Guselkumab and Golimumab Combination Therapy in Active Psoriatic Arthritis

Protocol CNTO1959PSA2003; Phase 2a
Amendment 2
CNTO1959 (guselkumab)
CNTO148 (golimumab)

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United States (US) sites of this study will be conducted under US Food & Drug Administration (FDA) Investigational New Drug (IND) regulations (21 CFR Part 312).

Regulatory Agency Identifier Number(s):
IND: 156196
EudraCT NUMBER: 2021-002012-31

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Date: 19 August 2022
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-356765, 3.0

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	19 August 2022
Amendment 1	06 October 2021
Original Protocol	08 June 2021

Amendment 2 (19 August 2022)

Overall Rationale for the Amendment: The proposed changes to the protocol, including changes to inclusion and exclusion criteria, are being made to facilitate recruitment of participants and to ensure a broader and more representative population is included in the study.

The changes made to the clinical protocol CNTO1959PSA2003 as part of Protocol Amendment 2 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.18, Appendix 18: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis, Study Population; 4.2. Scientific Rationale for Study Design; 5. Study Population; 5.1. Inclusion Criteria, Criterion 4	Removed inclusion criterion specifying that hsCRP must be ≥0.3 mg/dL at screening. Enrollment of subjects with hsCRP of <0.1 mg/dL was capped at 10%.	To facilitate recruitment and to ensure a broader and more representative study population (many current patients with active disease have hsCRP <0.3 mg/dL). The 10% cap is to ensure representative distribution of disease activity in the study population.
1.1. Synopsis, Objectives and Endpoints, Overall Design, Study Population, Primary Endpoint Analysis; 2.1. Study Rationale; 2.3.1. Risks for Study Participation; 2.3.3. Benefit-Risk Assessment for Study Participation; 3. Objectives and Endpoints; 4.1. Overall Design; 4.2. Scientific Rationale for Study Design; 5.1. Inclusion Criteria, Criterion 7; 5.2. Exclusion Criteria, Criterion 26; 9.4.2. Primary Endpoint	Changed enrollment criteria to allow patients to have had inadequate response with up to 2 prior anti-tumor necrosis factor α (TNFα) treatments (instead of 1).	To facilitate recruitment and to ensure a broader and more representative study population; per current standard of care this group is part of the target population to treat.
1.3. Schedule of Activities (SoA), Safety Assessments, eC-SSRS	"Physician's global assessment of disease activity" replaced with "enthesitis assessments" to be consistent with the sequence of events as listed in the vendor manual ERT eCOA Product Guide - Janssen CNTO1959PSA2003_v2.0.	Text clarified to indicate correct assessments conducted before eC-SSRS at the screening visit.

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA), Safety Assessments, Vital Signs	Respiratory rate added to notes description.	Text added to remain consistent with Section 8.2.2.
4.2. Scientific Rationale for Study Design	Modified statement about the target study population.	Clarification due to the study now allowing up to 2 prior anti-TNFα therapies.
6.8.4. Biologic Agents, Cytotoxic Drugs, JAK Inhibitors, or Investigational Agents	Added a table (Table 3) showing the half-lives and washout periods of anti-TNFα agents.	To provide clarity of the washout period length.
8.1.1.9. Magnetic Resonance Imaging of the Hand and Foot	Added note regarding enrollment of participants with other circumstances that preclude MRI evaluations.	Additional language added to allow for evaluation of circumstances that preclude MRI evaluation other than participant safety concerns.
8.2.2. Vital Signs	Removal of the specification of "(oral)" from the temperature measurements.	To accommodate the widespread use of contactless thermal scanners which have become the de-facto standard of care in many hospitals and medical offices since the COVID-19 pandemic.
8.2.7. Suicidal Ideation and Behavior Risk Monitoring	Removed text "At the screening visit, the eC-SSRS should be completed as the first assessment after signing informed consent and before any other tests, procedures, or other consultations. For subsequent visits, the eC-SSRS should be completed after all PROs and before any other tests, procedures, or other consultations."	To remain consistent with the text in Section 1.3, Schedule of Activities (SoA), Safety Assessments, eC-SSRS notes.
10.17. Appendix 17, Definition of Intolerance, Inadequate Initial Response, and Loss of Response to anti-TNFα Therapy	Removed the word "Eligible" from "Eligible participants must satisfy criteria A and B." of the intolerance definition.	To avoid confusion and clarify not referencing eligibility criteria.
Title Page; 8.3.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events; 10.3.4. Data Protection	Expanded "countries" terminology to "countries/territories."	Aligned with the current Janssen template.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 2a, Multicenter, Randomized, Double-blind Study Evaluating the Efficacy and Safety of Subcutaneously Administered Guselkumab and Golimumab Combination Therapy in Participants with Active Psoriatic Arthritis

Guselkumab (CNTO1959) is a fully human monoclonal antibody (mAb) directed against the p19 subunit of interleukin (IL)-23. The binding of guselkumab to IL-23 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.

Golimumab (CNTO148) is a fully human anti-tumor necrosis factor alpha (TNFα) mAb that binds to TNFα with high affinity. This interaction prevents the binding of TNFα to its receptors, thereby inhibiting the biological activity of TNFα. The overall anti-TNFα activity results in limited production or activity of inflammatory cytokines, thereby providing therapeutic benefit in various chronic inflammatory disorders, including psoriatic arthritis (PsA).

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of guselkumab+golimumab combination treatment in participants with active PsA and inadequate response (IR) to prior anti-tumor necrosis factor α (TNFα) therapy(ies) by assessing clinical response compared with guselkumab monotherapy	• Proportion of participants who achieve minimal disease activity (MDA) at Week 24
Major Secondary	
• **Efficacy:** To evaluate the efficacy of guselkumab+golimumab combination treatment in participants with active PsA and IR to prior anti-TNFα therapy(ies) by assessing the reduction in signs and symptoms of PsA compared with guselkumab monotherapy	• Proportion of participants who achieve American College of Rheumatology (ACR) 50 at Week 24 • Proportion of participants who achieve MDA at Week 16 • Proportion of participants who achieve Psoriasis Area and Severity Index (PASI) 90/100 at Week 24 among the participants with ≥3% body surface area (BSA) psoriatic involvement and an Investigator's Global Assessment (IGA) score of ≥2 (mild) at baseline • Proportion of participants an IGA-psoriasis response (ie, an IGA-psoriasis score of 0 [cleared] or 1 [minimal] AND ≥2 grade reduction from baseline) at Week 24 among participants with ≥3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline • Change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 24 • Resolution of enthesitis at Week 24 among the participants with enthesitis at baseline

Objectives	Endpoints
	• Resolution of dactylitis at Week 24 among the participants with dactylitis at baseline • Change from baseline in Short Form Health Survey (SF-36) Physical Component Score (PCS) at Week 24
Other Secondary	
• **Safety:** To evaluate the safety of guselkumab+golimumab combination treatment in participants with active PsA compared with guselkumab monotherapy	• Frequency and type of adverse events (AEs), serious adverse events (SAEs), reasonably related AEs, AEs leading to discontinuation of study intervention, infections, and injection-site reactions
• **PK and Immunogenicity:** To evaluate the pharmacokinetics (PK) and immunogenicity of guselkumab+golimumab combination treatment in participants with active PsA compared with guselkumab monotherapy	• Serum concentrations of guselkumab and golimumab • Incidence of antibodies to guselkumab or golimumab
Other	
• **Efficacy:** To evaluate the efficacy of guselkumab+golimumab combination treatment in participants with active PsA and IR to prior anti-TNFα therapy(ies) by assessing the reduction in signs and symptoms of PsA compared with guselkumab monotherapy	• Proportion of participants who achieve MDA by visit over time through Week 24 • Proportion of participants who achieve ACR 20 and ACR 70 at Week 24 • ACR 20/50/70 response at Week 16 • Change from baseline in PASI score by visit over time through Week 24 among participants with ≥3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline • Change from baseline in enthesitis score (based on Leeds Enthesitis Index [LEI]) by visit over time through Week 24 among the participants with enthesitis at baseline • Change from baseline in enthesitis score (based on Spondyloarthritis Research Consortium of Canada [SPARCC]) by visit over time through Week 24 among the participants with enthesitis at baseline • Change from baseline in dactylitis score by visit over time through Week 24 among the participants with dactylitis at baseline • Change from baseline in (Patient-Reported Outcomes Measurement Information System 29) PROMIS-29 at Week 24
• **Safety:** To evaluate the safety of guselkumab+golimumab combination treatment in participants with active PsA compared with guselkumab monotherapy	• Suicidal ideation and behavior • Laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry) • Vitals signs over time

Objectives	Endpoints
Exploratory	
• **Pharmacodynamic:** To evaluate the pharmacodynamic effects of guselkumab+golimumab combination treatment in participants with active PsA compared with guselkumab monotherapy	• Change from baseline in serum T helper 17 (Th17) cytokines and select inflammatory cytokines and other proteins in the IL-23 and TNFα pathways by visit over time
• **MRI:** To explore changes in imaging-based assessment for enthesitis and other joint pathologies in PsA after administration of guselkumab+golimumab combination therapy for 24 weeks in TNF-IR participants with active PsA compared with guselkumab monotherapy	• Change from baseline in magnetic resonance imaging (MRI) measures in a subset of participants with enthesitis at baseline • Change from baseline in Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) at Week 24 among participants ≥1 PsAMRIS at baseline • Change from baseline in Heel Enthesitis Magnetic Resonance Imaging Scoring System (HEMRIS) at Week 24 among participants ≥1 HEMRIS at baseline • Correlation between the changes from baseline in PsAMRIS and clinical endpoints (MDA, ACR 50, Disease Activity in Psoriatic Arthritis [DAPSA], LEI) at Week 24 • Correlation between PsAMRIS and clinical endpoints (MDA, ACR 50, DAPSA, LEI) at baseline (Week 0) • Correlation between the changes from baseline in HEMRIS and clinical endpoints (MDA, ACR 50, LEI, SPARCC, DAPSA) at Week 24 • Correlation between HEMRIS and clinical endpoints (MDA, ACR 50, DAPSA, SPARCC, LEI) at baseline (Week 0)

Hypothesis

The primary hypothesis of this study is that combination therapy with guselkumab+golimumab is superior to guselkumab monotherapy as assessed by the proportion of participants who achieve an MDA response at Week 24.

OVERALL DESIGN

This is a Phase 2a randomized, double-blind, active-controlled, parallel-group, multicenter, proof-of-concept (POC) clinical study designed to evaluate the efficacy and safety of combination therapy with guselkumab+golimumab (guselkumab CCI CCI + golimumab CCI CCI versus guselkumab monotherapy (guselkumab CCI CCI + placebo 0.5 mL for golimumab CCI in adults with active PsA who have a previous history of IR to either 1 or 2 anti-TNFα therapy(ies) either due to primary nonresponse or loss of efficacy. Note that the combination therapy will be administered via drug-device combination products which each contain only 1 of the aforementioned interventions; guselkumab, golimumab, and placebo will all be administered via separate devices.

A stable dose of concomitant NSAIDs, oral corticosteroids (≤10 mg/day prednisone equivalent), and selected nonbiologic DMARDs (methotrexate [MTX], sulfasalazine [SSZ], hydroxychloroquine [HCQ], and leflunomide [LEF]) will be allowed but are not required.

A Data Monitoring Committee (DMC) will be commissioned for this study.

NUMBER OF PARTICIPANTS

A target of approximately 90 participants will be enrolled in this study.

INTERVENTION GROUPS AND DURATION

There will be a screening period of up to 6 weeks, a 24-week double-blind and active-controlled treatment period, and a safety follow-up at Week 36 (approximately 16 weeks after the last dose of study intervention administration).

Participants who satisfy all inclusion and exclusion criteria will be randomly assigned to 1 of 2 treatment groups in a 2:1 ratio:

- Group 1 (n=60): Participants will receive subcutaneous (CCI guselkumab CCI + golimumab CCI combination therapy at Weeks CCI
- Group 2 (n=30): Participants will receive C guselkumab CCI + placebo 0.5 mL for golimumab at Weeks CCI

Database locks (DBLs) are scheduled at Week 24 and End of Study (Week 36). The first DBL will occur when all randomized participants 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 participants have either completed their final safety visit (Week 36) or have terminated study participation prior Week 36 (referred to as Final DBL).

An interim analysis is planned when 60 participants reach Week 24, dependent on enrollment rate. Details will be defined in the protocol and statistical analysis plan (SAP).

This study has been designed in accordance with other related studies for alignment, including CNTO1959PSA3005, PSA3001, and PSA3003.

The end of study is considered as the last visit for the last participant in the study.

STUDY POPULATION

The target study population is participants with active PsA who had IR to either 1 or 2 anti-TNFα therapy(ies). This population is appropriate to provide relevant efficacy and safety information for the intended use of combination biologic therapy in PsA. The relative balance of musculoskeletal and cutaneous disease within a given participant needs to be considered when assessing adequate treatment. Therefore, a TNFα-inadequate responder (TNF-IR) population with ≥3 tender and swollen joints and active plaque psoriasis is planned to enrich the population for those more likely to experience inadequate control of disease with current advanced therapies.

EFFICACY EVALUATIONS

Efficacy evaluations chosen for this study are consistent with those utilized to evaluate other therapies for PsA. Investigator assessments and electronic patient-reported outcomes (ePROs) of efficacy include the following:

- Joint Assessments
- MDA
- ACR 20/50/70
- Physician's Global Assessment of Disease Activity

- DAPSA
- Dactylitis assessments (Dactylitis Severity Score)
- Enthesitis assessments (LEI and SPARCC)
- PASI
- BSA % Involvement of Psoriasis
- IGA-Psoriasis
- Health Assessment Questionnaire Disability Index (HAQ-DI)
- Patient's Assessment of Pain
- Patient's Global Assessment of Disease Activity (Arthritis and Psoriasis)
- Patient's Global Assessment of Disease Activity (Arthritis)
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- Short Form Health Survey (SF-36)
- Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue
- Patient-Reported Outcomes Measurement Information System 29 Profile (PROMIS-29 v2.1)
- MRI of the hand and foot

PHARMACOKINETIC EVALUATIONS

Venous blood samples will be collected for measurement of serum concentrations of guselkumab and golimumab at the timepoints shown in the Schedule of Activities (SoA).

IMMUNOGENICITY EVALUATIONS

Serum samples for detection of antibodies to guselkumab and antibodies to golimumab will be collected from all participants according to the SoA. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Samples for the analysis of pharmacodynamic biomarkers will be collected. Serum level of T helper (Th)-17 cytokines, including but not limited to IL-17A, IL-17F, and IL-22, and select inflammatory cytokines may be measured to assess the pharmacodynamic effect of guselkumab or golimumab.

Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to guselkumab or golimumab and/or PsA, where local regulations permit. Assessments will include the evaluation of relevant biomarkers in serum, plasma, whole blood, and tissue biopsies (when available) collected as specified in the SoA, where local regulations permit.

PHARMACOGENOMIC (DNA) EVALUATIONS

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary where local regulations permit. Participant participation in pharmacogenomic research is optional.

SAFETY EVALUATIONS

Key safety assessments include AEs, clinical laboratory tests (hematology and chemistry), vital signs, monitoring for injection-site and hypersensitivity reactions, suicidality assessment, and early detection of active tuberculosis (TB).

STATISTICAL METHODS

Sample Size Determination

The planned enrollment in this study is approximately 90 participants. The sample size selection was determined based on the primary endpoint of proportion of participants who achieve an MDA response at Week 24. With an assumed response rate of 45% in the combination regimen (guselkumab CCI CCI C and golimumab CCI CCI CCI and 20% in the guselkumab CCI CCI monotherapy regimen, sample size of 60 in the combination regimen and 30 in the monotherapy regimen would achieve above 80% power using the one-sided Fisher's Exact test at significance level 0.1.

Statistical Analyses

In general, descriptive statistics, such as mean, standard deviation, median, interquartile range, minimum and maximum for continuous variables; counts and percentages for discrete variables will be used to summarize most data.

For binary response efficacy endpoints, treatment comparisons will generally be performed using an Exact test or a Cochran-Mantel-Haenszel (CMH) test or logistic regression, if applicable. For continuous efficacy endpoints, treatment comparisons will be performed using an analysis of covariance (ANCOVA), a mixed model for repeated measures (MMRM), or a constrained longitudinal data analysis (cLDA).

Statistical testing will be performed by using a 1-sided test, with 10% type I error. No multiplicity adjustment will be applied to the primary endpoint.

Primary Endpoint Analysis

The primary endpoint to be analyzed for the primary analysis is the proportion of participants who achieved an MDA response at Week 24. This endpoint will be analyzed based on primary estimand defined by the following 5 components:

- Population
  - Participants who are ≥18 to ≤65 years of age (inclusive), with active PsA and previous history of IR to either 1 or 2 anti-TNFα therapy(ies) either due to primary nonresponse or loss of efficacy.
- Treatment
  - Combination regimen: guselkumab CCI C CCI and golimumab CCI C CCI
  - Monotherapy regimen: guselkumab CCI C CCI and placebo 0.5 mL for golimumab C CCI
- Variable
  - Binary response variable, where a responder is defined as a participant with an MDA response at Week 24.
  - Participants with intercurrent events 1, 2, and 3 (described below) are considered as nonresponder/treatment failures.
  - For participants with intercurrent event 4 (described below), the variable values after this ICE will not be utilized/used.
- Intercurrent Events (ICEs) and Strategies

1) Initiated protocol-prohibited medications/therapies for PsA
2) Initiation or increased the dose of nonbiologic DMARDs (MTX, SSZ, HCQ, LEF) or oral corticosteroid over baseline for PsA
3) Discontinued study intervention due to any reason except due to study conduct affected by Coronavirus Disease 2019 (COVID-19)
4) Discontinued study intervention due to study conduct affected by COVID-19

- Note 1: ICEs in categories 1, 2, and 3 will be considered as nonresponders/ treatment failure and plan to be handled with the **composite strategy** as reflected in the Variable definition, ie, the occurrence of ICEs prior to Week 24 will be considered as treatment failures and will be treated as nonresponder regardless of the observed MDA response status.
- Note 2: ICE 4 plan to be handled with **hypothetical strategy**, as if the COVID-19 pandemic did not occur, and therefore participant had not experienced with these ICEs. Observed data through Week 24 after meeting ICE 4 will not be used and be considered as missing at random (MAR) and will be imputed by using multiple imputation (MI).
- Note 3: If participants experience multiple ICEs, then an ICE in categories 1-3 will supersede an ICE in category 4.
- Note 4: The detailed definition for each of the ICE will be included in SAP.

- Population-level Summary
  - Difference in proportion of responders between combination regimen (guselkumab CCI C CCI and golimumab CCI C CCI and monotherapy regimen (guselkumab CCI C CCI

The treatment effect of the combination regimen (guselkumab CCI C CCI and golimumab CCI C CCI versus monotherapy (guselkumab CCI C CCI will be tested using the Chi-square or CMH test stratified by the randomization strata levels. The magnitude of the effect will be estimated by the difference in MDA response rate between the 2 treatment groups with a 95% confidence interval calculated based on Wald statistics. A sensitivity analysis will be performed using a re-randomization test to evaluate the impact of the dynamic randomization.

Additional sensitivity/supplemental analyses which vary how intercurrent events (eg, alternative estimand) 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 MDA at Week 24.

Subgroup Analyses

Subgroup analysis will be performed to evaluate consistency in the primary efficacy endpoint by demographic characteristic, baseline disease characteristic, and baseline medication. Interaction of the treatment groups and the subgroups will also be provided when a subgroup has at least 2 categories.

Secondary Endpoints

Analyses will compare between treatment groups. The methods of analysis and the approach to control the Type I error for multiplicity, as well as the data handling rules, will be provided in the SAP.

Safety Analyses

The following analyses of AEs will be included to assess the safety of participants:

- 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.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or an SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test (eg, hematology, clinical chemistry). Reference ranges, National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), and multiples of the upper limit of normal (ULN) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus post-intervention cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the laboratory abnormalities will be made. A listing of participants with any laboratory results outside the reference ranges will be provided, including a summary of laboratory values above the ULN. Listings of participants with any abnormal postbaseline laboratory values of NCI-CTCAE Grade ≥2 will also be provided.

Vital Signs

Vital signs including temperature, pulse/heart rate, and blood pressure (systolic and diastolic) will be summarized over time, using descriptive statistics and/or graphically. The percentage of participants with values beyond clinically important limits will be summarized.

Other Analyses

Pharmacokinetic Analyses

Serum guselkumab and/or golimumab concentrations over time will be summarized for each treatment group using descriptive statistics. All concentrations below the lowest quantifiable (BQL) sample concentration of the analysis system dataset will be treated as zero in the summary statistics.

Population PK modeling will be conducted when appropriate. 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/or golimumab, 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.

Immunogenicity Analyses

The incidence and titers of antibodies to guselkumab and/or golimumab will be summarized for all participants who receive at least 1 dose of guselkumab and/or golimumab and have appropriate samples for detection of antibodies to guselkumab and/or golimumab (ie, participants with at least 1 sample obtained after their first dose of guselkumab).

The incidence of neutralizing antibodies (NAbs) to guselkumab and/or golimumab will be summarized for participants who are positive for antibodies to guselkumab and/or golimumab and have samples evaluable for NAbs to guselkumab and/or golimumab.

Biomarker and Pharmacodynamic Analyses

Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information or insufficient number of samples are available for analyses. Any biomarker samples received by the contract vendor or sponsor after the cutoff date will not be analyzed, and therefore, excluded from the biomarker analysis.

The biomarker analyses will be used to understand PsA, characterize the effects of guselkumab or golimumab to identify pharmacodynamics (PD) markers and biomarkers relevant to treatment, and determine if these markers can predict response to guselkumab or golimumab. The biomarker analysis may include but are not limited to serum Th17 cytokines, inflammatory markers, whole blood RNA profile, and other categories of biomarkers potentially involved in the development and the progression of PsA.

Changes in biomarkers over time may be summarized by intervention group. Associations between baseline levels and changes from baseline in select markers and clinical response may be explored.

Results of biomarker analyses may be presented in a separate report.

Pharmacokinetic/Pharmacodynamic Analyses

If data permit, the relationships between serum concentrations of guselkumab and golimumab and efficacy and/or relevant PD endpoints may be analyzed graphically. If a relationship is observed, a suitable PK/PD model may be developed to describe the exposure-response relationship. Analyses results may be summarized in a separate technical report.

Pharmacogenomic Analyses

Genetic (deoxyribonucleic acid [DNA]) analyses may be conducted only in participants who sign the consent form to participate in the pharmacogenomic sampling. These analyses are considered exploratory. DNA samples may be used for research related to guselkumab or golimumab or PsA. They may also be used to develop tests/assays related to guselkumab or golimumab and PsA. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate) in relation to guselkumab or golimumab or PsA clinical endpoints.

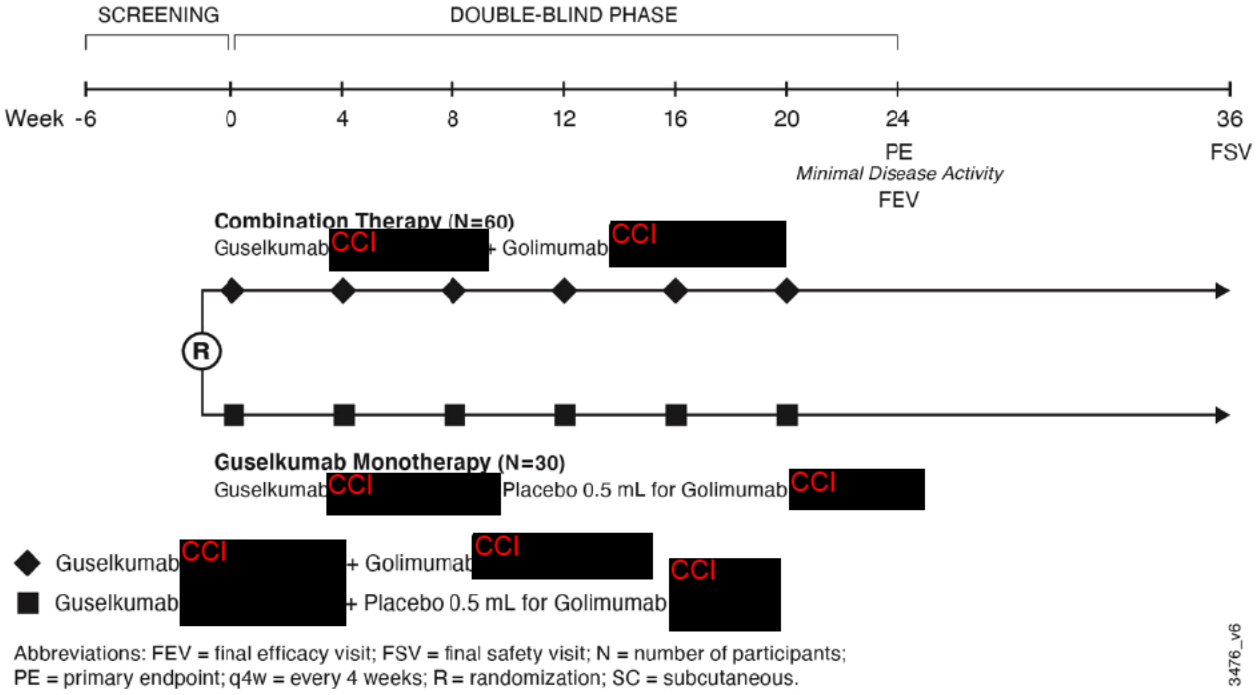
Results may be presented in a separate report.

Imaging Analyses

Post hoc analyses: Consistent with the exploratory nature of the MRI assessments to be conducted over the course of this study, refinements to the PsAMRIS and HEMRIS scoring systems or development of alternative image analysis algorithms may further improve the utility of MRI for characterizing peripheral joint pathology in PsA. As such, the sponsor and/or delegate may undertake post hoc analyses of the subject-level data acquired in this study. Any such analyses will not be included in the Clinical Study Report, but a separate supplemental report will be written to capture this work, if undertaken.

1.2. Schema

Figure 1: Schematic Overview of the Study



Abbreviations: FEV = final efficacy visit; FSV = final safety visit; N = number of participants; PE = primary endpoint; q4w = every 4 weeks; R = randomization; SC = subcutaneous.

1.3. Schedule of Activities (SoA)

Period	Screening	Active Treatment						Primary Efficacy Visit	Final Follow-up (16 weeks after last dose)	Early Termination	Notes
Week	**-6 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**36**		
Study Procedure	• The screening visit is to occur within 6 weeks before administration of study intervention 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 completes all laboratory tests at the first visit. The participant may then return for the remainder of the screening procedures only if the participant is eligible for the study as determined by the central laboratory test results. • The visit window is ±4 days (ie, plus or minus 4 days) for each clinic visit through Week 24. The visit window for Week 36 is +7 days. • All study procedures, evaluations, and assessments, including collection of blood samples, are to be completed before study intervention administration, unless otherwise specified. • If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: eC-SSRS, ePRO assessments, efficacy assessments, clinical safety laboratory assessments, PK, immunogenicity, and biomarkers. • Laboratory tests are listed in Section 10.2. • Participants who terminate study participation should complete an early termination visit (including MRI) approximately 16 weeks after their last study intervention administration.										
Screening/Administrative											
Informed consent (ICF)	X	Must be signed before first study-related activity.									
ICF for optional pharmacogenomic (DNA) sampling	X	To participate in the optional skin biopsy and/or DNA research components of this study, participants must sign the optional research ICFs indicating willingness to participate. Skin biopsies and blood samples for pharmacogenomic research will be collected only from participants who give informed consent.									
ICF for optional skin biopsy substudy	X										
Demographics/Baseline Characteristics	X										
Review medical history requirements	X										

Period	Screening	Active Treatment						Primary Efficacy Visit	Final Follow-up (16 weeks after last dose)	Early Termination	Notes
Week	**-6 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**36**		
Inclusion/exclusion criteria	X	X									Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documentation in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations. Check clinical status again before first dose of study intervention.
Prestudy therapy review for eligibility	X										
Preplanned surgery/ procedure(s)	X										
Study Intervention Administration											
Randomization		X									
Dispense/administer study intervention		X	X	X	X	X	X				Study intervention will be administered CCI C at the site through Week 20.
Efficacy Assessments											
Joint Assessments	X	X	X	X	X	X	X	X	X	X	
Physician's Global Assessment of Disease Activity		X	X	X	X	X	X	X	X	X	
Dactylitis assessments (DSS)		X	X	X	X	X	X	X	X	X	
Enthesitis assessments (LEI and SPARCC)	X	X	X	X	X	X	X	X	X	X	
PASI		X	X	X	X	X	X	X	X	X	
BSA % Involvement of Psoriasis		X	X	X	X	X	X	X	X	X	
IGA-Psoriasis		X	X	X	X	X	X	X	X	X	

Period	Screening	Active Treatment						Primary Efficacy Visit	Final Follow-up (16 weeks after last dose)	Early Termination	Notes
Week	**-6 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**36**		
HAQ-DI		X	X	X	X	X	X	X	X	X	All patient questionnaires should be completed after the eC-SSRS but before any other tests, procedures, or evaluations on the day of the visit for baseline and post-baseline visits. ePROs must be completed in the order they are shown in the SoA.
Patient's Assessment of Pain		X	X	X	X	X	X	X	X	X	
Patient's Global Assessment of Disease Activity (Arthritis and Psoriasis)		X	X	X	X	X	X	X	X	X	
Patient's Global Assessment of Disease Activity (Arthritis)		X	X	X	X	X	X	X	X	X	
BASDAI		X	X	X	X	X	X	X	X	X	
SF-36		X		X		X		X	X	X	
FACIT-Fatigue		X		X		X		X	X	X	
PROMIS-29 v2.1		X		X		X		X	X	X	
MRI of the hand and foot		X						X		X	The baseline MRI should be conducted during screening ≤14 days prior to the Week 0 visit, and the follow-up MRI should be completed ≤14 days prior to the Week 24 visit. MRI safety screening will be performed to assess participants against criteria that are contraindicated for MRI or GBCA administration (see Section 8.1.1.9).
Safety Assessments											
eC-SSRS	X	X	X	X	X	X	X	X	X	X	The eC-SSRS should be performed after the joint assessment and enthesitis assessments 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 participant completes prior to study intervention administration.
Physical examination (including skin)	X	X			X			X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	Vital signs include temperature, pulse/heart rate, respiratory rate, and blood pressure.
Weight		X									
Height		X									

Period	Screening	Active Treatment						Primary Efficacy Visit	Final Follow-up (16 weeks after last dose)	Early Termination	Notes
Week	**-6 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**36**		
12-lead ECG		X									12-lead ECG must be done prior to administration of study intervention.
Chest radiograph	X										Chest radiograph (posterior-anterior and lateral views, or per country regulations where applicable) may be obtained within 12 weeks before the Week 0 visit. Note: A chest CT scan is also acceptable in place of a chest radiograph.
TB evaluation	X	X	X	X	X	X	X	X	X	X	Participants must undergo TB evaluation (see Section 5.1) 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.
Pregnancy test	X	X	X	X	X	X	X	X	X	X	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 intervention.
Injection-site Reaction Evaluation		X	X	X	X	X	X				
Clinical Laboratory Tests											
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X	For fasting laboratory assessments, if the participant has not fasted before the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to provide the necessary sample(s) for the assessments.
QuantiFERON®-TB test	X										A tuberculin skin test is additionally required if the QuantiFERON-TB test is not approved/registered in the country in which this study is being conducted, with the exception noted in Inclusion Criterion 16.
Hepatitis B and C Serologies	X										
HIV antibody test	X										
Rheumatoid factor	X										This test is optional and will be performed only if needed to confirm whether CASPAR criteria are met.
hsCRP	X	X	X	X	X	X	X	X	X	X	

Period	Screening	Active Treatment						Primary Efficacy Visit	Final Follow-up (16 weeks after last dose)	Early Termination	Notes
Week	**-6 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**36**		
Lipid panel		X									
FSH	X										FSH is only required for female participants with amenorrhea for less than 12 months. Two FSH measurements are needed to confirm amenorrhea in these participants. This test should NOT be done for any female participant of childbearing potential or female participants with amenorrhea for at least 12 months.
eGFR	X						X				An eGFR must be calculated using the CKD-EPI method prior to performing the MRIs (see Section 8.1.1.9).
Clinical Pharmacology Assessments											
Serum guselkumab concentration		X	X	X	X	X	X	X	X	X	All blood samples must be collected before study intervention administration at visits when a study intervention administration is scheduled. Blood collected from 1 venipuncture will be divided into multiple aliquots of serum for the measurement of guselkumab and golimumab concentration, antibodies to guselkumab and antibodies to golimumab, and a back-up sample.
Serum golimumab concentration		X	X	X	X	X	X	X	X	X	
Antibodies to guselkumab		X	X		X			X	X	X	
Antibodies to golimumab		X	X		X			X	X	X	
Pharmacodynamics and Biomarkers											
Serum Biomarkers	X	X	X			X		X		X	
Plasma Biomarkers	X	X	X			X		X		X	
PBMC	X	X	X			X		X		X	PBMCs will be collected at sites where logistically feasible.
Whole blood (RNA)	X	X	X			X		X		X	
Skin biopsy (optional)		X						X		X	Optional skin biopsies may be collected at select sites, if feasible. Samples from a lesional and a non-lesional region will be collected at Week 0 and only a sample from a lesional region will be collected at Week 24.

Period	Screening	Active Treatment						Primary Efficacy Visit	Final Follow-up (16 weeks after last dose)	Early Termination	Notes
Week	**-6 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**36**		
Pharmacogenomics (DNA) Assessment											
Whole blood (DNA) (optional)		X									The pharmacogenomic (DNA) samples will be collected from a subset of participants who sign an optional genetics ICF. Blood samples for pharmacogenomic and epigenetic research will be collected only from participants who give informed consent for DNA research. The pharmacogenomic (DNA) sample should be collected at Week 0; however, if necessary, it may be collected at a later time point without constituting a protocol deviation.
Ongoing Participant Review											
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	

Abbreviations: BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BSA=body surface area; CASPAR=ClASsification criteria for Psoriatic Arthritis; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; CT=computed tomography; DNA=deoxyribonucleic acid; DSS=Dactylitis Severity Score; ECG=electrocardiogram; eC-SSRS=electronic Columbia-Suicide Severity Rating Scale; eGFR=estimated glomerular filtration rate; ePRO=electronic patient-reported outcome; FACIT-Fatigue=Functional Assessment of Chronic Illness Therapy-Fatigue; FSH=follicle-stimulating hormone; GBCA=gadolinium-based contrast agent; HAQ-DI=Disability Index of the Health Assessment Questionnaire; HIV=human immunodeficiency virus; hsCRP=high-sensitivity C-reactive protein; ICF=Informed Consent Form; IGA=Investigator's Global Assessment; LEI=Leeds Enthesitis Index; MRI=magnetic resonance imaging; PASI=Psoriatic Area and Severity Index; PBMC=peripheral blood mononuclear cell; PK= pharmacokinetics; PROMIS-29=Patient-Reported Outcomes Measurement Information System 29; CCI CCI [redacted] RNA=ribonucleic acid; CCI subcutaneous; SF-36=36-item Short Form Health Survey; SoA=Schedule of Activities; SPARCC=Spondyloarthritis Research Consortium of Canada; TB=tuberculosis.

2. INTRODUCTION

Guselkumab (CNTO1959) is a fully human monoclonal antibody (mAb) directed against the p19 subunit of interleukin (IL)-23. The binding of guselkumab to IL-23 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. A rapidly growing body of literature suggests that the IL-23/17 pathway contributes to the chronic inflammation underlying the pathophysiology of many immune-mediated diseases (Ouyang 2008; Tato 2006), including psoriasis, inflammatory bowel disease (IBD), ankylosing spondylitis (AS), and psoriatic arthritis (PsA). Susceptibility to psoriasis, PsA, and IBD has been shown to be associated with genetic polymorphisms in IL-23 and IL-23 receptor components (Bowes 2011; Duerr 2006; Liu 2008; Nair 2009; O'Rielly 2011).

The clinical development program for guselkumab includes completed, ongoing, or planned studies in adult participants with PsA, psoriasis, lupus nephritis, IBD, rheumatoid arthritis (RA), palmoplantar pustulosis, generalized pustular psoriasis, erythrodermic psoriasis, familial adenomatous polyposis, giant cell arteritis, celiac disease, and hidradenitis suppurativa as well as an ongoing study in pediatric participants with psoriasis.

Guselkumab (TREMFYA®) has been approved for the treatment of moderate to severe psoriasis and active PsA globally including Japan, Brazil, Australia, Taiwan, Ecuador, the European Union (EU), the United States (US), and Canada.

Golimumab (CNTO148) is a fully human anti-tumor necrosis factor alpha (TNFα) mAb that binds to TNFα with high affinity. This interaction prevents the binding of TNFα to its receptors, thereby inhibiting the biological activity of TNFα. The overall anti-TNFα activity results in limited production or activity of inflammatory cytokines, thereby providing therapeutic benefit in various chronic inflammatory disorders, including PsA.

Golimumab (SIMPONI®) 50 mg administered once a month has demonstrated an acceptable benefit/risk profile and is approved for subcutaneous (SC) administration in 105 countries globally, including the US, the EU, and Canada, for treatment of 1 or more of the following indications in adults: RA, PsA, AS, nonradiographic axial spondyloarthritis (nr-AxSpA), and ulcerative colitis (UC).

For the most comprehensive nonclinical and clinical information regarding guselkumab and golimumab, refer to the latest versions of the respective Investigator's Brochures (IBs).

The term "study intervention" throughout the protocol refers to the combination therapy (guselkumab+golimumab) and guselkumab monotherapy (guselkumab+placebo) administered as defined in Section 6.1, Study Interventions Administered. Note that the combination therapy will be administered via drug-device combination products which each contain only 1 of the aforementioned interventions; guselkumab, golimumab, and placebo will all be administered via separate devices (Section 6.1.1).

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.

The term "participant" throughout the protocol refers to the common term "subject."

2.1. Study Rationale

Psoriatic arthritis is a chronic inflammatory arthropathy of the peripheral and axial joints that affects approximately 0.02% to 0.25% of the general population (Setty 2007). In patients with psoriasis, the prevalence of PsA ranges from 6% to 48%; however, arthritis is not correlated with the extent of psoriasis skin disease (Gladman 2009). Psoriatic arthritis is a multi-faceted disease that impacts the joints, soft tissues, and skin, all of which affect quality of life. 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 the function of severely damaged joints. Psoriatic arthritis not only results in functional impairment and reduced quality of life but is also associated with premature mortality due to the increased prevalence of cardiovascular and respiratory disease compared with the general population (Ogdie 2015).

Current treatment options for PsA include conventional therapies such as nonsteroidal anti-inflammatory drugs (NSAIDs), intraarticular corticosteroid injections, low-dose systemic steroids, conventional synthetic disease-modifying antirheumatic drugs (DMARDs; eg, methotrexate [MTX], sulfasalazine [SSZ], and leflunomide [LEF]), and immunosuppressive drugs (eg, cyclosporine A, tacrolimus). Addition of biologic treatments for PsA, including TNFα inhibitors (etanercept, infliximab, adalimumab, golimumab, certolizumab), ustekinumab (an IL-12/IL-23 inhibitor), guselkumab (an IL-23 inhibitor), and secukinumab (an IL-17 inhibitor) significantly improved skin and joint responses in patients when used alone or on top of conventional DMARDS. Tofacitinib, a janus kinase (JAK) inhibitor is approved in several jurisdictions for the treatment of active PsA. However, in addition to the adverse events (AEs) associated with other biologic therapies, there are additional side effects associated with JAK inhibition including cytopenias, gastrointestinal perforations, and potential thromboembolic signal. Apremilast, an oral phosphodiesterase 4 inhibitor, is also available for the treatment of PsA; however, its use is associated with a lesser 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 to address the heterogeneous clinical manifestations of PsA and offer an improved benefit/risk profile for the individual patient. Most patients receiving biologics still desire greater relief from multiple domains such as joint pain, swelling, stiffness, and skin clearance. This is even more true for patients who have had an inadequate response (IR) to a prior biologic therapy. Patients with anti-TNFα experience were more likely to switch or discontinue their prescribed anti-TNFα agent and had a shorter time to discontinuation compared with anti-TNFα-naïve patients (Mease 2019). While there are 13 approved monotherapy options in PsA, only 4 of these therapies have extensively studied efficacy in anti-TNFα inadequate responder (TNF-IR) participants. It is important to note that the highest rate of minimal disease activity (MDA) seen across these

monotherapeutic agents in TNF-IR participants was ~25% (compared with ~35% for bio-naïve participants), leaving significant room for efficacy improvement. TNF-IR patients represent the greatest, current unmet need and are thus the targeted population for this study (Gladman 2017; McInnes 2015; Mease 2020; Nash 2017).

While both anti-IL-23 and anti-TNFα agents are established as monotherapy treatments for PsA, neither treatment achieves high rates of total disease control (ie, MDA) and remission. For example, only 14.8% of patients achieved MDA at 24 weeks compared with 3.1% patients on placebo in the Phase 3b Study PSA3003, which compared guselkumab with placebo in PsA patients with a history of IR or intolerance to anti-TNFα agents. However, there is scientific rationale that combination of the 2 classes of agents may lead to superior outcomes for TNF-IR patients. First, both IL-23 and TNFα play complementary roles and target different cell types in the PsA joint and regulate independent gene networks in psoriatic skin (Belasco 2015; Sherlock 2012; Zaba 2007; Zaba 2009). Furthermore, preclinical data (discussed in Section 2.2) demonstrated that the combinatorial inhibition of these 2 pathways not only targeted shared disease pathways but notably unique disease pathways suggesting a potential for synergistic efficacy. Taken all together, there are scientific data to support the notion that combination therapy may impact remission across multiple domains and arrive at total disease control.

Therefore, this study is being undertaken to evaluate the efficacy and safety of combining 2 approved therapies, golimumab and guselkumab, in PsA patients who have failed either 1 or 2 prior anti-TNFα biologic(s). For this study, total disease control will be measured by MDA assessment (see Section 8.1.1.6). Dose selection for this proof-of-concept (POC) study is driven by the highly stringent efficacy endpoint and refractory study population, despite differing from the currently approved labeling (see Section 4.3). Overall, this study will help define the benefit/risk profile and determine whether it is acceptable to move combination therapy into further development.

2.2. Background

Although mechanistic data from the joint in PsA is very limited owing to difficulty obtaining biopsies of this tissue, data are available from the genetically and clinically linked condition, IBD. Pathophysiological insights in IBD and other diseases linked with PsA (such as psoriasis itself) are likely to be informative for the biology of PsA because of shared or overlapping mechanisms. IBD is strongly associated with enthesiopathic arthritis such as PsA and enthesopathy is also associated with subclinical intestinal inflammation including IL-23 production (Ciccia 2009). Intestinal dysbiosis not only occurs in IBD but also in PsA (Scher 2015). Moreover, these conditions have shared genetic susceptibility factors in IL-23 pathway genes such as IL-23R (Brown 2020). Taken together, these observations support cautious use of findings in IBD to inform considerations around PsA.

2.2.1. Nonclinical Studies

While the sponsor has not performed combination toxicology studies, anti-TNFα and anti-IL-23 antibodies have been administered concomitantly to mice in a nonclinical model of colitis to evaluate the efficacy and molecular impact of the combination therapy on intestinal inflammation.

Multiple dose combinations of anti-TNFα (CNTO5048) and anti-IL-23 (CNTO3723) antibodies have been tested in the agonist anti-CD40 murine model of innate colitis. In this acute model of intestinal inflammation, mice received a single dose of antibodies (Day -1) and were sacrificed 7 days after the induction of inflammation (Day 0). Mice were weighed daily to monitor disease-associated wasting and colon tissue collected to assess intestinal inflammation. In the highest dose combination of 500 μg anti-TNFα and 500 μg anti-IL-23, no animals died, and all animals showed improvement in weight and histological inflammation scores compared with diseased control-treated (phosphate buffered saline or isotype injected) animals.

In summary, combination of anti-TNFα and anti-IL-23 antibodies administered to mice in a nonclinical model of colitis showed improvement in weight and histological inflammation scores in the absence of any acute toxicity. Neither guselkumab nor golimumab presented any apparent overlapping toxicities detectable in nonclinical toxicology studies that could be expected to be potentiated when administered in combination, and the probability of pharmacokinetics (PK) or pharmacodynamics (PD) interaction in the combination is considered low.

To determine the molecular impact of each therapeutic on intestinal inflammation, transcriptional signatures were generated and a human IBD gene network was established from intestinal biopsies from the CERTIFI (Crohn's Evaluation of Response to Ustekinumab Anti-Interleukin-12/23 for Induction) Crohn's disease study as a platform for bridging the preclinical data to human disease. Colonic gene signatures of anti-TNFα or anti-IL-23p19 antibody treatment in the CD40 antibody-induced colitis model were generated, and the human orthologues of these genes were mapped onto the human IBD network to generate treatment subnetworks. Analyses of colonic gene signatures showed that the treatment subnetworks for anti-TNFα and anti-IL-23p19 were enriched for myeloid and intestinal epithelial genes, respectively. A unique subnetwork for the combination treatment was enriched in fibroblasts and extracellular matrix organization, cell types, and pathways involved in wound repair and mucosal healing. These results suggest that combination therapy with anti-TNFα and anti-IL-23p19 improves efficacy by targeting shared and unique disease pathways.

Furthermore, combination therapy of anti-TNFα and anti-IL-23 antibodies administered to mice in a nonclinical model of non-enthesiopathic arthritis was conducted. In the collagen-induced arthritis mouse model of arthritis, the anti-TNFα antibody was efficacious but the effect was not sustained; the anti-IL-23 antibody demonstrated no activity. When the antibodies were combined in this model, the result was superior sustained efficacy over either monotherapy.

A comprehensive overview of nonclinical data is presented in Section 3 of the guselkumab and golimumab IBs.

2.2.2. Clinical Studies

For the most comprehensive clinical information regarding guselkumab and golimumab, refer to Section 4 of the latest versions of the respective guselkumab and golimumab IBs.

2.2.2.1. Current Status of Guselkumab Development

The clinical development program of guselkumab for the treatment of active PsA includes a completed global Phase 2 study (CNTO1959PSA2001 [hereafter referred to as PSA2001]) and 3 completed global Phase 3 studies (CNTO1959PSA3001 [hereafter referred to as PSA3001], CNTO1959PSA3002 [hereafter referred to as PSA3002], and CNTO1959PSA3003 [hereafter referred to as PSA3003]).

Human Pharmacokinetics and Immunogenicity

Guselkumab generally exhibited linear PK in the completed clinical studies to date. The systemic exposure (maximum observed concentration [C_{max}] and area under the curve [AUC]) of guselkumab increased in an approximately dose proportional manner after a single intravenous (IV) administration at doses ranging from 0.03 mg/kg to 10 mg/kg or after a single SC administration at doses ranging from 10 mg to 300 mg. Following a single 100 mg SC injection in healthy participants, guselkumab reached a mean (±standard deviation [SD]) C_{max} of 8.09±3.68 µg/mL by approximately 5.5 days. The mean half-life ($T_{1/2}$) of guselkumab was approximately 15 to 18 days in participants with plaque psoriasis or PsA. The mean absolute bioavailability (F%) of guselkumab following a single 100 mg SC administration was estimated to be approximately 47.6% to 54.9%. Pharmacokinetics of guselkumab was generally comparable across studies and study populations.

Following CC administration of guselkumab, trough serum guselkumab concentrations reached steady state by Week 20 for the CCI at Weeks 0 and 4 then every 8 weeks (q8w) group and by Week 12 for the CCI CCI (CCI group. Across the Phase 3 PsA studies, the median steady-state trough serum guselkumab concentrations following CC administration of guselkumab were 1.01 µg/mL in the CCI q8w group and 3.50 µg/mL in the CCI CCI group. The median steady-state trough serum guselkumab concentrations were approximately 3- to 5-fold higher in the CCI CCI group compared with those in the guselkumab CCI q8w group.

The overall incidence of antibodies to guselkumab was low in both participants with PsA and participants with psoriasis. In pooled data from Phase 2 and 3 studies in participants with psoriasis and PsA, the overall incidence of antibodies to guselkumab was 5% up to 52 weeks of treatment. In Phase 3 PsA studies, the incidence of antibodies to guselkumab through Week 52 was comparable between the 2 dose groups (CCI q8w: 4.8%; CCI CCI 4.6%).

Efficacy/Safety

Guselkumab has been approved for the treatment of adult patients with chronic moderate to severe plaque psoriasis in the US, the EU, and other countries worldwide. The approved dose of guselkumab for the treatment of plaque psoriasis is 100 mg administered SC at Week 0, Week 4, and q8w thereafter. This was primarily based on 2 large, Phase 3, placebo-controlled clinical Studies CNTO1959PSO3001 and CNTO1959PSO3002 in participants with moderate to severe plaque psoriasis.

The clinical development program for guselkumab in the treatment of active PsA includes a completed Phase 2 global study (PSA2001) and 3 completed Phase 3 global studies: PSA3001, PSA3002, and PSA3003.

For studies PSA3001 and PSA3002, results obtained through Week 24 demonstrated favorable efficacy and safety profiles for both the guselkumab SC 100 mg q4w and q8w dose regimens for the treatment of active PsA. These results have led to the approval of guselkumab to treat adult patients with active PsA in the US, the EU, and other global markets.

Results from the Phase 3b Study CNTO1959PSA3003 study in which participants with PsA who had an IR to up to 2 prior anti-TNFα therapies were treated with guselkumab 100 mg q8w demonstrated superiority of guselkumab over placebo for signs and symptoms of the joints and skin psoriasis, improved physical function, and improvement in the physical component of health-related quality of life.

2.2.2.2. Current Status of Golimumab Development

The clinical development program for golimumab in the treatment of active PsA includes 2 completed Phase 3 studies: Study C0524T08 and CNTO148PSA3001. Golimumab has been approved for the treatment of adult patients with the following indications: RA, PsA, AS, nr-AxSpA, and UC.

Human Pharmacokinetics and Immunogenicity

In all studies to date, golimumab has demonstrated approximately linear PK when administered IV over a dose range of 0.1 mg/kg to 10 mg/kg or SC over a dose range of 50 mg to 400 mg. Median time to reach maximum serum golimumab concentration following SC administration of golimumab ranged from 2 to 6 days. A median terminal $T_{1/2}$ of approximately 2 weeks was observed following both IV (100 mg) and SC administration of golimumab (50 mg or 100 mg). The overall absolute mean SC bioavailability of golimumab was estimated to be 51%, regardless of injection site. No gender-related PK differences were observed with golimumab after correction for weight.

In a completed Phase 3 study in participants with PsA (C0524T08), median trough serum golimumab concentrations following 50 mg q4w or 100 mg q4w SC administration of golimumab generally reached steady state by Week 12. The median steady state trough serum concentration at 50 mg q4w were 0.46 µg/mL and 0.33 µg/mL in participants with and without baseline MTX use. The apparent total systemic clearance was lower in PsA participants who received concomitant MTX compared with those who did not receive concomitant MTX.

Following SC administration in participants with RA, PsA, or AS, antibodies to golimumab, nearly all neutralizing in vitro, were detected by the enzyme immunoassay method in 5% of golimumab-treated participants through Week 52. Similar rates were shown across rheumatologic indications. Treatment with concomitant MTX resulted in a lower proportion of participants with antibodies to golimumab than participants receiving SC golimumab without MTX (approximately 3% versus 8%, respectively).

Efficacy/Safety

In C0524T08, 405 participants with PsA despite current or previous DMARD or NSAID therapy were randomized to receive SC placebo, golimumab 50 mg q4w, or golimumab 100 mg q4w. All participants began receiving golimumab at Week 24. Participants were followed through Week 256 for efficacy and Week 268 for safety. The coprimary endpoints (the proportion of participants achieving an American College of Rheumatology (ACR) 20 response at Week 14, and the change from baseline in total radiographic scores of the hands and feet at Week 24) and all major secondary efficacy endpoints were met. Clinical improvements in PsA participants previously seen at Week 24 were maintained through Week 256.

In another completed Phase 3 study CNTO148PSA3001, 480 participants with active PsA were randomized to receive IV placebo or golimumab 2 mg/kg infusions at Weeks 0, 4, and q8w with placebo participants crossing over to active treatment at Week 24. Participants were followed through Week 52 for efficacy and through Week 60 for safety. The primary endpoint of this study was the proportion of participants who achieved an ACR 20 response at Week 14. All primary, major secondary, and other statistically-controlled efficacy endpoints were met. At Week 24, the golimumab group had significantly less radiographic damage than placebo, as measured by the mean change from baseline in total modified van der Heijde Modified Sharp score.

2.2.2.3. Current Status of Combination Treatment (Guselkumab+Golimumab) Development

The CNTO1959UCO2002 (VEGA) study is currently ongoing in participants with UC to assess combination therapy with guselkumab+golimumab versus either agent alone for a 12-week induction period followed by an additional 24-week monotherapy period. The data safety monitoring board (DSMB) has not recommended any changes to the protocol based on its review of unblinded safety data. Additionally, review of blinded data from the clinically-complete 12-week induction phase has not identified unexpected patterns in the reported AEs.

2.3. Benefit-Risk Assessment

Given the well-established efficacy and safety of each monotherapy in PsA (Section 2.1), the high unmet medical need in the TNF-IR population, and the expected clinical benefit of combination therapy, this Phase 2a POC clinical study will evaluate the efficacy and safety of short-term combination therapy with guselkumab and golimumab compared with guselkumab alone in the treatment of participants with PsA. The safety profiles of guselkumab and golimumab are well characterized based on data from large clinical programs leading to their respective approvals and accumulated postmarketing experience. Detailed information about the known and expected benefits and risks of guselkumab or golimumab may be found in their respective IBs. Based on the available data and the safety measures in this protocol, the overall benefit/risk assessment for participation in this study is deemed acceptable.

2.3.1. Risks for Study Participation

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Worsening of PsA	Efficacy of golimumab in PsA patients with IR to prior anti-TNFα therapy(ies) has not been investigated. Observational study data suggest that cycling to another TNFα inhibitor may be associated with decreased efficacy, particularly in patients who switched due to inadequate therapeutic response.	• Participants assigned to golimumab therapy will also receive guselkumab (combination arm). • During the study, participants will be permitted to continue treatment of PsA with certain standard-of-care medications (Section 6.8). • Participants will discontinue study intervention if it is not in their best interest or if they need to initiate protocol-prohibited medications (Sections 6.8 and 7.1).
Risks Due to Study Interventions (Guselkumab and Golimumab)		
Serious infections and reactivation of latent infections	Available animal and human data suggest that blockade of IL-23 may be associated with an increased infection risk. Infections have been identified as adverse reactions of guselkumab, including respiratory infections, herpes simplex, tinea infections, and gastroenteritis. The anti-TNFα class has been extensively studied and has a well-defined safety profile. Known risks for anti-TNFα agents such as golimumab include infections, including serious infections, tuberculosis (TB), and opportunistic infections. Concomitant use of other immunosuppressants (MTX and corticosteroids) with dual biologic therapy may be associated with increased infection risk.	• Participants with a history of, or ongoing, chronic or recurrent infectious disease, including human immunodeficiency virus (HIV), Hepatitis B or C virus (HBV, HCV), will be excluded from the study. Similarly, participants with evidence of active or untreated latent TB will be excluded from the study (Section 5.2). • Participants who have received a live viral or bacterial vaccination within 16 weeks of baseline will be excluded from the study. In addition, participants must agree not to receive a live viral or live bacterial vaccination during the study and for 16 weeks after receiving the last dose of study intervention (Section 5.2). • Participants will be instructed to seek medical attention if they develop signs or symptoms suggestive of an infection, and investigators are instructed in the protocol to monitor for signs or symptoms of infections, including TB (Section 5.2). • Discontinuation of a participant's study intervention must be strongly considered if the participant develops a serious infection, including but not

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
		limited to sepsis or pneumonia. In addition, any serious infection should be discussed with the medical monitor or designee, and study intervention should be withheld until the clinical assessment is complete (Section 8.2.11). • To reduce the risks associated with immunosuppression, concomitant immunosuppressants have been limited (eg, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, or tacrolimus) must have been discontinued for at least 4 weeks before the first administration of study intervention. Concurrent use of MTX and oral corticosteroids (≤10 mg/day of prednisone, Section 6.8) is not allowed. • Participants older than 65 years of age are excluded from the study due to immunosenescence, which is defined as the state of dysregulated immune function that contributes to an increased susceptibility of the elderly to infection.

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Hypersensitivity reactions, including serious hypersensitivity reactions and anaphylaxis	Serious hypersensitivity reactions including anaphylaxis have been reported in postmarketing experience with guselkumab in psoriasis patients. Hypersensitivity, including anaphylaxis, urticaria, and rash have been identified as adverse drug reactions for guselkumab and golimumab.	• Participants with known allergy, hypersensitivity, or intolerance to guselkumab and/or golimumab or their excipients will be excluded from the study (Section 5.2). • Sites are instructed that before any administration of study intervention, appropriately trained personnel and medications (eg, injectable epinephrine) must be available to treat hypersensitivity reactions, including anaphylaxis. In addition, all participants must be observed carefully for signs and symptoms of a hypersensitivity reaction (eg, urticaria, pruritis, angioedema, wheezing, dyspnea, or hypotension) (Section 8.2.10). • Any participant who develops a serious hypersensitivity reaction such as anaphylaxis must discontinue study intervention (Section 7.1).
Malignancy	Malignancy is considered a potential risk based on pharmacological class risk for all immunosuppressants. Lymphoma and leukemia are known risks of golimumab. The currently available data do not show an increased risk for malignancies in patients treated with guselkumab. However, a risk of malignancy cannot be excluded.	• Those participants who currently have a malignancy or have a history of malignancy within 5 years prior to screening (with exceptions noted in Section 5.2) will be excluded from the study. Additionally, participants who have 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 will be excluded from the study (Section 5.2). • During the conduct of the study, participants will undergo regular clinical monitoring including routine safety laboratory assessments to evaluate any changes in health status that may indicate a possible malignancy. • Participants who develop a malignancy during the study (with the exception of no more than 2 localized basal cell skin

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
		cancers that are treated with no evidence of recurrence or residual disease) will be discontinued from study intervention (Section 7.1). • To reduce risk of malignancy associated with immunosuppressants, concomitant immunosuppressants have been limited to only MTX or oral corticosteroid (≤10 mg/day of prednisone) (Section 6.8). Immunosuppressants (eg, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, or tacrolimus) must be discontinued for at least 4 weeks before the first administration of study intervention.
Liver injury	Transaminase increases have been identified as an adverse reaction of guselkumab. In PsA studies transaminase increases were observed with a higher incidence with a maintenance dose of 100 mg q4w compared with 100 mg q8w. A case of possible drug-induced liver injury (DILI) was reported in a clinical study of guselkumab for treatment of Crohn's disease, in a participant who received 1200 mg IV q4w induction therapy (see guselkumab IB, Section 4.4.6 Inflammatory Bowel Disease, for details). For golimumab, in the controlled period of RA and PsA pivotal trials, mild ALT elevations (>1 and <3×upper limit of normal [ULN]) occurred in similar proportions of golimumab-treated and control patients; in the AS and nr-AxSpA studies, more golimumab-treated patients than control patients had mild ALT elevations. In the controlled period of RA and AS pivotal trials, ALT elevations ≥5×ULN were uncommon and seen in more golimumab-treated patients	• During the conduct of the study, liver function tests will be monitored at regular intervals in accordance with regulatory guidance (FDA 2009). In addition, there is no induction dose in this study. • Participants with marked liver enzyme elevations or symptoms or signs of liver dysfunction (eg, jaundice), should undergo a thorough investigation for possible causes of liver injury. A participant must have their study intervention discontinued if the participant has severe liver test abnormalities that are not transient and are not explained by other etiologies (Section 7.1.1).

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
	than control patients. This trend was not observed in the PsA population; no cases were reported in the nr-AxSpA study.	
Risks Due to Study Procedures		
Radiation	A chest x-ray will be performed at screening if the participant has not had a chest x-ray within 12 weeks prior to the first administration of study intervention. The exposure from 1 standard chest x-ray is 0.1 mSV, comparable to 10 days of exposure to natural background radiation. (www.acr.org)	• Exposure to radiation through radiographs is kept to a minimum by not requiring a chest X-ray to be performed at screening if one is available from within 12 weeks prior to the first administration of study intervention. • Pregnancy testing at screening is included in order to minimize exposure and avoid study-related procedures such as x-rays.
Risk associated with magnetic resonance imaging (MRI)	For MRIs, there is a risk for allergic reactions to the contrast dye. Participants who are allergic to or sensitive to medications, contrast dye, should notify the radiologist or technologist. Magnetic fields may cause injury to individuals with metallic implants or paramagnetic objects contained within their body	• MRI safety screening (metallic implants or devices, contrast allergy, renal disease, claustrophobia) will be conducted during the screening period.
Risks associated with skin biopsy (optional substudy)	Mild bleeding, pain, discomfort, and infection may occur as part of biopsy procedure.	Trained and experienced physicians will be performing the procedure during this study.

2.3.2. Benefits for Study Participation

All participants will have the potential benefit of receiving active treatment in this study as there is no placebo treatment arm. The safety profiles of guselkumab and golimumab are well characterized due to large clinical programs leading to their respective approvals (eg, psoriasis and PsA for guselkumab and RA, PsA, AS, nr-AxSpA, and UC for golimumab).

2.3.3. Benefit-Risk Assessment for Study Participation

Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with guselkumab or golimumab are justified by the anticipated benefits that may be afforded to participants with PsA who have a history of IR to prior anti-TNFα therapy(ies).

Based on the available data and the safety measures in this protocol, the overall benefit/risk assessment for using the selected dose regimens for combination therapy

(guselkumab+golimumab) and guselkumab monotherapy in this study is deemed acceptable based on the below considerations. For guselkumab, the main risk, as described in Section 5 of the guselkumab IB, is infection. Other potential safety concerns, also described in greater detail in the guselkumab IB, are based on guselkumab being an immunomodulatory mAb and include malignancy and hypersensitivity. The approved dose and regimen of guselkumab 100 mg q8w was well-tolerated in participants with moderate to severe plaque psoriasis through 5 years of treatment and no new safety concerns were identified in the open-label treatment period of the study (Griffiths 2020). The safety profile of guselkumab in participants with PsA treated with the approved doses and regimens of guselkumab 100 mg q4w or q8w for up to 2 years is generally consistent with that demonstrated in the psoriasis indication; an increased incidence of liver enzyme elevations was observed in the guselkumab q4w group (Clinical Study Report 112-Week CNTO1959PSA3002). The proposed guselkumab dose for this study has been shown to have favorable efficacy in Phase 3 PsA studies (see Section 4.3). Additionally, in the EU this dose is approved for patients at high risk of joint damage according to clinical judgment. This POC study will evaluate for superior efficacy of combination therapy that goes well beyond guselkumab monotherapy using a high bar efficacy endpoint (MDA) to ultimately define the benefit/risk in a refractory patient population (TNF-IR patients), thus the guselkumab CCI CCI dose was selected for this study. Additional details about the dose selection rationale for guselkumab are provided in Section 4.3.

The anti-TNFα class of agents has been extensively studied and has a well-defined safety profile. Known risks for anti-TNFα agents such as golimumab include infections, including serious infections, TB, and opportunistic infections. Other known risks include, but are not limited to, lymphoma, leukemia, lupus-like syndrome, and demyelinating disorders (SIMPONI USPI, SmPC). The dose regimen of golimumab in this study is comparable to the currently approved dose (once a month versus q4w) and is consistent with the dose regimens evaluated in Phase 3 studies (eg, CNTO148PSA3001).

Given the risk of serious infections associated with the anti-TNFα class and combination biologic use, the eligibility criteria and screening assessments of this study are designed to exclude participants with chronic/active infections or a predisposition to infections. Measures to ensure the early detection of TB, such as chest radiograph and QuantiFERON®-TB test, are outlined in Section 8.2.12, and participants with a history of latent or active TB are excluded from this study. To reduce the risks associated with immunosuppression, systemic immunosuppressants (eg, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, or tacrolimus) must be discontinued for at least 4 weeks before the first administration of study intervention. Additionally, participants taking more than 10 mg of prednisone or equivalent are excluded from the study, as well as concurrent use of MTX and oral corticosteroids. Participants will be closely monitored for signs and symptoms of infection during and after treatment. Safety evaluations will include AEs, clinical laboratory tests (hematology and chemistry), vital signs and physical examinations, a baseline electrocardiogram (ECG), hypersensitivity reactions, AEs temporally associated with infusion, injection-site reactions, and early detection of active TB. The safety follow-up period for this study is 16 weeks after the last dose of study intervention.

Based on the prospect of clinical efficacy with the study interventions being evaluated, the well characterized safety profiles of guselkumab and golimumab, and the safety measures in place, the overall benefit/risk of participation in this clinical study is acceptable.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of guselkumab+golimumab combination treatment in participants with active PsA and IR to prior anti-TNFα therapy(ies) by assessing clinical response compared with guselkumab monotherapy	• Proportion of participants who achieve MDA at Week 24
Major Secondary	
• **Efficacy:** To evaluate the efficacy of guselkumab+golimumab combination treatment in participants with active PsA and IR to prior anti-TNFα therapy(ies) by assessing the reduction in signs and symptoms of PsA compared with guselkumab monotherapy	• Proportion of participants who achieve ACR 50 at Week 24 • Proportion of participants who achieve MDA at Week 16 • Proportion of participants who achieve Psoriasis Area and Severity Index (PASI) 90/100 at Week 24 among the participants with ≥3% body surface area (BSA) psoriatic involvement and an Investigator Global Assessment (IGA) score of ≥2 (mild) at baseline • Proportion of participants with an IGA-psoriasis response (ie, an IGA-psoriasis score of 0 [cleared] or 1 [minimal] AND ≥2 grade reduction from baseline) at Week 24 among participants with ≥3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline • Change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 24 • Resolution of enthesitis at Week 24 among the participants with enthesitis at baseline • Resolution of dactylitis at Week 24 among the participants with dactylitis at baseline • Change from baseline in Short Form Health Survey (SF-36) Physical Component Score (PCS) at Week 24

Objectives	Endpoints
Other Secondary	
• **Safety:** To evaluate the safety of guselkumab+golimumab combination treatment in participants with active PsA compared with guselkumab monotherapy	• Frequency and type of AEs, serious adverse events (SAEs), reasonably related AEs, AEs leading to discontinuation of study intervention, infections, and injection-site reactions
• **PK and Immunogenicity:** To evaluate the PK and immunogenicity of guselkumab+golimumab combination treatment in participants with active PsA compared with guselkumab monotherapy	• Serum concentrations of guselkumab and golimumab • Incidence of antibodies to guselkumab or golimumab
Other	
• **Efficacy:** To evaluate the efficacy of guselkumab+golimumab combination treatment in participants with active PsA and IR to prior anti-TNFα therapy(ies) by assessing the reduction in signs and symptoms of PsA compared with guselkumab monotherapy	• Proportion of participants who achieve MDA by visit over time through Week 24 • Proportion of participants who achieve ACR 20 and ACR 70 at Week 24 • ACR 20/50/70 response at Week 16 • Change from baseline in PASI score by visit over time through Week 24 among participants with ≥3% BSA psoriatic involvement and an IGA score of ≥2 (mild) at baseline • Change from baseline in enthesitis score (based on Leeds Enthesitis Index [LEI]) by visit over time through Week 24 among the participants with enthesitis at baseline • Change from baseline in enthesitis score (based on Spondyloarthritis Research Consortium of Canada [SPARCC]) by visit over time through Week 24 among the participants with enthesitis at baseline • Change from baseline in dactylitis score by visit over time through Week 24 among the participants with dactylitis at baseline • Change from baseline in Patient-Reported Outcomes Measurement Information System 29 (PROMIS-29 v2.1) at Week 24
• **Safety:** To evaluate the safety of guselkumab+golimumab combination treatment in participants with active PsA compared with guselkumab monotherapy	• Suicidal ideation and behavior • Laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry) • Vitals signs over time

Objectives	Endpoints
Exploratory	
• **Pharmacodynamic:** To evaluate the pharmacodynamic effects of guselkumab+golimumab combination treatment in participants with active PsA compared with guselkumab monotherapy	• Change from baseline in serum T helper 17 (Th17) cytokines and select inflammatory cytokines and other proteins in the IL-23 and TNFα pathways by visit over time
• **MRI:** To explore changes in imaging-based assessment for enthesitis and other joint pathologies in PsA after administration of guselkumab+golimumab combination therapy for 24 weeks in TNF-IR participants with active PsA compared with guselkumab monotherapy	• Change from baseline in MRI measures in a subset of participants with enthesitis at baseline • Change from baseline in Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) at Week 24 among participants ≥1 PsAMRIS at baseline • Change from baseline in Heel Enthesitis Magnetic Resonance Imaging Scoring System (HEMRIS) at Week 24 among participants ≥1 HEMRIS at baseline • Correlation between the changes from baseline in PsAMRIS and clinical endpoints (MDA, ACR 50, Disease Activity in Psoriatic Arthritis [DAPSA], LEI) at Week 24 • Correlation between PsAMRIS and clinical endpoints (MDA, ACR 50, DAPSA, LEI) at baseline (Week 0) • Correlation between the changes from baseline in HEMRIS and clinical endpoints (MDA, ACR 50, LEI, SPARCC, DAPSA) at Week 24 • Correlation between HEMRIS and clinical endpoints (MDA, ACR 50, DAPSA, SPARCC, LEI) at baseline (Week 0)

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

The primary hypothesis of this study is that combination therapy with guselkumab+golimumab is superior to guselkumab monotherapy as assessed by the proportion of participants who achieve an MDA response at Week 24.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2a randomized, double-blind, active-controlled, parallel-group, multicenter, POC clinical study designed to evaluate the efficacy and safety of combination therapy with guselkumab+golimumab (guselkumab CCI CCI + golimumab CCI CCI versus guselkumab monotherapy (guselkumab CCI CCI + placebo 0.5 mL for golimumab CCI in adults with active PsA who have a previous history of IR to either 1 or 2 anti-TNFα therapy(ies) either due to primary nonresponse or loss of efficacy. Note that the combination therapy will be administered via drug-device combination products which each contain only 1 of the aforementioned interventions; guselkumab, golimumab, and placebo will all be administered via separate devices (Section 6.1.1).

A stable dose of concomitant NSAIDs, oral corticosteroids (≤10 mg/day prednisone equivalent), and selected nonbiologic DMARDs (MTX, SSZ, hydroxychloroquine [HCQ], LEF) will be allowed but are not required.

A target of approximately 90 participants will be enrolled in this study.

There will be a screening period of up to 6 weeks, a 24-week double-blind and active-controlled treatment period, and a safety follow-up at Week 36 (approximately 16 weeks after the last dose of study intervention administration).

Participants who satisfy all inclusion and exclusion criteria will be randomly assigned to 1 of 2 treatment groups in a 2:1 ratio:

- Group 1 (n=60): Participants will receive CC guselkumab CCI + golimumab CCI combination therapy at Weeks CCI
- Group 2 (n=30): Participants will receive CC guselkumab CCI + placebo 0.5 mL for golimumab at Weeks CCI

Database locks (DBLs) are scheduled at Week 24 and End of Study (Week 36). The first DBL will occur when all randomized participants 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 participants have either completed their final safety visit (Week 36) or have terminated study participation prior Week 36 (referred to as Final DBL).

An interim analysis (IA) is planned when 60 participants reach Week 24, dependent on enrollment rate. Details will be defined in the protocol and statistical analysis plan (SAP).

This study has been designed in accordance with other related studies for alignment, including CNTO1959PSA3005, PSA3001, and PSA3003.

A Data Monitoring Committee (DMC) will be commissioned for this study. Refer to Committees Structure in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations for details.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

Study Population

The target study population is participants with active PsA who had IR to either 1 or 2 anti-TNFα therapy(ies). This population is appropriate to provide relevant efficacy and safety information for the intended use of combination biologic therapy in PsA. The relative balance of musculoskeletal and cutaneous disease within a given participant needs to be considered when assessing adequate treatment. Therefore, a TNF-IR population with ≥3 tender and swollen joints and active plaque psoriasis is planned to enrich the population for those more likely to experience inadequate control of disease with current advanced therapies. Though hsCRP level is not a criterion for inclusion, up to 10% of study participants with hsCRP level <0.1 mg/dL at the screening visit can be enrolled in the study. The study population will be stratified using dynamic central randomization stratified by baseline (Week 0) nonbiologic DMARDs use, skin biopsy substudy enrollment status, tender joint count, the PASI, and the participant's pain visual analog scale (VAS) score.

When an initial anti-TNFα has failed or inadequately controls disease activity, cycling through another anti-TNFα or switching to another mechanism of action such as anti-IL-17, anti-IL-12/23, anti-IL-23, JAK inhibitors, or phosphodiesterase type 4 inhibitors has been recommended (Gossec 2020). Therefore, the target study population is restricted to just prior anti-TNFα therapy(ies) (other than golimumab) and no prior non-TNFα biologic therapies.

Blinding, Control, Study Phase/Periods, Intervention Groups

A monotherapy active control will be used to determine the sensitivity of the clinical endpoints in this study. Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Study Phases and Duration of Treatment

There will be 3 phases in this study: screening, double-blind, 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 double-blind phase of the study will be from Weeks 0 to 24 and includes the active treatment phase and the primary efficacy visit. The primary endpoint will be evaluated at the primary efficacy visit at Week 24. This duration will provide adequate time to evaluate the efficacy and short-term safety of combination therapy in PsA.
- The safety follow-up phase of the study will be from Week 24 to the final safety visit at Week 36 (approximately 16 weeks after the last dose of study intervention administration at Week 20). The safety follow-up period allows for monitoring of participants for a period equivalent to approximately 5 times the half-life of guselkumab and golimumab.

Study Evaluations

Efficacy evaluations chosen for this study were established in previous studies of therapeutic biologic agents for the treatment of PsA. Electronic patient-reported outcomes (ePROs) 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 US/EU regulatory guidance documents.

Safety evaluations include collecting information on AEs, review of concomitant medications, vital signs, laboratory assessments, physical examinations, and early detection of TB.

All study participants will undergo MRI of the hand and foot at baseline and Week 24 to evaluate the differential effect of the 2 treatment regimens under study on peripheral joint pathology. Through the different mechanisms by which to generate tissue contrast with MRI, scans of PsA provide insight to a range of pathological manifestations such as synovitis, enthesitis, bone edema, bone erosion, and osteoproliferation. Though MRI is generally not used at a primary diagnostic modality for clinical patient management, the development of standardized, semi-quantitative frameworks for the acquisition and evaluation of MRIs by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) initiative has contributed to its increased adoption as an objective and sensitive adjunct to clinical examination for monitoring therapeutic response in the interventional study setting (Kampylafka 2018). In this study, acquired MRI datasets of the hand and foot will be assessed for inflammatory and structural damage of the articular joints by central readers following the Psoriatic Arthritis Magnetic Resonance Imaging Scoring System (PsAMRIS) (Østergaard 2009). In addition, given the prevalence of peripheral enthesitis in PsA and the evolving appreciation for the central role enthesitis is hypothesized to play in the pathogenesis of PsA (Benjamin 2009; McGonagle 2007; Schett 2017), central readers will also assess heel enthesitis following the recently devised HEMRIS (Mathew 2019). Both PsAMRIS and HEMRIS provide a comprehensive framework by which to noninvasively evaluate pathologic features associated with PsA.

Serum samples will be collected to evaluate the PK of guselkumab and golimumab, as well as the immunogenicity of guselkumab and golimumab as described in the Schedule of Activities (SoA; Section 1.3).

DNA Collection

Optional pharmacogenomic samples may be obtained from participants only when specific consent is provided by signing the optional genetic research informed consent form (ICF). It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention 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 an intervention. The goal of the pharmacogenomic component is to collect deoxyribonucleic acid (DNA) to allow the identification of genetic factors that may influence the PK, PD, efficacy, safety, or tolerability of guselkumab or golimumab and to identify genetic factors associated with PsA or the response to guselkumab and golimumab treatment.

Biomarker Collection

Biomarker samples will be collected to evaluate the cellular and molecular mechanism of action and treatment responses of guselkumab or golimumab or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to an intervention. Optional skin biopsy samples may be obtained in the skin biopsy substudy from participants who provide specific consent. Biopsy samples will be analyzed to explore disease biomarkers and treatment effects at the tissue level. The goal of the biomarker analyses is to evaluate the PD of guselkumab or golimumab and aid in evaluating the intervention-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.

Collection of biomarker samples, including samples from the optional pharmacogenomic collection, will only occur where local regulations permit and may not occur at all clinical sites.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants 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 participants 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 although monotherapy targeting IL-23 and TNFα have shown early efficacy in PsA population, the efficacy of combined therapy has not been shown in PsA TNF-IR subpopulation and the response to guselkumab+golimumab in PsA is theoretical at this time.

The total blood volume to be collected from each participant in this study is less than the American Red Cross standard limit for whole blood donation (approximately 475 mL q8w) and is, therefore, considered an acceptable amount of blood to be collected over this time (www.redcrossblood.org).

4.3. Justification for Dose

The combination dose regimen of guselkumab CCI CCI and golimumab CCI CCI is selected for this Phase 2a study to evaluate if CCI efficacy could be achieved in TNF-IR participants with PsA. This dose regimen is chosen based on PK, efficacy, and safety data from guselkumab and golimumab monotherapy studies in participants with PsA.

For guselkumab, the dose regimen of 100 mg at Weeks 0 and 4 followed by q8w was approved for the treatment of PsA in both EU and US and 100 mg q4w is approved in EU for PsA patients at high risk for joint damage. In guselkumab monotherapy PsA studies (PSA3001 and PSA3002), although the cumulative evidence did not indicate an apparent dose-response trend between guselkumab 100 mg q8w and 100 mg q4w dose regimens in treating signs and symptoms of PsA, there were some numerical differences between the 2 dose regimens in certain high bar efficacy

endpoints (eg, IGA 0) and inhibition of radiographic progression. Furthermore, a potential greater benefit of the 100 mg q4w regimen compared with the 100 mg q8w regimen was observed in a post hoc analysis of PSA3001, especially among patients with prior anti-TNFα treatment experience including prior IR. Specifically, in TNF-IR participants in PSA3001, a greater proportion of participants in the guselkumab 100 mg q4w group consistently achieved higher responses across multiple endpoints such as ACR 50 (29% versus 13%), ACR 70 (18% versus 7%), and MDA (29.4 versus 6.7%) responses at Week 24 compared with the 100 mg q8w group. Taken together, the CCI CCI dose regimen may achieve better efficacy in an TNF-IR population. Given the high bar efficacy endpoint (ie, MDA) and a more refractory study population of TNF-IR participants, the guselkumab CCI CCI dose regimen was selected to test for superior efficacy of combination therapy that goes well beyond the most efficacious guselkumab monotherapy regimen in this POC study. In addition, CCI dosing for guselkumab will allow us to synchronize the CC administration with golimumab in the combination therapy.

From a safety perspective, no dose-related trend (100 mg q8w versus 100 mg q4w) in AEs, SAEs, AEs leading to study intervention discontinuation, infections, and serious infections was observed in guselkumab Phase 3 PsA studies. One dose-related adverse reaction identified in these studies is an increase in liver transaminase alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels which occurred at a higher incidence in the guselkumab 100 mg q4w group than in the 100 mg q8w group. The majority of ALT/AST elevations were mild (eg, National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE] toxicity Grade 1) and most cases were transient and resolved spontaneously, did not result in study intervention interruptions or discontinuations, and were not associated with clinically significant increases in bilirubin. There were no cases that satisfied the criteria for Hy's law (total bilirubin >2×ULN and either ALT or AST ≥3×ULN) in guselkumab-treated participants.

For golimumab, 50 mg once a month is the approved PsA dose regimen in both the US and EU. In golimumab Phase 3 PsA study (C0524T08), no apparent dose-response trend (50 mg q4w versus 100 mg q4w) was observed in ACR response and inhibition of radiographic progression between 2 dose regimens studied. From a safety perspective, the overall safety profile was generally similar between the golimumab 50 mg and 100 mg dose groups in Study C052T08. Since no apparent dose-response trend was observed in PsA, golimumab CCI CCI is included in the combination.

Overall, the combination dose regimen of guselkumab CCI CCI and golimumab CCI CCI is considered appropriate to be tested in this Phase 2a study and would maximize the opportunity to achieve POC.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last visit for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

A participant will be considered to have completed the study if the participant has completed assessments at Week 24 of the double-blind phase and the safety follow-up at Week 36.

Participants who prematurely discontinue study intervention for any reason before completion of the double-blind phase (Week 24) should complete the specified study visits and the final safety follow-up visit as outlined in Section 1.3. Participants will not be considered to have completed the study unless they have completed the safety follow-up.

5. STUDY POPULATION

Screening for eligible participants will be performed within 6 weeks before administration of the study intervention. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

Note: Though hsCRP level is not a criterion for inclusion, up to 10% of study participants with hsCRP level <0.1 mg/dL at the screening visit can be enrolled in the study.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

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

Age

1. Be ≥18 (or the legal age of consent in the jurisdiction in which the study is taking place) to ≤65 years of age, inclusive.

Type of Participant and Disease Characteristics

2. Criterion modified per Amendment 1.

   2.2. Medically stable on the basis of physical examination, medical history, and vital signs performed at screening. Any abnormalities must be consistent with the underlying illness in the study population and this determination must be recorded in the participant's source documents and initialed by the investigator.

3. Have a diagnosis of PsA for ≥6 months prior to the first administration of study intervention and meet ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria at screening.

4. Criterion modified per Amendment 2.

   4.1 Have active PsA as defined by having at least 3 swollen joints and at least 3 tender joints at screening and at baseline.

5. Have at least 1 of the following PsA subsets: distal interphalangeal joint involvement, polyarticular arthritis with absence of rheumatoid nodules, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis.

6. Have active plaque psoriasis, with at least one psoriatic plaque of ≥2 cm diameter or nail changes consistent with psoriasis.

Concomitant or Previous Medical Therapies Received

7. Criterion modified per Amendment 2.

   7.2. Have an IR to anti-TNFα therapy(ies), defined as presence of active PsA despite previous treatment with either 1 or 2 prior anti-TNFα agent(s) and the following:

   a. Lack of benefit to either 1 or 2 prior anti-TNFα therapy(ies), as documented in the participant history by the treating physician, after at least 12 weeks of etanercept, adalimumab, or certolizumab pegol therapy, or at least 14 weeks of infliximab, or any biosimilar of these 4 therapies. Documented lack of benefit may include inadequate improvement in joint counts, physical function, or disease activity

   b. The last dose of anti-TNFα therapy must have occurred greater than 5 half-lives of the drug prior to first study intervention administration (washout period).

8. If currently using nonbiologic DMARDs (limited to MTX, SSZ, HCQ, or LEF), participants should have received treatment for at least 3 months and the dose must be stable for at least 4 weeks before first administration of study intervention and should have no serious toxic side effects attributable to the nonbiologic DMARD. If not currently using MTX, SSZ, or HCQ, must not have received these treatments for at least 4 weeks before first administration of study intervention. If not currently using LEF, must not have received LEF for at least 12 weeks prior to first administration of study intervention (see also Section 6.8, Concomitant Therapy).

   In addition, the following stable dose criteria must be met:

   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.

9. If using NSAIDs or other analgesics for PsA at baseline, participants must be on a stable dose for at least 2 weeks prior to the first administration of study intervention. If currently not using NSAIDs or other analgesics for PsA, must not have received NSAIDs or other analgesics for PsA within 2 weeks prior to the first administration of study intervention.

10. If using oral corticosteroids at baseline, participants must be on a stable dose equivalent to ≤10 mg of prednisone/day for at least 2 weeks prior to the first administration of study intervention. If not currently using oral corticosteroids, the participant must not have received oral corticosteroids within 2 weeks prior to the first administration of study intervention (see also Section 6.8, Concomitant Therapy).

Sex and Contraceptive/Barrier Requirements

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

12. Before randomization, a woman must be (as defined in Appendix 5: Contraceptive and Barrier Guidance)

a. Not of childbearing potential **OR**

b. Of childbearing potential and

- Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 16 weeks after receiving the last administration of study intervention. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention. Examples of highly effective methods of contraception are located in Appendix 5: Contraceptive and Barrier Guidance.

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

13. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 16 weeks after receiving the last administration of study intervention.

14. A male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person. Male participants should also be advised of the

benefit for a female partner to use a highly effective method of contraception as a condom may break or leak.

15. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 16 weeks after receiving the last dose of study intervention (the end of relevant systemic exposure).

Tuberculosis Screening and Vaccination History

16. Are considered eligible according to the following TB screening criteria:

    a. Have no history of latent or active TB before screening. An exception is made for participants who have a history of latent TB and:
        - are currently receiving treatment for latent TB, **OR**
        - will initiate treatment for latent TB before the first administration of study intervention, **OR**
        - have documentation of having completed appropriate treatment (as per local guidelines) for latent TB within 5 years before the first dose of study intervention. It is the responsibility of the investigator to verify the adequacy of previous anti-tuberculous treatment and provide appropriate documentation. Participants with a history and documentation of having completed appropriate treatment for latent TB more than 5 years before the first dose of study intervention are not eligible.

    b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.

    c. Have had no known 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 before the first administration of study intervention.

    d. Within 8 weeks before the first administration of study intervention, have a negative QuantiFERON-TB test result, or have a newly identified positive QuantiFERON-TB test result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated before the first administration of study intervention (see Section 8.2.12).

        NOTE: A negative tuberculin skin test result (see Appendix 8 [Section 10.8]) is additionally required if the QuantiFERON-TB test is not approved/registered in the country in which this protocol is being conducted. In Ukraine, while the QuantiFERON-TB test is not approved/registered, it is acceptable, and an additional tuberculin skin test is not required. The QuantiFERON-TB test and the tuberculin skin test are not required at screening for participants with a history of latent TB, if active TB has been ruled out, and if appropriate treatment has been initiated/completed as described above in Inclusion Criterion 16a. The

frequency of TB testing can be increased depending on local health authority requirements.

e. Have a chest radiograph (both posterior-anterior and lateral views, or per country regulations where applicable), taken within 12 weeks before the first administration of study intervention and read by a radiologist or qualified pulmonologist, with no evidence of current, active TB or old, inactive TB. A chest computed tomography scan is also acceptable if already available or obtained outside of the study protocol.

17. Agree not to receive a live viral or live bacterial vaccination during the study, or within 16 weeks after the last administration of study intervention.

18. Agree not to receive a Bacillus Calmette-Guérin (BCG) vaccination during the study, and within 16 weeks after the last administration of study intervention.

Screening Laboratory Test Parameters

19. Have screening laboratory test results within the following parameters:

a.	Hemoglobin	≥8 g/dL	(International System [SI]: ≥8.5 g/L)
b.	White blood cells	$\geq 3.5\times10^3/\mu L$	(SI: ≥3.5 GI/L)
c.	Neutrophils	$\geq 1.5\times10^3/\mu L$	(SI: ≥1.5 GI/L)
d.	Platelets	$\geq 100\times10^3/\mu L$	(SI: ≥100 GI/L)
e.	Serum creatinine	≤1.5 mg/dL	(SI: ≤133 µmol/L)

f. AST, ALT, and alkaline phosphatase levels must be ≤1.5×ULN 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 participant eligible if the previously abnormal laboratory test result is within acceptable the range on repeat testing in the central laboratory. **No rescreening is permitted for abnormal ALT or AST (see Section 7.1.1).**

Informed Consent

20. Must sign an ICF indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study.

21. Must sign a separate ICF if the participant agrees to provide optional DNA and/or skin biopsy samples for research (where local regulations permit). Refusal to give consent for the optional DNA and/or skin biopsy research samples does not exclude a participant from participation in the study.

22. Must be willing and able to adhere to the lifestyle restrictions specified in this protocol (see Section 5.3).

5.2. Exclusion Criteria

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

Medical Conditions

1. Criterion modified per Amendment 1.

   1.1. Has a history or current signs or symptoms of severe, progressive, or uncontrolled renal insufficiency (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2), hepatic, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic (with the exception of PsA), psychiatric, genitourinary, or metabolic disturbances.

2. 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.

3. Has a history of, or concurrent, congestive heart failure, including medically controlled, asymptomatic congestive heart failure.

4. Has a history of a demyelinating disorder such as multiple sclerosis or optic neuritis.

5. Has other inflammatory diseases that might confound the evaluations of benefit of guselkumab and/or golimumab therapy, including but not limited to RA, AS, nr-AxSpA, systemic lupus erythematosus, or lyme disease (confirmed by western blot).

6. Has the arthritis mutilans subset of PsA.

7. Has a nonplaque form of psoriasis (eg, erythrodermic, guttate, or pustular).

8. Has current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium).

9. 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.

10. Currently has a malignancy or 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 prior to the first study intervention

administration or cervical carcinoma in situ that has been adequately treated with no evidence of recurrence for at least 3 months prior to the first study intervention administration).

11. Has or has had a herpes zoster infection within 2 months before screening.

12. 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.

13. Has a transplanted organ (with exception of a corneal transplant >3 months prior to the first administration of study intervention).

14. 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.

15. Has unstable suicidal ideation or suicidal behavior in the last 6 months, that may be defined as an electronic Columbia-Suicide Severity Rating Scale (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 participant will be made at the judgment of the investigator.

16. Has had major surgery (eg, requiring general anesthesia and hospitalization) within 8 weeks prior to screening, or will not have fully recovered from such surgery, or has such surgery planned during the time the participant is expected to participate in the study (36 weeks). Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.

17. 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.

18. 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 prior to screening.

19. Has a history of active granulomatous infection, including histoplasmosis, or coccidioidomycosis, before screening. Refer to Inclusion Criterion 16 for information regarding eligibility with a history of latent TB.

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

21. Has persistently indeterminate (indeterminate on repeat sampling) QuantiFERON-TB test results. Indeterminate results should be handled as described in Section 8.2.12.

22. Criterion modified per Amendment 1.

22.1. During the 6 weeks prior to baseline, has had **any** of the following: (a) confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (test positive) **OR** (b) suspected SARS-CoV-2 infection (clinical features of Coronavirus Disease 2019 [COVID-19] without documented test results) **OR** (c) close contact with a person with known or suspected SARS-CoV-2 infection.

- Exception: may be included with a documented negative result for a validated SARS-CoV-2 test
  - i) obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, [eg, fever, cough, dyspnea])

  AND

  - ii) with absence of all conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit

Note on COVID-related exclusion:

- The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations/guidance from authorities/ standards-of-care.

Precaution: for those who may carry a higher risk for severe COVID-19 illness, follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

Prior/Concomitant Therapy

23. Contraindications to the use of guselkumab or golimumab per local prescribing information

24. Taken any disallowed therapies as noted in Section 6.8, Concomitant Therapy before the planned first dose of study intervention.

25. Criterion modified per Amendment 1.

    25.1. Has received prior treatment with golimumab or guselkumab or has documented intolerance to prior anti-TNFα therapy (see Appendix 17 [Section 10.17]) in the patient history by the treating physician.

26. Criterion modified per Amendment 2.

    26.1 Has received more than 2 prior anti-TNFα agents (or biosimilars).

27. Has previously received any biologic treatment (other than an anti-TNFα agent) including, but not limited to ustekinumab, secukinumab (AIN457), tildrakizumab (MK3222), ixekizumab (LY2439821), brodalumab (AMG827), risankizumab (BI-655066), or other investigative biologic treatment for PsA or psoriasis.

28. Has ever received tofacitinib, baricitinib, filgotinib, peficitinib (ASP015K), decernotinib (VX-509), or any other JAK inhibitor.

29. Has received any systemic immunosuppressants (eg, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, or tacrolimus) within 4 weeks of the first administration of study intervention.

30. Has received nonbiologic DMARDs other than MTX, SSZ, HCQ, and LEF within 4 weeks before the first administration of study intervention.

31. Is receiving MTX AND oral corticosteroids within 2 weeks prior to the first administration of study intervention.

32. Is receiving 2 or more nonbiologic DMARDs specified in Section 6.8 at baseline.

33. Has known allergies, hypersensitivity, or intolerance to guselkumab and/or golimumab or their excipients.

34. 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 Section 6.8) within 4 weeks of the first administration of study intervention.

35. 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 intervention. Low-potency topical corticosteroids are allowed at any time.

36. Has received epidural, intraarticular, intramuscular (IM), or IV corticosteroids, including adrenocorticotropic hormone during the 4 weeks before first administration of study intervention.

37. Has received lithium within 4 weeks of the first administration of any study intervention.

38. Has received an experimental antibody or biologic therapy (other than those listed everywhere else in this section) within 6 months prior to the first administration of study intervention, 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 intervention or is currently enrolled in another study using an investigational agent or procedure.

39. Has received apremilast within 4 weeks prior to the first administration of study intervention.

Other Exclusions

40. Has received or plans to receive any live, attenuated vaccine within 16 weeks before the first dose of study intervention or within 16 weeks after the last dose of study intervention. Live, attenuated influenza vaccines are permitted as late as 16 weeks before the first dose of study intervention. Non-live vaccines approved or authorized for emergency use (eg, COVID-19) by local health authorities are allowed.

41. Have had a BCG vaccination within 12 months of screening visit.

42. Received an investigational intervention or used an invasive investigational medical device within 3 months before the planned first dose of study intervention or received an investigational biological product within 3 months or 5 half-lives, whichever is longer, before the planned study intervention, or is currently enrolled in an investigational study.

43. Is pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 16 weeks after the last dose of study intervention.

44. Is planning to father a child while enrolled in this study or within 16 weeks after the last dose of study intervention.

45. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

46. Has a history of drug or alcohol abuse according to Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-V) criteria within 12 months prior to the first administration of study intervention.

47. Positive HIV antibody test.

48. Tests positive for HBV infection (Section 10.9) or who is seropositive for antibodies to HCV at screening.

49. 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.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that the participant no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the study to be eligible for participation:

1. Criterion modified per Amendment 1.

   1.1. Refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

   Vaccination History

   It is recommended to be up-to-date on all age-appropriate vaccinations prior to screening per routine local medical guidelines. It is strongly recommended for study participants to receive locally-approved (or emergency use-authorized) COVID-19 vaccination prior to study entry. Study participants should follow applicable local vaccine labeling, guidelines, and standards-of-care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (see also Section 6.8.7).

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. Agree to avoid prolonged sun exposure and agree not to use of tanning booths or other ultraviolet (UV) light sources during study.

4. Are willing to refrain from the use of complementary therapies for PsA or psoriasis including ayurvedic medicine, traditional Taiwanese, Korean, or Chinese medicines, and acupuncture within 2 weeks before the first study intervention administration and through Week 24.

5. Are willing to refrain from using oral corticosteroids and MTX in combination during the treatment period.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

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

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time. No rescreening is permitted for abnormal ALT or AST (see Inclusion Criterion 19, Section 5.1). Rescreened participants should be assigned a new participant number, undergo the informed consent process, and then start a new screening phase.

5.5. Criteria for Temporarily Delaying Administration of Study Intervention

Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Appendix 7 (Section 10.7).

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Interventions Administered

Study intervention administration must be captured in the source documents and the electronic case report form (eCRF).

Guselkumab, golimumab, and placebo will be manufactured and provided under the responsibility of the sponsor. Refer to the guselkumab and golimumab IBs for a list of excipients.

For a definition of study intervention overdose, refer to Section 6.7, Treatment of Overdose.

Note that the combination therapy will be administered via drug-device combination products which each contain only 1 of the aforementioned interventions; guselkumab, golimumab, and placebo will all be administered via separate devices (Section 6.1.1).

Description of Interventions

Group/Arm Name	Group 1	Group 2
Intervention Name	Guselkumab + golimumab	Guselkumab + placebo
Unit Dose Strength(s)	CCI guselkumab; CCI golimumab	CCI guselkumab
Dosage Level(s) and Frequency	CCI guselkumab + CCI golimumab CCI	CCI guselkumab + placebo 0.5 mL for golimumab CCI
Route of Administration	C via single-use CCI	C via CCI CCI
Dosing Instructions	Guselkumab CCI mL will be provided in a single-use CCI assembled with the CCI . Golimumab CCI 0.5 mL will be provided in a single-use CCI assembled with the CCI .	Guselkumab CCI mL will be provided in a single-use CCI assembled with the CCI . Placebo 0.5 mL for golimumab will be provided a single-use CCI assembled with the CCI device.
Uses	Experimental	Active + placebo comparator
Investigational Medicinal Product (IMP)	Yes	Yes
Non-Investigational Medicinal Product (NIMP)	No	No

6.1.1. Combination Products

For this protocol, the term "combination products" refers to single integral drug-device combinations. Guselkumab, golimumab, and placebo will all be administered separately via separate devices. The sponsor-manufactured drug-device combination products for use in this study are:

- CCI Plus for guselkumab,
- CCI for golimumab, and
- CCI for placebo 0.5 mL for golimumab.

Additional details on the CCI are provided in the guselkumab and golimumab IBs.

All drug-device combination product deficiencies (including failure, malfunction, improper or inadequate design, manufacturer error, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the study. For studies in drug-device combination

products, these deficiencies will be reported as product quality complaints (PQCs; see Appendix 4 [Section 10.4]: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting) and appropriately managed by the sponsor.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

Guselkumab, golimumab, and placebo for golimumab will be supplied to the study sites for CC administration. Guselkumab will be supplied as a CCI mL sterile liquid in a single-dose CCI CCI (open-label). Golimumab will be supplied as a CCI 0.5 mL sterile liquid in a single-dose CCI (double-blind), and placebo for golimumab will be supplied as a 0.5 mL sterile liquid in a single-dose CCI (double-blind).

All study intervention must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C) and protected from exposure to light. Do not freeze the study interventions. The products are designed for single use only.

Refer to the study site investigational product and procedures manual (SIPPM) for additional guidance on study intervention preparation, handling, and storage.

Accountability

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

Study intervention 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 intervention 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 intervention will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials, such as used syringes, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study intervention 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 intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor.

Further guidance and information for the final disposition of unused study interventions are provided in the SIPPM.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Dynamic central randomization will be implemented in conducting this study. Participants will be assigned to 1 of 2 intervention groups based on an algorithm implemented in the interactive web response system (IWRS) before the study. Dynamic central randomization minimizes the imbalance in the distribution of the number of participants across intervention groups within the levels of each individual stratification factor: baseline nonbiologic DMARDs use, skin biopsy substudy enrollment status, tender joint count, the PASI, and the participant's pain VAS score. Based on the algorithm, the IWRS will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant.

Blinding

To maintain the study blind, the study intervention container will have a label containing the study name, study intervention number, reference number, and storage instruction. A tear-off label is designed to be torn off, separated from the study intervention container, and attached to the participant's source documents. The label will not identify the study intervention in the container. However, if it is necessary for a participant's safety, the study blind may be broken, and the identity of the study intervention ascertained. The study intervention number will be entered in the eCRF when the study intervention is administered. The study interventions will be identical in appearance and will be packaged in identical containers.

Data that may potentially unblind the intervention assignment (ie, study intervention allocation and serum concentration, biomarker, anti-golimumab antibodies, or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate prior to unblinding.

Under normal circumstances, the blind should not be broken until all participants have completed the study Week 24 visit and the database is finalized. The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented by the IWRS, in the appropriate section of the eCRF, and in the source document. The

documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded should continue to return for scheduled evaluations. At Week 24, the data will be unblinded to some sponsor personnel while participants are still participating in the study. Identification of sponsor personnel who will be unblinded to participant level data will be documented prior to unblinding. Investigational sites and study participants are going to remain blinded until study end.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an IA is specified, the randomization codes and, if required, the translation of randomization codes into intervention and control groups will be disclosed to those authorized and only for those participants included in the IA.

6.4. Study Intervention Compliance

The details of each study intervention administration will be recorded in the eCRF, including date and time of CC injection.

Study-site personnel will maintain a log of all study intervention administered. Study intervention supplies for each participant will be inventoried and accounted for. Information regarding study intervention administrations that are administered outside of the scheduled windows or missed will be recorded. Participant charts and worksheets may be reviewed and compared with the data entries on the eCRFs to ensure accuracy. Although it is understood that treatment may be interrupted for many reasons, compliance with the treatment schedule is strongly encouraged.

6.5. Dose Modification

Any dose/dosage adjustment should be overseen by medically-qualified study-site personnel (principal or subinvestigator unless an immediate safety risk appears to be present).

No treatment/dose adjustment will be permitted through the study.

6.6. Continued Access to Study Intervention After the End of the Study

Participants will be instructed that study intervention will not be made available to them after they have completed/discontinued study intervention and that they should return to their primary physician to determine standard-of-care.

No continued access will be proposed for this study after the 20-week active treatment period. At the end of their participation in the study, the participants will be instructed that they should return to their primary physician to determine standard-of-care, if applicable.

6.7. Treatment of Overdose

For this study, any dose of guselkumab or golimumab greater than the highest dose at a single dosing visit will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for AE/SAE and laboratory abnormalities.
- Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

6.8. Concomitant Therapy

Prestudy therapies administered up to 30 days before the first dose of study intervention must be recorded at screening.

Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study intervention to 16 weeks after the last dose of study intervention. Concomitant therapies should also be recorded beyond 16 weeks after the last dose of study intervention only in conjunction with SAEs that meet the criteria outlined in Serious Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study intervention must be recorded in the eCRF.

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 participants' 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 participant's medical record.

Permitted concomitant medications for PsA and the maximum allowed doses during the study as specified in the following sections are summarized in Table 1.

Table 1: Permitted Concomitant Medications for PsA and the Maximum Allowed Doses During the Study	
Permitted Concomitant Medications for PsA[a]	**Maximum Allowed Dose**
NSAIDs and other analgesics	Marketed dose approved in the country where the study is being conducted
Oral corticosteroids	Equivalent to 10 mg/day of prednisone
Methotrexate (MTX)[b]	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. It is recommended that all participants 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.	

- Participants should not initiate any new treatment for PsA through Week 24.
- Participants should not initiate any investigational treatment through Week 24.
- Participants may not be receiving more than one nonbiologic DMARD from baseline through Week 24 (see further details in Section 6.8.1). At baseline, participants are permitted to enter the study on a stable dose of one nonbiologic DMARD (limited to MTX, SSZ, HCQ, or LEF) up to the maximum allowed dose specified in Table 1.
- Participants may not be receiving concomitant MTX and oral corticosteroids within 2 weeks prior to the first administration of study intervention.
- Concomitant medication review will occur at study visits identified in the SoA (Section 1.3).

6.8.1. Nonbiologic DMARDs

6.8.1.1. Permitted Nonbiologic DMARDs

Participants are permitted to enter the study on a stable dose of one nonbiologic DMARD (limited to MTX, SSZ, HCQ, or LEF) up to the maximum allowed dose specified in Table 1. Only 1 of these nonbiologic DMARDs is allowed from baseline through Week 24; participants receiving 2 or more nonbiologic DMARDs at baseline are excluded from study participation.

At any time during the study, the dose of the permitted nonbiologic 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 2 for protocol requirements of the permitted nonbiologic DMARDs.

Table 2: Protocol Requirements of the Permitted Nonbiologic DMARDs			
Permitted Nonbiologic DMARDs	**Baseline Usage**	**Prior to Week 0**	**Week 0 through Week 24**
Methotrexate (MTX)	Yes	Treatment should have	Stable dose and route of

Table 2: Protocol Requirements of the Permitted Nonbiologic DMARDs			
Permitted Nonbiologic DMARDs	**Baseline Usage**	**Prior to Week 0**	**Week 0 through Week 24**
		started at least 3 months prior to the first administration of study intervention. MTX routes of administration and doses should be stable for at least 4 weeks prior to the first administration of the study intervention.	administration (oral, IM, or C permitted) required unless unacceptable side effects
	No	Discontinued at least 4 weeks prior to the first administration of study intervention.	
Sulfasalazine (SSZ) or Hydroxychloroquine (HCQ)	Yes	Treatment should have started at least 3 months prior to the first administration of study intervention. Dose should be stable for at least 4 weeks prior to the first administration of the study intervention.	Stable dose required unless unacceptable side effects
	No	Discontinued at least 4 weeks prior to the first administration of study intervention.	Not allowed
Leflunomide (LEF)	Yes	Treatment should have started at least 3 months prior to the first administration of study intervention. Dose should be stable for at least 4 weeks prior to the first administration of the study intervention.	Stable dose required unless unacceptable side effects
	No	Discontinued at least 12 weeks prior to the first administration of study intervention.	Not allowed

Concomitant medication review will occur at study visits identified in the SoA (Section 1.3).

6.8.1.2. Prohibited Nonbiologic DMARDs and Apremilast

All other nonbiologic 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 intervention and remain prohibited through Week 24.

6.8.1.3. 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 intervention and remain prohibited through Week 24. If any of these systemic immunosuppressants is initiated during the study, study intervention must be permanently discontinued.

Systemic immunosuppressants do not refer to corticosteroids; see Section 6.8.2 for restrictions regarding the use of corticosteroids.

6.8.2. Corticosteroids

6.8.2.1. Oral Corticosteroids

Participants 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 intervention and continue on this dose through Week 24.

Otherwise, throughout the study, the dose of oral corticosteroids may be decreased at the discretion of the investigator only if the participant develops unacceptable side effects.

Participants not using oral corticosteroids at baseline for PsA must have discontinued oral corticosteroids at least 2 weeks prior to the first administration of study intervention and must not receive oral corticosteroids through Week 24 of the study for PsA.

6.8.2.2. Corticosteroids - Intravenous, Intramuscular, or Epidural Administration

Intravenous, IM, or epidural administration of corticosteroids for the treatment of PsA are not allowed through Week 24.

Long-term (>2 weeks) oral, IV, IM, or epidural corticosteroid use for indications other than PsA or psoriasis is not allowed through Week 24. Short-term (≤2 weeks) oral, IV, IM, 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.

6.8.2.3. Corticosteroids - Intraarticular Injection

Intraarticular corticosteroid injections for PsA should be avoided, especially during the first 24 weeks of the study. If the investigator feels an intraarticular corticosteroid injection is warranted, consult with the medical monitor prior to administration of the injection.

6.8.2.4. 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.

6.8.3. Nonsteroidal Anti-inflammatory Drugs and Other Analgesics

For participants 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 intervention and continue through Week 24. 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 eCRF. For topical and analgesic patches, the dose should be stable through Week 24 and may be changed only if the participant develops unacceptable side effects.

Participants 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 intervention and must not receive NSAIDs or other analgesics for PsA through Week 24 of the study.

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.

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

Participants with any prior or current use at baseline of biologic agents (other than an anti-TNFα agent), cytotoxic agents, or JAK inhibitors will not be allowed in the study.

The concomitant use of biologic agents, cytotoxic agents, JAK inhibitors, and investigational drugs is not allowed. Biologic agents include, but are not limited to anakinra, etanercept, adalimumab, infliximab, ustekinumab, alefacept, efalizumab, rituximab, natalizumab, certolizumab pegol, bimekizumab, tildrakizumab, secukinumab, ixekizumab, brodalumab, 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, upadacitinib, and decernotinib. If any of these medications are used, study intervention must be permanently discontinued.

Participants must have discontinued using an anti-TNFα agent at least 5 half-lives prior to first study intervention administration (Table 3), per inclusion criterion 7b.

Table 3: Anti-TNFα Agent Half-lives

Anti-TNFα agent	Half-life	Washout period (5 half-lives)
adalimumab	10-20 days	50-100 days
etanercept	70-132 hours	350- 660 hours
infliximab	9.5 days	47.5 days
certolizumab	11 days	55 days

6.8.5. Complementary Therapies

The use of complementary therapies, including ayurvedic medicine, traditional Chinese medications, or nonmedicinal therapy such as acupuncture for PsA or psoriasis, is not allowed from 2 weeks prior to the first administration of study intervention through Week 24.

6.8.6. 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; nonmedicated shampoos may be used on the day of a study visit.

Low-potency topical corticosteroids may be used on the face and groin only. 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 24.

Phototherapy including UV B light or tanning beds are not permitted during the study. Participants should be encouraged to avoid prolonged sun exposure during the study.

6.8.6.1. Systemic Therapy for Psoriasis

Concurrent use of systemic therapy for psoriasis (eg, psoralen with UV A light, systemic retinoids, cyclosporine, or tacrolimus, with the exception of those in Table 1) must be discontinued at least 4 weeks prior to the first administration of study intervention and is not permitted during the study; if a systemic antipsoriatic treatment (except those in Table 1) is initiated during the study, study intervention must be permanently discontinued.

Participants must not receive any biologic outside of the protocol or participate in any other clinical study with an investigational agent while in this study and must terminate study participation if they do. Prior to termination of study participation, participants should complete evaluations for a study intervention discontinuation visit as described in Section 7.

6.8.7. Vaccines

It is highly recommended that study participants be up-to-date with COVID-19 and influenza (flu) vaccines where possible prior to study entry.

When considering use of locally-approved non-live vaccines (including emergency use-authorized COVID-19 vaccines) in study participants, follow applicable local vaccine labeling, guidelines, and standards-of-care for participants receiving immune-targeted therapy.

For study participants receiving a locally-approved (including emergency use-authorized) COVID-19 vaccine, in order to help identify acute reactions potentially related to COVID-19 vaccine, it is recommended where possible that vaccine and study intervention be administered on different days, separated by as large an interval as is practical within the protocol.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention.
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention.
- The participant becomes pregnant.
- The participant is unable to adhere to the study visit schedule or comply with protocol requirements.
- A diagnosis of opportunistic infection is made.
- The participant is deemed ineligible according to the following TB screening criteria:
  - A diagnosis of active TB is made.
  - A participant 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 participant undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON-TB test result and/or 2 indeterminate QuantiFERON-TB test results on repeat testing (refer to Section 8.2.12) (and/or a positive tuberculin skin test result in countries in which the QuantiFERON-TB test is not approved/registered or the tuberculin skin test is mandated by local health authorities).

    The frequency of TB testing can be increased depending on local health authority requirements.

    Note: In Ukraine, while the QuantiFERON-TB test is not approved/registered, it is acceptable, and an additional tuberculin skin test is not required.
  - A participant receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.
- The participant has a serious adverse reaction that is temporally related to an injection including a hypersensitivity reaction resulting in bronchospasm, wheezing and/or dyspnea that requires ventilatory support OR that results in symptomatic hypotension with either a decrease in systolic blood pressure of 30% from a participant's baseline value or systolic blood pressure <90 mm Hg (Sampson 2006). In general, discontinuation of study intervention administration must be considered for participants who develop a severe injection-site reaction.

- The participant 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 intervention. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.
- The participant has a malignancy including squamous cell skin cancer. Consideration may be given to allowing participants who develop ≤2 basal cell skin cancers that are adequately treated with no evidence of residual disease to continue to receive study intervention, after consultation with sponsor medical monitor or designee.
- The participant has severe liver test abnormalities that are not transient and are not explained by other etiologies, as described in Appendix 6 (Section 10.6).
- The participant develops recurrent or chronic serious infection, which are defined as follows:
  - A recurrent serious infection will be defined as the same infectious diagnosis reported more than once, that is judged to have met criteria to be categorized as an SAE (see Appendix 4 [Section 10.4]) in at least 2 instances, in the same patient and within the treatment period. This definition assumes that the first occurrence of the serious infection was fully resolved after a standard course of treatment and based on clinical assessment. Standard treatment may include antimicrobials with or without other indicated interventions and should be consistent with expert treatment guidelines (where they exist) and with local practice.
  - A chronic serious infection will be defined as an infection that is judged to have met criteria to be categorized as an SAE (see Appendix 4 [Section 10.4]) that fails to fully resolve after a standard course of treatment based on clinical assessment.
- The participant develops congestive heart failure.
- The participant is diagnosed with a demyelinating disorder.
- The participant develops symptoms suggestive of a lupus-like syndrome and is positive for antibodies against double-stranded DNA.
- The sponsor may elect to terminate the study at any time, and if the sponsor decides not to continue development for any reason, study intervention will no longer be provided to any participants.

Temporary discontinuation of a participant's study intervention is required under the following condition:

- The participant develops a serious or severe infection, including but not limited to sepsis or pneumonia.

  Note: Study intervention must be withheld until:

  1. Clinical assessment is complete,
  2. Discussion with the medical monitor or designee has occurred, and
  3. Sponsor approval must be granted to resume study intervention.

Discontinuation of a participant's study intervention must be strongly considered under the following conditions:

- If the participant initiates treatment with prohibited therapies, the medical monitor or designee should be notified for possible discontinuation of study intervention.
- Discontinuation of study intervention should be considered for participants 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 postbaseline (after Week 0) eC-SSRS assessment. Discussion of such participants with the medical monitor or designee is required.
- The participant develops a severe injection-site reaction, but not meeting the criteria specified above.
- The participant has hematology abnormalities as described below:
  - Two sequential absolute neutrophil counts $<0.75\times10^3/\mu L$ (SI: $<0.75\times10^9$ /L)
  - Two sequential absolute lymphocyte counts $<0.5\times10^3/\mu L$ (SI: $<0.5\times10^9$/L)
  - Two sequential hemoglobin values <8.0 g/dL (SI: <80.0g/L) or a decrease of >30% from baseline
  - Two sequential platelet counts $<75\times10^3/\mu L$ (SI: $<75\times10^9$/L)

  Note: These laboratory abnormalities should be discussed with the medical monitor or designee, and study intervention should be withheld until the clinical assessment is complete.

If a participant discontinues study intervention prior to Week 20 visit, they should be encouraged to return for all early termination assessments (see Section 1.3). The MRI of the hand, foot, and heel should be performed 2 to 4 weeks after the last administration of study intervention. The final safety assessments will be conducted at the next scheduled visit that occurs approximately 16 weeks after the last dose of study intervention.

7.1.1. Liver Chemistry Stopping Criteria

Stopping of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in the algorithm below in Appendix 6 (Section 10.6) Liver Safety: Suggested Actions and Follow-up Assessments or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in the best interest of the participant.

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

Participants who Discontinue Study Intervention Prior to the Week 20 Visit

If a participant discontinues study intervention prior to Week 20 visit, they should be encouraged to return for all early termination assessments (see Section 1.3). The MRI of the hand, foot, and heel should be performed 2 to 4 weeks after the last administration of study intervention. The final safety assessments will be conducted at the next scheduled visit that occurs approximately 16 weeks after the last dose of study administration of study intervention.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply as local regulations permit.

Withdrawal of consent should be an infrequent occurrence in clinical studies (Rodriguez 2015), therefore, prior to the start of the study the sponsor and the investigator should discuss and reach a clear understanding of what constitutes withdrawal of consent in the context of the available reduced follow-up mechanisms listed.

7.2.1. Withdrawal From the Use of Research Samples

A participant 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 participant's original separate informed consent for optional research samples.
- The participant 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 participant 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 participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 3: Regulatory, Ethical, and

Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, emails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The SoA (Section 1.3) summarizes the frequency and timing of efficacy, PK, immunogenicity, PD, biomarker, pharmacogenomic, and safety measurements applicable to this study.

All ePRO assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant responses. Refer to the ePRO completion guidelines for instructions on the administration of ePROs.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: eC-SSRS, ePRO assessments, efficacy assessments, clinical safety laboratory assessments, PK, immunogenicity, and biomarkers. Blood collections for PK and PD assessments should be kept as close to the specified time as possible. Other

measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and/or the eCRF.

The total blood volume to be collected from each participant will not exceed 500 mL.

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

All assessments will be conducted at the study sites; participants will not be provided with diaries for at-home assessment completion.

Home Health Care and Telehealth Visits

Home health care and telehealth visits may be implemented by or with approval from the sponsor and per the clinical judgment of the investigator, where feasible and permissible by local policy.

Participants for whom there is no safety concern may have home health care and telehealth (conducted via phone or video conference) visits.

Study procedures such as physical exams, vitals/height/weight, TB evaluation, ePRO assessments, and Concomitant Medication and Adverse Event review may be performed with home health care and telehealth visits. Protocol-specified laboratory assessments (Section 1.3) for efficacy and safety may be collected during home health care visits.

Telehealth visits (conducted via phone or video conference) may be implemented by or with approval from the sponsor and per clinical judgment of the investigator for certain circumstances when warranted where feasible and permissible by local policy, regulations (as applicable) and for participants for whom there is no safety concern.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to the SoA (Section 1.3) 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.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Guselkumab IB
- Golimumab IB

- SIPPM
- Laboratory Manual
- Peripheral blood mononuclear cells (PBMC) Manual
- Biopsy Manual
- Sample ICF
- Electronic Data Capture (eDC) Manual
- Electronic PRO (ePRO) electronic tablet device and User Manual
- ePRO questionnaires and ePRO completion guidelines
- Electronic clinical outcome assessment (eCOA) Manual
- MRI Manual
- Tablet device and site user guide, if the study site is participating in electronic informed consent
- IWRS Manual
- eCRF guidelines

8.1. Efficacy Assessments

Efficacy evaluations chosen for this study are consistent with those utilized to evaluate other therapies for PsA.

8.1.1. Psoriatic Arthritis Response Evaluations

8.1.1.1. Joint Count (Tender and Swollen)

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 participant should also perform the joint assessments for that participant at every subsequent visit.

Through Week 24, the IJA should have no other contact (other than joint assessments) with the participant once the participant is randomized, should not be the treating physician, should not discuss the participant's clinical status with the participant or other site personnel during the joint assessment, and will not be permitted to review the participants medical records or the eCRFs, or any of the previous joint assessments. The IJA should maintain a neutral attitude during joint

assessment and should limit interactions with the participant 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 participant and/or performing physician global assessments or administering study intervention.

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

If an IJA was trained by the sponsor (with joint assessments) in a previous Janssen 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.

8.1.1.2. Nonevaluable Joints

Joints should only be designated as "nonevaluable" 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, artificial joint, 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 participant's prior joint procedures/injections (eg, if the participant was the IJA's patient prior to study participation).

8.1.1.3. American College of Rheumatology (ACR) 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 (Felson 1995) 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:
   - Participant's assessment of pain VAS
   - Participant's Global Assessment of Disease Activity (arthritis, VAS)
   - Physician's Global Assessment of Disease Activity (VAS)
   - Participant's assessment of physical function as measured by HAQ-DI

– C-reactive protein (CRP)

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

The assessments (other than joint counts) that are used to calculate ACR responses are described below.

8.1.1.4. Dactylitis Score

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) (Gladman 2007; Gladman 2013).

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 the start of the study is encouraged.

It is strongly recommended that the same person who performs the baseline dactylitis assessments for a participant should also perform the dactylitis assessments for that participant at every subsequent visit through Week 24.

8.1.1.5. Enthesitis Assessments

Enthesitis will be assessed by the IJA using the LEI (Healy 2008) and the SPARCC.

The LEI was developed to assess enthesitis in participants 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 SPARCC developed a measure for enthesitis in general spondyloarthritis (ie, not limited to PsA or AS) which evaluates the presence or absence of pain by applying local pressure to the following entheses:

- Supraspinatus insertion, left and right
- Medial epicondyle humerus, left and right
- Lateral epicondyle humerus, left and right
- Greater trochanter, left and right
- Quadriceps-to-Patella, left and right
- Patellar-to-tibia, left and right
- Achilles tendon insertion, left and right

- Plantar fascia, 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 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 participant should also perform the enthesitis assessments for that participant at every subsequent visit.

8.1.1.6. Minimal Disease Activity

Minimal Disease Activity defines a satisfactory state of disease activity that includes the 5 domains of PsA (joint symptoms, skin psoriasis, participant's assessment of pain and disease activity, physical function, and enthesitis). Participants are classified as achieving MDA if they fulfilled 5 of 7 outcome measures: tender joint count ≤1; swollen joint count ≤1; PASI ≤1 or BSA ≤3%; participant's pain VAS score of ≤15; participant's global disease activity VAS (arthritis and psoriasis) score of ≤20; Disability Index of the Health Assessment Questionnaire (HAQ-DI) score ≤0.5; and tender entheseal points ≤1. (Coates 2010)

8.1.1.7. Physician's Global Assessment of Disease Activity

The physician is asked to assess the participant's arthritis on a 100 mm VAS, with the left end indicating "No arthritis activity" and the right end indicating "Extremely active arthritis."

8.1.1.8. Disease Activity Index for Psoriatic Arthritis (DAPSA)

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), participant's assessment of pain (0-10 VAS), and participant's global assessment of disease activity (arthritis, 0-10 VAS) (Helliwell 2014b). The cutoffs for disease activity are 18.5 (low) to 45.1 (high) (Helliwell 2014a).

8.1.1.9. Magnetic Resonance Imaging of the Hand and Foot

The MRI assessments of hand and foot joints will be conducted at all study sites as specified in the SoA (Section 1.3). A sponsor-identified central imaging vendor will liaise with study sites to qualify imaging centers for study participation, and train imaging center staff on the operational aspects of conducting the MRI component of this study. A separate imaging manual will be provided prior to the start of the study that details specific requirements regarding study participant preparation in advance of a scanning session, positioning within the scanner, the MRI acquisition protocol, and electronic transfer of data to the central imaging vendor.

The standard series of MRI scans associated with the PsAMRIS and HEMRIS assessments include acquisitions made after intravenous injection of a gadolinium-based contrast agent (GBCA). Due to the planned use of gadolinium contrast for these MRI assessments, an eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method prior to each MRI hands/feet collection. Prior to MRI scanning, an MR-safety screening will be performed per

procedures established by the local imaging center to assess participants against criteria that are contraindications for MRI or the use of GBCA.

Additionally, the investigator/study coordinator will be required to complete the MRI screening worksheet provided by the sponsor before the MRI scans to screen for and document any contraindications to GBCA administration or MRI, which include, but are not limited to:

- contraindications to MRI
  - metal implants, devices, paramagnetic objects contained with the body, and excessive or metal-containing tattoos;
  - a body habitus that exceeds the physical limitations of any component of the MRI system (eg, magnet bore size or radiofrequency coil size) based on the investigator's judgment at screening;
  - history of severe claustrophobia that will impact an individual's ability to undergo MRI despite mild sedation/treatment with an anxiolytic.
- contraindications to GBCA administration for the study
  - recent (<1 year) GBCA administration;
  - acute kidney injury;
  - known previous reaction to GBCA that precludes additional exposure to gadolinium;
  - severe renal impairment (eGFR <30 mL/min/1.73 m^2);
  - moderate renal impairment (eGFR <60 and ≥30 mL/min/1.73 m^2);
    - for participants with moderate renal impairment the investigator should consult with the site radiologist and sponsor to determine if the participant has additional risk factors that may preclude them from administration of GBCA.

Study participants identified during screening to have any contraindication to use of GBCA may still participate in the MRI component of this study, however, only the non-GBCA enhanced scans should be acquired. If safety concerns arise beyond those associated with use of GBCA that preclude MRI evaluation, enrollment in the study may still be permitted and MRI will not be a required evaluation for such participants.

Note: If there are other circumstances that preclude MRI evaluations for a participant, the investigator should consult with medical monitor and sponsor to determine if the participant enrollment in the study may still be permitted.

Baseline MRI scanning will be conducted during screening ≤14 days prior to the Week 0 visit, and follow-up scanning will be conducted ≤14 days prior to the Week 24 visit (refer to the SoA, Section 1.3). Participants who discontinue from the study after Week 4, but prior to Week 20, should be scheduled for an early termination MRI assessment to be conducted 2 to 4 weeks after the last administration of study intervention. All MRI scanning sessions should be scheduled well in advance to allow for proper alignment with the window of -14 to 0 days around the target scanning visit.

In advance of the baseline MRI scanning visit, determination of the right or left hand and foot to undergo scanning should be made based on which has greater clinical manifestations of disease. This determination should be relayed to the imaging center staff at the time of scan scheduling to ensure the appropriate hand and foot are imaged. For the hand, the side with the highest count of tender and swollen joints should be imaged. The decision tree for selection of the foot should be based on the following hierarchy:

- image the foot with heel enthesitis;
- if both feet have heel enthesitis, image the foot with the highest count of tender and swollen joints;
- if neither foot has heel enthesitis, image the foot with the highest count of tender and swollen joints.

Assessments of acquired MRI scans will be performed by a panel of expert central readers using the HEMRIS and PsAMRIS frameworks following procedures to be developed in a study-specific image analysis manual.

The Outcome Measures in Rheumatology (OMERACT) Heel Enthesitis MRI Scoring system (HEMRIS) is developed by consensus-based MRI definitions of key entheseal pathologies in the heel (Mathew 2019; Mathew 2020).

The OMERACT Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) assesses MRI features (synovitis, tenosynovitis, periarticular inflammation, bone edema, bone erosion, and bone proliferation) in the hands and feet of PsA patients (Østergaard 2009; Glinatsi 2015).

8.1.2. Psoriasis Response Evaluations

8.1.2.1. Body Surface Area Involvement

The BSA of psoriasis is measured using the palm method at the timepoints indicated in the SoA (Section 1.3). The size of the BSA with psoriatic lesions is estimated based on the number of palms of the participant, each palm (from the basis of wrist to the proximal interphalangeal joints including thumb) is equivalent to 1% BSA.

8.1.2.2. Psoriasis Area and Severity Index (PASI)

The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy (Fredriksson and Pettersson 1978). 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 participant at baseline should also perform the PASI evaluations for the participant at all subsequent visits through Week 24. 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 the start of the study is encouraged.

8.1.2.3. Investigator's Global Assessment (IGA) of Psoriasis

The IGA documents the investigator's assessment of the participant's psoriasis at a given time point. Overall lesions are graded for induration, erythema, and scaling 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 participant'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 participant at baseline should also perform the IGA evaluations for the participant at all subsequent visits through Week 24. 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 the start of the study is encouraged.

8.1.3. Patient-reported Outcomes

- The ePRO instruments will be provided in the local language in accordance with local guidelines.
- The ePRO instruments must be available for regulators and for Institutional Review Board/Independent Ethics Committee (IRB/IEC) submissions, therefore the ePRO instruments or screen shots need to be attached to the protocol or provided in a companion manual with the instruments that will be submitted with the protocol.
- The ePRO and AE data will not be reconciled with one another.

8.1.3.1. Disability Index of the Health Assessment Questionnaire (HAQ-DI)

The functional status of the participant will be assessed by the HAQ-DI (Fries 1980). 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 an 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 demonstrated (Husted 1998). It has also been shown to be responsive to changes in a participant's disease (Mease 2015). In PsA, a decrease in score of 0.35 has been determined to indicate a meaningful improvement (Mease 2011). A sample HAQ-DI assessment tool is provided in Appendix 10 (Section 10.10).

8.1.3.2. Patient's Assessment of Pain

Patient's assessment of pain: Participants will be asked to assess their average pain during the prior week on a 100 mm VAS, with the left end indicating "no pain" and the right end indicating "the worst possible pain." A sample patient's assessment of pain assessment tool is provided in Appendix 11 (Section 10.11).

8.1.3.3. Patient's Global Assessment of Disease Activity

Patient's global assessment of disease activity (arthritis and psoriasis): Participants will be asked to rate how they felt during the prior week regarding their psoriasis and arthritis on a 100 mm VAS, with the left end indicating "Excellent" and the right end indicating "Poor." A sample patient's global assessment of disease activity (arthritis and psoriasis) assessment tool is provided in Appendix 12 (Section 10.12).

Patient's global assessment of disease activity (arthritis): Participants will be asked to rate how they felt during the prior week regarding their arthritis on a 100 mm VAS, with the left end indicating "Excellent" and the right end indicating "Poor." A sample patient's global assessment of disease activity (arthritis) assessment tool is provided in Appendix 12 (Section 10.12).

8.1.3.4. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a patient self-assessment for AS that consists of 6 questions relating to the 5 major symptoms of AS (Garrett 1994). Participants will complete the BASDAI using a 10-unit VAS to indicate the degree of their symptoms over the past week. Higher scores indicate greater disease severity and a score decrease of 50% or 2 points is considered clinically meaningful (Zochling 2006).

The scale consists of 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]). A sample BASDAI assessment tool is provided in Appendix 13 (Section 10.13).

8.1.3.5. Short Form 36 (SF-36)

The 36-item Short Form Health Survey (SF-36) will be used to measure health status and quality of life. It uses a multi-domain instrument with 36 items that is self-administered by participants. It includes 8 subscales that covered a range of functioning: physical functioning, physical role functioning, bodily pain, general mental health (psychological distress and well-being), emotional role functioning, social functioning, vitality (energy and fatigue), and general health perception. The scoring yields a PCS, a Mental Component Summary, and subscale scores. Higher scores represent better outcomes, with an increase of 5 points considered to be clinically meaningful. A sample SF-36 assessment tool is provided in Appendix 14 (Section 10.14).

8.1.3.6. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)

Fatigue has been identified as an important symptom and a unique concept in addition to the core disease measures of patients with PsA (Chandran 2007). The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue questionnaire consists of 13 questions that assess a participant'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 (Cella 2005). A sample FACIT-Fatigue assessment tool is provided in Appendix 15 (Section 10.15).

8.1.3.7. Patient-Reported Outcomes Measurement Information System 29 (PROMIS-29 v2.1)

Patient-Reported Outcomes Measurement Information System 29 Profile (PROMIS-29 v2.1): A profile instrument intended for adults (ages 18+) and consists of a collection of short forms containing 4 items for each of 7 PROMIS domains (depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to participate in social roles and activities) and an additional pain intensity 0-10 numeric rating scale (Ware 1994). The PROMIS-29 Profile is universal rather than disease-specific and assesses all domains over the past 7 days except for physical function, which has no timeframe specified. The raw score of each domain is converted into a standardized score with a mean of 50 and an SD of 10 (T-Score). The standardized T-score is reported as the final score for each participant. Pain intensity is presented as raw responses (0-10). For PROMIS domains of depression, anxiety, physical function, pain interference, and fatigue, a score of 50 is the average for the US general population with a SD of 10, because testing was performed on a large sample of the general population. However, the other 2 domains (ability to participate in social roles and activities and sleep disturbance) were not centered in a national sample. For these 2 domains, a score of 50 represents the average of the calibration sample which was generally more enriched for chronic illness, and a score of 50 likely represents somewhat sicker people than the general population. A higher PROMIS T-score represents more of the concept being measured. For negatively-worded concepts like anxiety, a T-score of 60 is one SD worse than average. By comparison, an anxiety T-score of 40 is one SD better than average. However, for positively-worded concepts like physical function, a T-score of 60 is better than average while a T-score of 40 is worse. All ePRO measurements are to be conducted before any tests, procedures, or other consultations for that visit to prevent influencing participant perceptions. A sample PROMIS-29 assessment tool is provided in Appendix 16 (Section 10.16).

8.2. Safety Assessments

Details regarding the Independent DMC are provided in Committees Structure in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

Physical examinations will be performed by the investigator or designated physician as specified in the SoA (Section 1.3). Any abnormalities or changes in severity noted during the review of body systems should be documented in the source document.

While assessment of the participants for safety and efficacy requires some physical examination by an investigator at all visits, a more complete, detailed physical examination should be performed as specified in the SoA (Section 1.3). Total body skin examination will be performed to evaluate for any suspected malignant skin lesions including basal cell carcinoma, squamous cell carcinoma, and melanoma.

8.2.2. Vital Signs

Temperature, pulse/heart rate, respiratory rate, blood pressure will be assessed.

Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

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

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.

8.2.3. Height and Weight

Height and weight will be measured as specified in the SoA (Section 1.3).

8.2.4. Electrocardiograms

A 12-lead ECG will be performed at Week 0.

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before

ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

8.2.5. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in the SoA (Section 1.3) and Appendix 2: Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

8.2.6. 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 intervention administration visit. Pregnancy tests must be completed, and the result must be negative before the administration of any intervention for that visit. All pregnancy test results must be recorded in study source documents.

8.2.7. Suicidal Ideation and Behavior Risk Monitoring

Participants being treated with study intervention should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior.

No signal of suicidal ideation and behavior has been observed in the clinical trials of guselkumab to date. However, in light of 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 suicidal ideation and behavior among study participants. The eC-SSRS measures 5 possible levels of suicidal ideation and 4 possible suicidal behaviors, as well as nonsuicidal self-injurious behavior. The assessment is a fully structured, participant self-report eC-SSRS-questionnaire, including standardized questions, follow-up prompts, error handling routines, and scoring conventions (Mundt 2013; Posner 2011).

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. Participants will complete the eC-SSRS questionnaire using the sponsor-provided electronic device. Study site personnel will train the participants 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 SoA (Section 1.3). During a visit, participants will be directed to a private, quiet place with the electronic device to complete the assessment. Participants 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.

Participants with significant suicidal ideation and behavior may require up to 10 minutes to answer all relevant questions.

At the conclusion of each assessment, the eC-SSRS Findings Report can be viewed electronically. At screening ("In the last 6 months") and Week 0, participants with an Ideation level (1-5) or any suicidal behaviors or with a response of "YES" for nonsuicidal, 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. Participants with an Ideation level (1-5) on the eC-SSRS or any suicidal behaviors or with a response of "YES" for nonsuicidal, self-injurious behavior at any postbaseline visit will also be referred to an appropriate mental health professional for evaluation. If a participant's psychiatric disorder can be adequately treated with psychotherapy and/or pharmacotherapy then the participant, 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 participant should not leave the site at screening or be dosed at dosing visits before the eC-SSRS Findings Report (both for negative and positive reports) is reviewed by the investigator and the participant's risk has been assessed and follow-up determined, as appropriate. For each Ideation level and s, 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: Participant 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 participant has a positive suicidal indication including for an incomplete-positive assessment), the site can immediately see the outcome via the electronic device.

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

Interruption or the discontinuation of study intervention should be considered for any participant 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 postbaseline (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 participants with the medical monitor or designee is required (see Section 7.1). 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.

8.2.8. Concomitant Medication Review

Concomitant medications will be reviewed at each visit and recorded in the source documents and eCRF.

8.2.9. Injection-Site Reactions

A study intervention injection-site reaction is any adverse reaction at a CC study intervention injection-site. The injection sites will be evaluated for reactions and any injection-site reaction will be recorded as an AE.

8.2.10. Hypersensitivity Reactions

Before any administration of study intervention at the study site, appropriately trained personnel and medications (eg, antihistamines, injectable epinephrine) must be available to treat hypersensitivity reactions, including anaphylaxis. All participants must be observed carefully for signs and symptoms of a hypersensitivity reaction (eg, urticaria, pruritis, angioedema, wheezing, dyspnea, or hypotension).

8.2.11. Infections

Investigators are required to evaluate participants for any signs or symptoms of infection at every scheduled visit. Study intervention administration should not be given to a participant with a clinically significant, active infection. If a participant develops a serious infection, including but not limited to sepsis or pneumonia, study intervention must be temporarily discontinued (Section 7). Any serious infection should be discussed with the medical monitor or designee, and study intervention should be withheld until the clinical assessment is complete.

8.2.12. Tuberculosis Evaluations

8.2.12.1. Initial Tuberculosis Evaluation

Participants must undergo testing for TB (refer to Appendix 8 [Section 10.8]) 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 participant 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 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 to evaluate a participant who is high risk of having latent TB. If either the QuantiFERON-TB test or the tuberculin skin test is positive, the participant is considered to have latent TB infection for the purposes of eligibility for this study.

Participants with a negative QuantiFERON-TB test result (and a negative tuberculin skin test result in countries in which the QuantiFERON-TB test is not approved/registered or the tuberculin skin is mandated by local health authorities) are eligible to continue with pre-randomization procedures. Participants with a newly identified positive QuantiFERON-TB 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 participants. If no local country guidelines for immunocompromised participants exist, US guidelines should be followed, or the participant will be excluded from the study.

A participant whose first QuantiFERON-TB test result is indeterminate should have the test repeated. In the event that the second QuantiFERON-TB test result is also indeterminate, the participant 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 participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor's or designee's medical monitor and recorded in the participant's source documents and initialed by the investigator.

8.2.12.2. Ongoing Tuberculosis Evaluation

Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, participants must be evaluated for signs and symptoms of active TB at scheduled visits (refer to the SoA in Section 1.3) or by telephone contact approximately every 8 to 12 weeks. 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 participant 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 participants may present as disseminated disease or with extrapulmonary features. Participants with evidence of active TB should be referred for appropriate treatment.

Participants 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 test, a repeat tuberculin skin test in countries in which the QuantiFERON-TB 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 participant's risk of developing active TB and whether treatment is warranted. Study intervention administration should be interrupted during the investigation. A positive QuantiFERON-TB test or tuberculin skin test result should be considered detection of latent TB. Participants with a newly identified positive QuantiFERON-TB 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 participants. If no local country guidelines for immunocompromised participants exist, US guidelines should be followed, or the participant will be excluded from the study. If the QuantiFERON-TB test result is indeterminate, the test should be repeated. Participants should be encouraged to return for all subsequent scheduled study visits according to the protocol. Participants who discontinue treatment for latent TB prematurely or who are noncompliant with therapy must immediately discontinue further administration of study intervention and be encouraged to return for all subsequent scheduled study visits according to the SoA (Section 1.3).

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and PQCs, from clinical studies are crucial for the protection of participants, 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.

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

For study intervention that meets the definition of a drug-device combination product, malfunctions or deficiencies of a device constituent will be reported as a PQC.

Further details on AEs, SAEs, and PQCs can be found in Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety.

Serious Adverse Events

All SAEs, as well as PQCs, 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.

Serious adverse events, including those spontaneously reported to the investigator within 16 weeks after the last dose of study intervention, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

A **possible Hy's law case** is defined by the occurrence of ALT/AST ≥3×ULN together with total bilirubin (Tbili) ≥2×ULN or international normalized ratio (INR) >1.5 (if measured). Any possible Hy's law case is considered an important medical event and should be reported to the sponsor in an expedited manner using the Serious Adverse Event Form, even before all other possible causes of liver injury have been excluded. (INR criterion is not applicable to participants receiving anticoagulants.)

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the eCRF, which must be completed and reviewed 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 transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.3.2. 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 participant is the preferred method to inquire about AE occurrence.

Solicited Adverse Events

Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned.

Unsolicited Adverse Events

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

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or

PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events

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.

An anticipated event is an AE that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study the following SAEs will be considered anticipated events:

- Worsening of psoriasis
- Worsening of PsA

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis indicates that the anticipated event occurs more frequently in the intervention group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries/territories in which the studies are conducted.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants 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 an SAE reporting form. Any participant who becomes pregnant during the study must discontinue further study intervention.

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

8.3.6. Adverse Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first study intervention administration(s) in participants in this clinical study must be reported by the investigator to the sponsor or designee within 24 hours after being made aware of the event, according to the procedures in Appendix 4 (Section 10.4). 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.

8.4. Pharmacokinetics

Serum samples will be used to evaluate the PK of guselkumab or golimumab. Serum collected for PK 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. Participant confidentiality will be maintained.

8.4.1. Evaluations

Venous blood samples will be collected for measurement of serum concentrations of guselkumab and golimumab, and antibodies to guselkumab and antibodies to golimumab at the timepoints shown in the SoA (Section 1.3). Serum samples will also be collected at the final visit from participants who discontinue study intervention or were withdrawn from the study. At visits where PK and immunogenicity will be evaluated, 1 blood draw of sufficient volume can be used. Each sample will be split into 5 aliquots: 1 aliquot each for serum guselkumab concentration, serum golimumab concentration, antibodies to guselkumab, antibodies to golimumab, and 1 aliquot as a back-up. Samples must be collected before study intervention administration at visits when a study intervention administration is scheduled. The exact dates and times of blood sample collection must be recorded in the laboratory requisition form.

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

8.4.2. Analytical Procedures

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

8.4.3. Pharmacokinetic Parameters and Evaluations

Parameters

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

Pharmacokinetic/Pharmacodynamic Evaluations

The relationship between serum concentrations of guselkumab or golimumab and efficacy measures or relevant biomarker(s) may be examined when appropriate.

8.5. Genetics and Pharmacogenomics

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary where local regulations permit. Participant participation in pharmacogenomic research is optional.

Genetic (DNA) variation may be an important contributory factor to interindividual variability in drug response and associated clinical outcomes. Genetic and epigenetic factors may also serve as markers for disease susceptibility and prognosis and may identify population subgroups that respond differently to an intervention.

The optional pharmacogenomic samples may be analyzed for identification of genetic and epigenetic factors that may be associated with the disease and/or the response to the treatments. This research may consist of the analysis of 1 or more candidate genes, or the analysis of genetic and epigenetic markers throughout the genome, or analysis of the entire genome (as appropriate) in relation to the disease and the treatments.

8.6. Biomarkers

Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to guselkumab or golimumab and/or PsA, where local regulations permit. Assessments (detailed below) will include the evaluation of relevant biomarkers in serum, plasma, whole blood, and tissue biopsies (when available) collected as specified in the SoA (Section 1.3), where local regulations permit.

Data collected from these samples may be used for exploratory research that include the following objectives:

1. To understand the molecular effects of guselkumab or golimumab

2. To understand PsA pathogenesis

3. To understand why individual participants may respond differently to guselkumab or golimumab

4. To develop diagnostic tests to identify PsA populations that may be responsive or non-responsive to treatment with guselkumab or golimumab

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for

biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

8.6.1. Pharmacodynamics

Samples for the analysis of pharmacodynamic biomarkers will be collected. Serum level of T helper (Th)-17 cytokines, including but not limited to IL-17A, IL-17F, and IL-22, and select inflammatory cytokines may be measured to assess the pharmacodynamic effect of guselkumab or golimumab.

8.6.2. Serum and Plasma Biomarkers

Blood samples will be collected from all participants for serum and plasma-based biomarker analyses, where local regulations permit. Serum and plasma may be analyzed for levels of specific proteins, other inflammation-related molecules, and/or broad panel of analytes relevant to PsA pathogenesis and guselkumab or golimumab treatment.

8.6.3. Whole Blood Gene Expression Profile

Whole blood will be collected by venipuncture from participants for RNA expression analysis, where local regulations permit. Total RNA will be isolated and used for differential gene expression analyses to identify gene expression patterns that are relevant to guselkumab or golimumab treatment and/or PsA, and to evaluate markers that can predict clinical response. Transcriptomic studies may be conducted using microarray, and/or alternative equivalent technologies, which facilitate the simultaneous measurement of the relative abundances of multiple RNA species resulting in a transcriptome profile for each blood sample. The samples may also be used for targeted assessment of genes relevant to the disease and/or the treatment. These analyses may be used to evaluate the changes in gene expression profiles that may correlate with biological response relating to PsA and/or the action of guselkumab or golimumab, and may also be used to identify population subgroups that respond differently to an intervention.

8.6.4. Peripheral Blood Mononuclear Cells

If operationally feasible, whole blood will also be collected and processed for PBMC isolation and cryopreserved for later analysis. Analysis may include but is not limited to flow cytometric assessment of cell populations, transcriptomics, single cell transcriptomics, or functional assessment of cells in response to guselkumab or golimumab treatment and/or related to PsA pathogenesis. These analyses may not be performed if cryopreserved PBMC samples do not meet the quality or quantity standard required for the assessments.

8.6.5. Tissue Biomarkers

Biopsies from lesional and nonlesional skin may be collected from participants who consent to this optional substudy component of the study (with a separate ICF), as fixed blocks, slides, fresh or frozen samples, where local regulations permit. Samples from lesional and nonlesional regions will be collected at Week 0 and a lesional sample only at Week 24. Tissue samples may be analyzed for levels of proteins, transcripts, and other inflammation-related molecules and/or soluble factors

relevant to PsA pathogenesis and guselkumab or golimumab treatment. Histopathological assessments of the tissue samples, including but not limited to immunohistochemistry, may also be performed. Analyses may include, but are not limited to, tissue proteomic and transcriptomic assessment of cell populations to identify cellular biomarkers associated with PsA pathogenesis and/or guselkumab or golimumab treatment as permitted by relevant and advancing technologies.

8.7. Immunogenicity Assessments

Serum samples for detection of antibodies to guselkumab and/or antibodies to golimumab will be collected from all participants according to the SoA (see Section 1.3). Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. Samples collected for 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. Participant confidentiality will be maintained.

Serum samples will be screened for antibodies binding to guselkumab and/or golimumab and the titer of confirmed positive samples will be reported. Serum samples that test positive for antibodies to guselkumab and/or golimumab will be further characterized to determine if antibodies to guselkumab and/or antibodies to golimumab could neutralize the biological effects of guselkumab and/or golimumab in vitro (ie, neutralizing antibodies [NAbs] to guselkumab and/or golimumab). Other analyses may be performed to verify the stability of antibodies to guselkumab and/or golimumab and/or further characterize the immunogenicity of guselkumab and/or golimumab.

Analytical Procedures

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

8.8. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

The primary hypothesis of this study is that combination therapy with guselkumab and golimumab is superior to guselkumab monotherapy as assessed by the proportion of participants who achieve an MDA response at Week 24.

9.2. Sample Size Determination

The planned enrollment in this study is approximately 90 participants. The sample size selection was determined based on the primary endpoint of proportion of participants who achieve an MDA

response at Week 24. With an assumed response rate of 45% in the combination regimen (guselkumab CCI CCI CC and golimumab CCI CCI CCI and 20% in the guselkumab CCI CCI monotherapy regimen, sample size of 60 in the combination regimen and 30 in the monotherapy regimen would achieve above 80% power using the one-sided Fisher's Exact test at significance level 0.1. The MDA response rate in the guselkumab CCI CCI monotherapy regimen is based on indirect estimation of different dose/population from PSA3001, PSA3002 and PSA3003. Table 4 shows the power to detect a difference in the proportion of participants achieving MDA response between combination regimen and monotherapy regimen with various assumptions.

Table 4: Statistical Power for Treatment Difference in MDA Response at Week 24

MDA Response Rate			
Guselkumab CCI CCI	Guselkumab CCI CCI + Golimumab CCI CCI	Difference (Δ)	Power
20%	35%	15%	48%
20%	40%	20%	67%
20%	**45%**	**25%**	**82%**
25%	35%	10%	29%
25%	40%	15%	47%
25%	45%	20%	65%
25%	50%	25%	80%

Abbreviations: MDA=minimal disease activity; CCI CCI

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Full Analysis Set (FAS)	All participants who were randomized in the study and received at least one (complete or partial) administration of study intervention. Participants will be analyzed according to the intervention they were randomized into, ie, regardless of the intervention that participants receive. This analysis set will be used for the efficacy analysis.
Safety Analysis Set (SAS)	All participants who were randomized in the study and received at least one (complete or partial) administration of study intervention. Participants will be analyzed according to the intervention they received, ie, regardless of the intervention that participants randomized to.
PK Analysis Set (PAS)	All participants who were randomized in the study and received at least one (complete) administration of study intervention and had at least one valid blood sample drawn for PK analysis. Participants will be analyzed according to the intervention they received, ie, regardless of the intervention that participants randomized to.

9.4. Statistical Analyses

Database locks are scheduled at Week 24 and End of Study (Week 36). The first DBL will occur when all randomized participants 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 participants have either completed their final safety visit (Week 36) or have terminated study participation prior Week 36 (referred to as Final DBL).

The SAP will be finalized prior to the first DBL (ie, once all participants complete Week 24) and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

In general, descriptive statistics, such as mean, SD, median, interquartile range, minimum and maximum for continuous variables; counts and percentages for discrete variables will be used to summarize most data.

For binary response efficacy endpoints, treatment comparisons will generally be performed using an Exact test or a Cochran-Mantel-Haenszel (CMH) test or logistic regression, if applicable. For continuous efficacy endpoints, treatment comparisons will be performed using an analysis of covariance (ANCOVA), a mixed model for repeated measures (MMRM), or a constrained longitudinal data analysis (cLDA).

Statistical testing will be performed by using a 1-sided test, with 10% type I error. No multiplicity adjustment will be applied to the primary endpoint.

9.4.2. Primary Endpoint

The primary endpoint to be analyzed for the primary analysis is the proportion of participants who achieved an MDA response at Week 24. This endpoint will be analyzed based on primary estimand defined by the following 5 components:

- Population
  - Participants who are ≥18 to ≤65 years of age (inclusive), with active PsA and previous history of IR to either 1 or 2 anti-TNFα therapy(ies) either due to primary nonresponse or loss of efficacy.
- Treatment
  - Combination regimen: guselkumab CCI CC CCI and golimumab CCI CC CCI
  - Monotherapy regimen: guselkumab CCI CC CCI and placebo 0.5 mL for golimumab CC CCI
- Variable
  - Binary response variable, where a responder is defined as a participant with an MDA response at Week 24.
  - Participants with intercurrent events 1, 2, and 3 (described below) are considered as nonresponder/treatment failures.
  - For participants with intercurrent event 4 (described below), the variable values after this Intercurrent Event (ICE) will not be utilized/used.

- Intercurrent Events and Strategies
    1) Initiated protocol-prohibited medications/therapies for PsA
    2) Initiation or increased the dose of nonbiologic DMARDs (MTX, SSZ, HCQ, LEF) or oral corticosteroid over baseline for PsA
    3) Discontinued study intervention due to any reason except due to study conduct affected by COVID-19
    4) Discontinued study intervention due to study conduct affected by COVID-19
        - Note 1: ICEs in categories 1, 2, and 3 will be considered as nonresponders/ treatment failure and plan to be handled with the **composite strategy** as reflected in the Variable definition, ie, the occurrence of ICEs prior to Week 24 will be considered as treatment failures and will be treated as nonresponder regardless of the observed MDA response status.
        - Note 2: ICE 4 plan to be handled with **hypothetical strategy**, as if the COVID-19 pandemic did not occur, and therefore participant had not experienced with these ICEs. Observed data through Week 24 after meeting ICE 4 will not be used and be considered as missing at random (MAR) and will be imputed by using multiple imputation (MI).
        - Note 3: If participants experience multiple ICEs, then an ICE in categories 1 to 3 will supersede an ICE in category 4.
        - Note 4: The detailed definition for each of the ICE will be included in SAP.
- Population-level Summary
    – Difference in proportion of responders between combination regimen (guselkumab CCI CC CCI and golimumab CCI CC CCI and monotherapy regimen (guselkumab CCI CC CCI

The treatment effect of the combination regimen (guselkumab CCI CC CCI and golimumab CCI CC CCI versus monotherapy (guselkumab CCI CC CCI will be tested using the Chi-square or CMH test stratified by the randomization strata levels or logistic regression, if applicable. The magnitude of the effect will be estimated by the difference in MDA response rate between the 2 treatment groups with a 95% confidence interval calculated based on Wald statistics. A sensitivity analysis will be performed using a re-randomization test to evaluate the impact of the dynamic randomization.

Additional sensitivity/supplemental analyses which vary how intercurrent events (eg, alternative estimand) 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 MDA at Week 24.

Subgroup Analyses

Subgroup analysis will be performed to evaluate consistency in the primary efficacy endpoint by demographic characteristic, baseline disease characteristic, and baseline medication. Interaction of the treatment groups and the subgroups will also be provided when a subgroup has at least 2 categories.

9.4.3. Secondary Endpoints

Secondary endpoints are provided in Section 3. Analyses will compare between treatment groups. The methods of analysis and the approach to control the Type I error for multiplicity, as well as the data handling rules, will be provided in the SAP.

9.4.4. Other Endpoints

Other endpoints are provided in Section 3. They 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.

9.4.5. Exploratory Endpoints

Exploratory endpoints are provided in Section 3. They will be descriptively summarized either at a single time point or 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.

9.4.6. Safety Analyses

All safety analyses will be made on the SAS (refer to Section 9.3 for definition).

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 16 weeks is considered to be treatment-emergent. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

The following analyses of AEs will be included to assess the safety of participants:

- 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.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or an SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test (eg, hematology, clinical chemistry). Reference ranges, NCI-CTCAE, and multiples of ULN will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline

results will be presented in pre- versus post-intervention cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the laboratory abnormalities will be made. A listing of participants with any laboratory results outside the reference ranges will be provided, including a summary of laboratory values above the ULN. Listings of participants with any abnormal postbaseline laboratory values of NCI-CTCAE Grade ≥2 will also be provided.

Vital Signs

Vital signs including temperature, pulse/heart rate, and blood pressure (systolic and diastolic) will be summarized over time, using descriptive statistics and/or graphically. The percentage of participants with values beyond clinically important limits will be summarized.

9.4.7. Other Analyses

A DMC will be established as noted in Committees Structure in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations.

Pharmacokinetic Analyses

The PK evaluable population is defined as all the participants who received at least 1 complete dose of guselkumab and/or golimumab and had at least 1 valid blood sample drawn for PK analysis after their first dose of guselkumab and/or golimumab.

Serum guselkumab and/or golimumab concentrations over time will be summarized for each treatment group using descriptive statistics. All concentrations below the lowest quantifiable (BQL) sample concentration of the analysis system dataset will be treated as zero in the summary statistics.

Population PK modeling will be conducted when appropriate. 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/or golimumab, 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.

Immunogenicity Analyses

The incidence and titers of antibodies to guselkumab and/or golimumab will be summarized for all participants who receive at least 1 dose of guselkumab and/or golimumab and have appropriate samples for detection of antibodies to guselkumab and/or golimumab (ie, participants with at least 1 sample obtained after their first dose of guselkumab).

The incidence of NAbs to guselkumab and/or golimumab will be summarized for participants who are positive for antibodies to guselkumab and/or golimumab and have samples evaluable for NAbs to guselkumab and/or golimumab.

A listing of participants who are positive for antibodies to guselkumab and/or golimumab will be provided. Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

Biomarker and Pharmacodynamic Analyses

Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information or insufficient number of samples are available for analyses. Any biomarker samples received by the contract vendor or sponsor after the cutoff date will not be analyzed, and therefore, excluded from the biomarker analysis.

The biomarker analyses will be used to understand PsA, characterize the effects of guselkumab or golimumab to identify PD markers and biomarkers relevant to treatment, and determine if these markers can predict response to guselkumab or golimumab. The biomarker analysis may include but are not limited to serum Th17 cytokines, inflammatory markers, whole blood RNA profile, and other categories of biomarkers potentially involved in the development and the progression of PsA.

Changes in biomarkers over time may be summarized by intervention group. Associations between baseline levels and changes from baseline in select markers and clinical response may be explored.

Results of biomarker analyses may be presented in a separate report.

Pharmacokinetic/Pharmacodynamic Analyses

If data permit, the relationships between serum concentrations of guselkumab and golimumab and efficacy and/or relevant PD endpoints may be analyzed graphically. If a relationship is observed, a suitable PK/PD model may be developed to describe the exposure-response relationship. Analyses results may be summarized in a separate technical report.

Pharmacogenomic Analyses

Genetic (DNA) analyses may be conducted only in participants who sign the consent form to participate in the pharmacogenomic sampling. These analyses are considered exploratory. DNA samples may be used for research related to guselkumab or golimumab or PsA. They may also be used to develop tests/assays related to guselkumab or golimumab and PsA. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate) in relation to guselkumab or golimumab or PsA clinical endpoints.

Results may be presented in a separate report.

Imaging Analyses

Post hoc analyses: Consistent with the exploratory nature of the MRI assessments to be conducted over the course of this study, refinements to the PsAMRIS and HEMRIS scoring systems or development of alternative image analysis algorithms may further improve the utility of MRI for characterizing peripheral joint pathology in PsA. As such, the sponsor and/or delegate may

undertake post hoc analyses of the subject-level data acquired in this study. Any such analyses will not be included in the Clinical Study Report, but a separate supplemental report will be written to capture this work, if undertaken.

9.5. Interim Analysis

An IA is planned when 60 participants (two-thirds of the target population) complete Week 24.

The primary goal of this IA is to obtain an early indication on combination therapy efficacy to determine feasibility of advancing future study planning activities. The IA data will be reviewed by an independent Interim Analysis Committee (IAC; see Section 10.3.6 for more details).

The SAP will describe the planned IA in greater detail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ACR	American College of Rheumatology
AE	adverse events
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AS	ankylosing spondylitis
AST	aspartate aminotransferase
AUC	area under the curve
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BCG	Bacillus Calmette-Guérin
BSA	body surface area
CASPAR	ClASsification criteria for Psoriatic ARthritis
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum observed concentration
CMH	Cochran-Mantel-Haenszel
COA	clinical outcome assessment (paper or electronic as appropriate for this study)
COVID-19	Coronavirus Disease 2019
CRP	C-reactive protein
DAPSA	Disease Activity in Psoriatic Arthritis
DBL	database lock
DILI	drug-induced liver injury
DMARD	disease-modifying antirheumatic drugs
DMC	Data Monitoring Committee
DSM-V	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
DNA	deoxyribonucleic acid
DSS	Dactylitis Severity Score
ECG	electrocardiogram
eCRF	electronic case report form
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
ePRO	electronic patient-reported outcome(s)
EU	European Union
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
FOIA	Freedom of Information Act
FSH	follicle-stimulating hormone
GBCA	gadolinium-based contrast agent
GCP	Good Clinical Practice
HAQ	Health Assessment Questionnaire
HAQ-DI	Disability Index of the Health Assessment Questionnaire
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HEMRIS	Heel Enthesitis Magnetic Resonance Imaging Scoring System
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
hsCRP	high-sensitivity C-reactive protein
IA	Interim Analysis
IAC	Interim Analysis Committee
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICE	Intercurrent Event
ICF	informed consent form
ICH	International Council on Harmonisation

IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IJA	independent joint assessor
IL	interleukin
IM	intramuscular
INR	international normalized ratio
IR	inadequate response
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
JAK	janus kinase
LEF	leflunomide
LEI	Leeds Enthesitis Index
mAB	monoclonal antibody
MDA	minimal disease activity
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTX	methotrexate
NAbs	neutralizing antibodies
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
nr-AxSpA	nonradiographic axial spondyloarthritis
NSAID	nonsteroidal anti-inflammatory drug
OMERACT	Outcome Measures in Rheumatology Clinical Trials
PASI	Psoriatic Area and Severity Index
PBMC	peripheral blood mononuclear cell
PCC	protocol clarification communication
PCS	Physical Component Score
PD	pharmacodynamic(s)
CCI	[redacted]
[redacted]	[redacted] CCI [redacted]
[redacted]	[redacted] [redacted]
PK	pharmacokinetic(s)
POC	proof-of-concept
PPD	purified protein derivative
PQC	Product Quality Complaint
PROMIS-29	Patient-Reported Outcomes Measurement Information System 29
PsA	psoriatic arthritis
PsAMRIS	Psoriatic Arthritis Magnetic Resonance Imaging Score
CCI	CCI [redacted]
q8w	every 8 weeks
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Safety Analysis Set
C	subcutaneous
SD	standard deviation
SF-36	36-item Short Form Health Survey
SI	International System
SIPPM	study site investigational product and procedures manual
SoA	Schedule of Activities
SPARCC	Spondyloarthritis Research Consortium of Canada
SSZ	sulfasalazine
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	half-life
TB	tuberculosis
Tbili	total bilirubin

Th17	T helper 17
TNFα	tumor necrosis factor alpha
TNF-IR	anti-TNFα inadequate response
TU	tuberculin units
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
UV	ultraviolet
VAS	visual analog scale

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the SoA (Section 1.3) by the central laboratory:

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet count
Red blood cell count
Hemoglobin
Hematocrit</td><td><u>RBC Indices:</u>
MCV
MCH
% Reticulocytes</td><td><u>White Blood Cell (WBC) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.</td></tr>
<tr><td rowspan="2">Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Bicarbonate
Blood urea nitrogen (BUN)
Creatinine
Glucose (nonfasting)
Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic
Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic
Gamma-glutamyltransferase (GGT)
Total and Direct bilirubin
Alkaline phosphatase</td><td>Creatine phosphokinase (CPK)
Lactic acid dehydrogenase (LDH)
Uric acid
Calcium
Phosphate
Albumin
Total protein
Cholesterol
Triglycerides
Magnesium
Estimated glomerular filtration rate (eGFR) calculated using the CKD-EPI method (see Section 8.1.1.9)</td></tr>
<tr><td colspan="3">Note: Details of liver chemistry stopping criteria and required actions and follow-up are given in Appendix 6 (Section 10.6), Liver Safety.

Potential Hy's law case (ALT or AST ≥3×ULN and Tbili ≥2×ULN) reporting requirements are defined in Section 8.3.1.</td></tr>
<tr><td>Other</td><td colspan="3">• Serum and Urine Pregnancy Testing for women of childbearing potential only
• Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and HCV antibody)
• Rheumatoid factor (optional)
• High-sensitivity C-reactive protein (hsCRP)
• Lipid panel - Total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (Week 0 only)
• Follicle-stimulating hormone (screening only)
• QuantiFERON-TB test</td></tr>
</table>

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. Regulatory and Ethical Considerations

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 participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

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 participants, 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) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

In situations where a departure from the protocol is unavoidable during the study, 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 eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

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.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention 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, participant 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 participant:

- 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

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 participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants 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 participants
- 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 participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant 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 participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB 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 intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants 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 participants, 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).

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 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

10.3.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.3.3. Informed Consent Process

Each participant 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 participant 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 participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants 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 participant will receive for the treatment of his or her disease. Finally, they will be told that the investigator will maintain a participant 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 participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant or legally acceptable representative is authorizing such access.

The participant 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 the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF.

Participants 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 participant 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 participant.

If the participant 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 participant is obtained.

Participants who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally acceptable representative.

10.3.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants 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 participants confidential.

The informed consent obtained from the participant 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/territories.

The participant 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 and biomarker research is not conducted under standards appropriate for the return of data to participants. 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 participants 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.

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

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

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

10.3.6. Committees Structure

Data Monitoring Committee

An independent external DMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the participants enrolled in this study. This committee will consist of at least one medical expert in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter.

Interim Analysis Committee

An internal unblinded IAC will be established to review IA data, as specified in Section 9.5. This committee will consist of physicians, statisticians, clinical pharmacologists, and pharmacometricians unaffiliated with the study; committee membership responsibilities, authorities, and procedures will be documented in its charter. Recommendations based on the IA results, which will be specified in the IAC SAP/Charter, will be communicated to the sponsor. Further details of the IA will be provided in the IAC SAP/Charter.

10.3.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding guselkumab or golimumab 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 but not limited to biomarker, pharmacogenomic, and/or imaging 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 or golimumab, 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 for the study. Results of pharmacogenomic, biomarker, and/or imaging 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 participant 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 (ICMJE) 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 18 months after the study end date, 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 ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.3.8. Data Quality Assurance

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, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor may review the eCRF 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.

10.3.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in the eCRF. All eCRF 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 eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, 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 eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into the eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative 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 an eCRF are needed after the initial entry into the eCRF, 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.

10.3.10. Source Documents

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: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable. Given that PROs are reports of a patient's health condition that come directly from the patient, without interpretation by a clinician or anyone else, the responses to ePRO measures entered by study participants into source records cannot be overridden by site staff or investigators.

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 data will be recorded directly into the eCRF and will be considered source data:

- Race
- History of all nicotine use, eg, cigarettes (including e-cigarettes or the equivalent of e-cigarettes), cigars, chewing tobacco, patch, gum
- Blood pressure and pulse/heart rate

- Height and weight
- Details of physical examination
- Investigator-completed scales and assessments and PROs

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

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

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

An eSource 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. These data are electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

10.3.11. Monitoring

The sponsor will use a combination of monitoring techniques, central, remote, or 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. At these visits, the monitor will compare data entered into the eCRF 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 eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source 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.

10.3.12. 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. Participant 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.

10.3.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, 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.

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

10.3.14. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study/Site 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 participants by the investigator
- Discontinuation of further study intervention development

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. 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 Council 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 All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

For combination products with a device constituent, AEs include those resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the device. It includes any AE resulting from use error or from intentional misuse of the investigational device.

Serious Adverse Event

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

- Results in death
- Is life-threatening
  (The participant 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 participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

For combination products with a device constituent, SAEs include adverse device effects that resulted in any of the consequences characteristic of an SAE. An unanticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 2.3. Benefit-Risk Assessment).

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 or golimumab, the expectedness of an AE will be determined by whether or not it is listed in the IB.

10.4.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is determined by the investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.4.3. 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 participant (eg, laboratory abnormalities).

10.4.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding

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

10.4.5. Procedures

All Adverse Events

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

For all studies with an outpatient phase, including open-label studies, the participant 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 participant 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 personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from 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 intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

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

The cause of death of a participant in a study within 16 weeks of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered an SAE.

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form and safety report form of the eCRF, which must be completed and reviewed by a physician from the study site, and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted in a secure manner electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.4.6. Product Quality Complaint Handling

Definition

A 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, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue

during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

This definition includes any PQC related to a device constituent in a combination product, including those used in the administration of the study intervention or the comparator. A device deficiency is an inadequacy of a device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

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.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

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

10.5. Appendix 5: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **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 (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile (for the purpose of this study)**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

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.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

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 participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• 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 intervention. 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 participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) 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 participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention. c) Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy During the Study

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor or designee 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, preterm birth) are considered SAEs and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further study intervention.

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

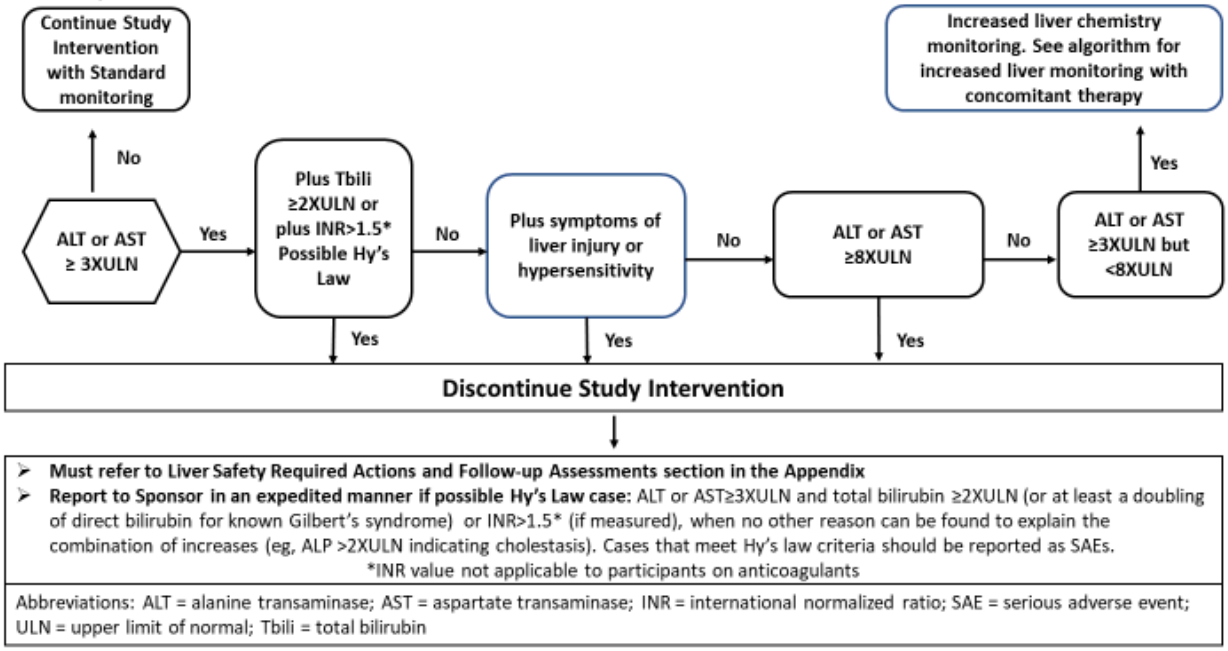
10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

10.6.1. Stopping Algorithm

10.6.1.1. STOPPING CRITERIA AND INCREASED MONITORING - ALT or AST

Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met.

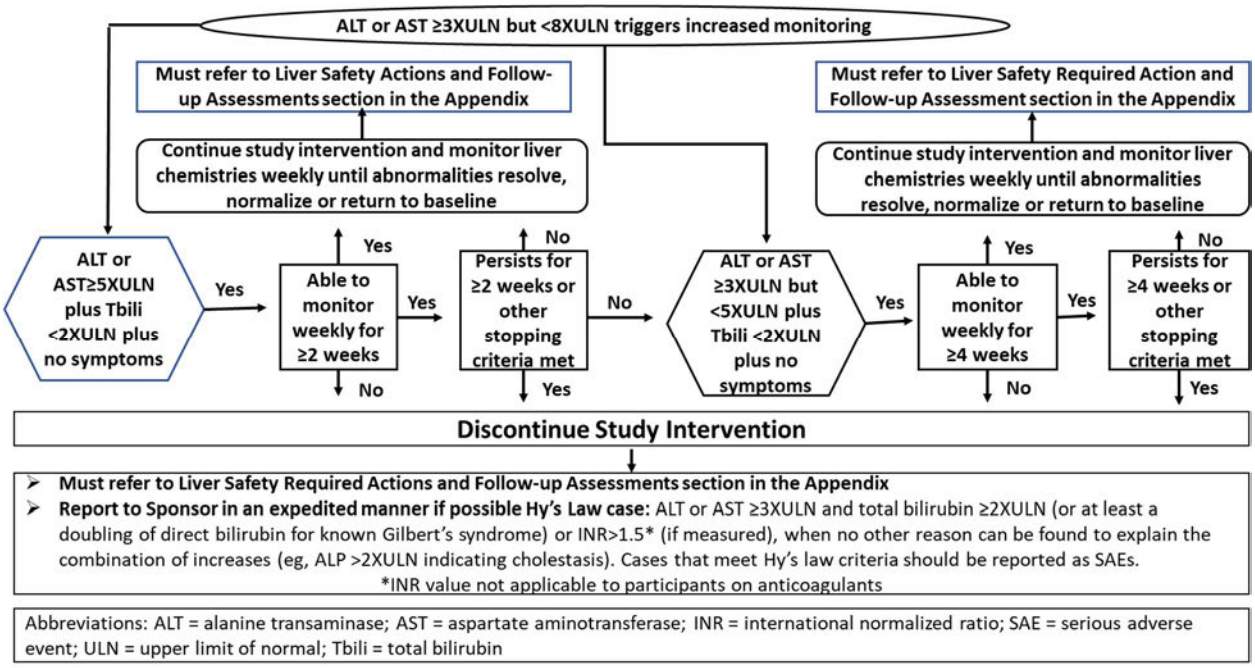
Phase 3-4 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm (no preexisting liver disease)



10.6.1.2. INCREASED MONITORING WITH CONTINUED STUDY INTERVENTION - ALT or AST

Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met.

Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



10.6.2. FOLLOW-UP ASSESSMENTS

10.6.2.1. Liver Chemistry Stopping Criteria and Follow-up Assessments

Phase 3-4 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Liver Chemistry Stopping Criteria	
ALT/AST-absolute	ALT or AST ≥8×ULN
ALT/AST Increase	ALT or AST ≥5×ULN but <8×ULN persists for ≥2 weeks ALT or AST ≥3×ULN but <5×ULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT or AST ≥3×ULN **and** total bilirubin ≥2×ULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome)
INR[2]	ALT or AST ≥3×ULN **and** INR >1.5, if INR measured
Cannot Monitor	ALT or AST ≥5×ULN but <8×ULN and cannot be monitored weekly for ≥2 weeks ALT or AST ≥3×ULN but <5×ULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT or AST ≥3×ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions, Monitoring and Follow-up Assessments	
Actions	**Follow-Up Assessments**
• **Immediately** discontinue study intervention • Report the event to the sponsor within **24 hours** • Complete the eCRF as per eCRF completion guidelines and complete an SAE data collection tool if the event also met the criteria for an SAE[2] • Perform follow-up assessments as described in the Follow-up Assessment column • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**) **MONITORING:** **<u>If ALT or AST- ≥3×ULN AND total bilirubin ≥2×ULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome) or INR >1.5 (if measured):</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total and direct	• Viral hepatitis serology[4] • Obtain blood sample for PK analysis 1 week after the most recent dose[5] • Obtain a serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) • Fractionate bilirubin • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity on the eCRF as per eCRF completion guidelines • Record use of concomitant medications (including acetaminophen, herbal remedies, recreational drugs and other over-the-counter medications) • Record alcohol use on the eCRF as per eCRF completion guidelines **<u>If ALT ≥3×ULN AND total bilirubin ≥2×ULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome)</u>**

bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline • A specialist or hepatology consultation is recommended **For all other criteria** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline **RESTART/RECHALLENGE** • **Do not restart/rechallenge** participant with study intervention.	**or INR >1.5 (if measured)** obtain the following in addition to the assessments listed above**:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins • Serum acetaminophen adduct, when available, assay to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease; complete in the eCRF as per eCRF completion guidelines • Liver biopsy may be discussed with local specialist if available, for instance: – In participants when serology raises the possibility of autoimmune hepatitis (AIH) – In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention – In participants with acute or chronic atypical presentation: hepatic vascular disorder, chronic hepatitis fibrosis, micro vesicular statosis • If liver biopsy conducted complete in the eCRF as per eCRF completion guidelines

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, stop study intervention if ALT or AST ≥3×ULN **and** total bilirubin ≥2×ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT or AST ≥3×ULN **and** total bilirubin ≥2×ULN (or at least a doubling of direct bilirubin for known Gilbert's syndrome) or ALT or AST ≥3×ULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria met (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: hepatitis A immunoglobulin M (IgM) antibody; HBsAgG and HBcAB; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody. In those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta

antibody. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) [Le Gal, 2005].

5. PK sample may not be required for participants known to be receiving placebo or non-comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the PK blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Reference Manual.

10.6.2.2. Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention	
Criteria	**Actions**
ALT or AST - ≥5×ULN and <8×ULN **and** total bilirubin <2×ULN or INR <1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks OR ALT or AST - ≥3×ULN and <5×ULN **and** total bilirubin <2×ULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the sponsor **within 24 hours** of learning of the abnormality to discuss participant safety • Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin) until the abnormalities resolve, stabilize, or return to baseline • If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Section 10.6.1 • If ALT or AST - decreases from ALT or AST - ≥5×ULN and <8×ULN to ≥3×ULN but <5×ULN, continue to monitor liver chemistries weekly • If, after 4 weeks of monitoring, ALT or AST - <3×ULN and total bilirubin <2×ULN, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to baseline

References:

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.

European Association for the Study of the Liver (EASL) Clinical Practice Guidelines: Drug-induced liver injury. Journal of Hepatology 2019;70 (6):1222-1261.

Hunt CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.

James LP, Letzig L, Simpson PM, et al. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009;37:1779-1784.

Le Gal F, Gordien E, Affolabi D, et al. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363-2369.

Papay JI, Clines D, Rafi R, et al. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

10.7. Appendix 7: Guidance on Study Conduct During the COVID-19 Pandemic

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation or quarantine of participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study-site personnel being unavailable, isolated, or reassigned to critical tasks.

The sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government guidelines or requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at unacceptable risk, study intervention will be discontinued, and study follow-up will be conducted.

If, as a result of the COVID-19 pandemic, visits cannot be conducted in person at the study site, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted, after consultation with the participant, investigator, and the sponsor.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance.

If a participant has tested positive for COVID-19, the investigator should contact the sponsor's medical officer or designee to discuss plans for administration of study intervention, performing study assessments, and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the CSR.

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of patient care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:
  - remote (eg, by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and patients for study procedures (eg, those related to safety monitoring / efficacy evaluation / study intervention storage and administration [including training where pertinent])
  - procurement of study intervention by patients (or designee) or shipment of study intervention from the study site directly to patients for at-home administration

  - laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed
  - other procedures may be conducted at an appropriate facility

- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the eCRF.
  - other relevant study data elements impacted by the pandemic should also be documented / labeled as "COVID-19-related" in eCRFs and / or other study systems, as directed by detailed sponsor guidance. These may include missed / delayed / modified study visits / assessments / dosing, and instances where temporary measures such as those above are implemented.
- The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).

10.8. Appendix 8: 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. Participants should never be allowed to read their own tuberculin skin test results. If a participant fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a participant 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 participants, and this definition is to be applied in this study to maximize the likelihood of detecting latent TB, even though the participants may not be immunocompromised at baseline.

In the US, 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, country-specific guidelines for immunocompromised participants should be consulted for the interpretation of tuberculin skin test results. If no local country guidelines for immunocompromised participants exist, US guidelines must be followed.

Treatment of Latent Tuberculosis

Local country guidelines for immunocompromised participants should be consulted for acceptable anti-tuberculous treatment regimens. Participants with active or latent TB will not continue receiving treatment with study intervention.

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.

Menzies RI. Tuberculin skin testing. In: Reichman LB, Hershfield ES (eds). *Tuberculosis, a comprehensive international approach*. 2nd ed. New York, NY: Marcel Dekker, Inc; 2000:279-322.

10.9. Appendix 9: HBV Screening with HBV DNA Testing

Participants must undergo screening for 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):

- Participants who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this protocol.
- Participants who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this protocol, regardless of the results of other hepatitis B tests.
- Participants who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of HBV DNA. If the HBV DNA test is **positive**, the participant ***is NOT eligible*** for this study. If the HBV DNA test is **negative**, the participant ***is eligible*** for this study. In the event the HBV DNA test cannot be performed, the participant ***is NOT eligible*** for this study.

For participants who **are not eligible for this protocol due to HBV test results**, consultation with a physician with expertise in the treatment of hepatitis B virus infection is recommended.

These eligibility criteria based on HBV test results are also represented in Table 5 below.

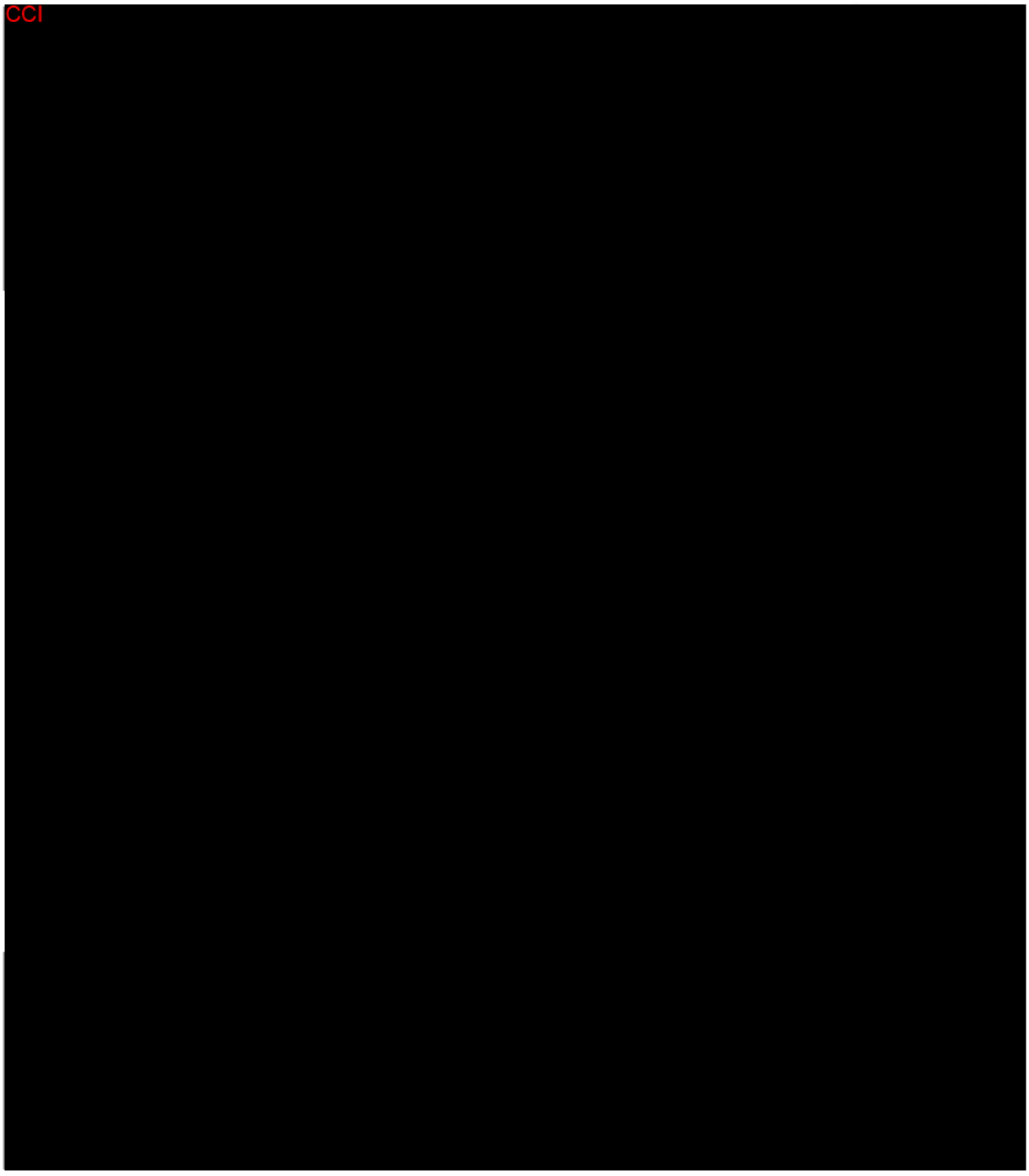
Table 5: Eligibility Based on Hepatitis B Virus Test Results

HEPATITIS B TEST RESULT			STATUS
Hepatitis B surface antigen (HBsAg)	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**	
negative	negative	negative	**Eligible**
negative	(+)	negative	
negative	(+)	(+)	
(+)	negative *or* (+)	negative *or* (+)	**Not eligible**
negative	negative	(+)	**(Require testing for presence of 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.

For participants who **are not eligible for this protocol due to HBV test results**, consultation with a physician with expertise in the treatment of hepatitis B virus infection is recommended.

10.10. Appendix 10: Disability Index of the Health Assessment Questionnaire (HAQ-DI)



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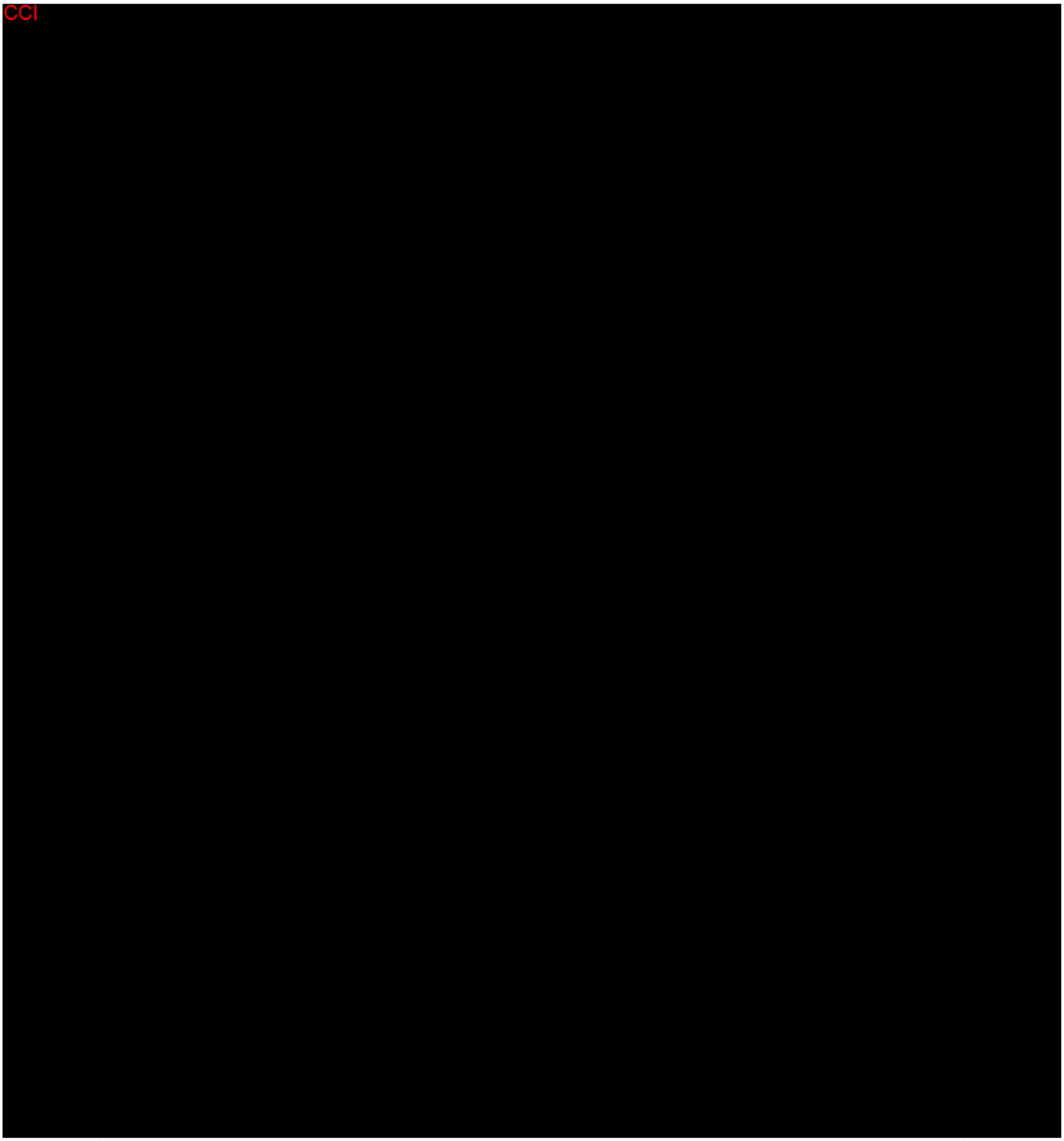


HAQ-DI – United States/English
HAQ-DI_AU1.0-eng-USori.doc

10.11. Appendix 11: Patient's Assessment of Pain

WORKSHEET

PATIENT ASSESSMENT

For answering the following questions, we have supplied you with a horizontal line. The ends of the horizontal line represent the very best and the very worst situation. Please put a single vertical line across the horizontal line at the spot that you feel best reflects the answer to the question (at the ends or somewhere in between). You must complete this form independently at each visit. Therefore, you MUST NOT review your prior assessments when completing current assessments.

DON'T **DO**

1. Patient's Assessment of Pain

On average, how much pain have you had because of your condition in the past week?

no pain — the worst possible pain

2. Patient's Global Assessment of Disease Activity

Considering all the ways your arthritis affects you, on average, how have you been doing in the past week?

very well — very poor

10.12. Appendix 12: Patient's Global Assessment of Disease Activity

10.12.1. Patient's Global Assessment of Disease Activity (Arthritis and Psoriasis)

Global (PGA)
In all the ways in which your PSORIASIS and ARTHRITIS, as a whole, affects you, how would you rate the way you felt over the past week?

Excellent _____ Poor

10.12.2. Patient's Global Assessment of Disease Activity (Arthritis)

Global (PGA)
In all the ways in which your ARTHRITIS, as a whole, affects you, how would you rate the way you felt over the past week?

Excellent _____ Poor

10.13. Appendix 13: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

Date completed | | | | | | | | |
dd mm yy

BASDAI

Please answer the following questions by drawing a vertical mark through the line.

All questions refer to the last 7 days.

Fatigue
1. How would you describe your overall level of fatigue/tiredness?

None ——————————————— Very severe |_|_|_| mm

Spinal pain
2. How would you describe your overall level of neck, back or hip pain resulting from ankylosing spondylitis?

None ——————————————— Very severe |_|_|_| mm

Peripheral arthritis (inflammation of the joints)
3. How would you describe your overall level of pain/swelling in joints other than the neck, back or hips?

None ——————————————— Very severe |_|_|_| mm

Enthesitis (inflammation of the sites where tendons or ligaments insert into the bone)
4. How would you describe your overall level of discomfort from any areas tender to the touch or pressure?

None ——————————————— Very severe |_|_|_| mm

Severity of morning stiffness
5. How would you describe your overall level of morning stiffness from the time you wake up?

None ——————————————— Very severe |_|_|_| mm

Duration of morning stiffness
6. How long does your morning stiffness last from the time you wake up?

0 hours ——————————————— 2 or more hours
1 hour

|_|_|_| mm

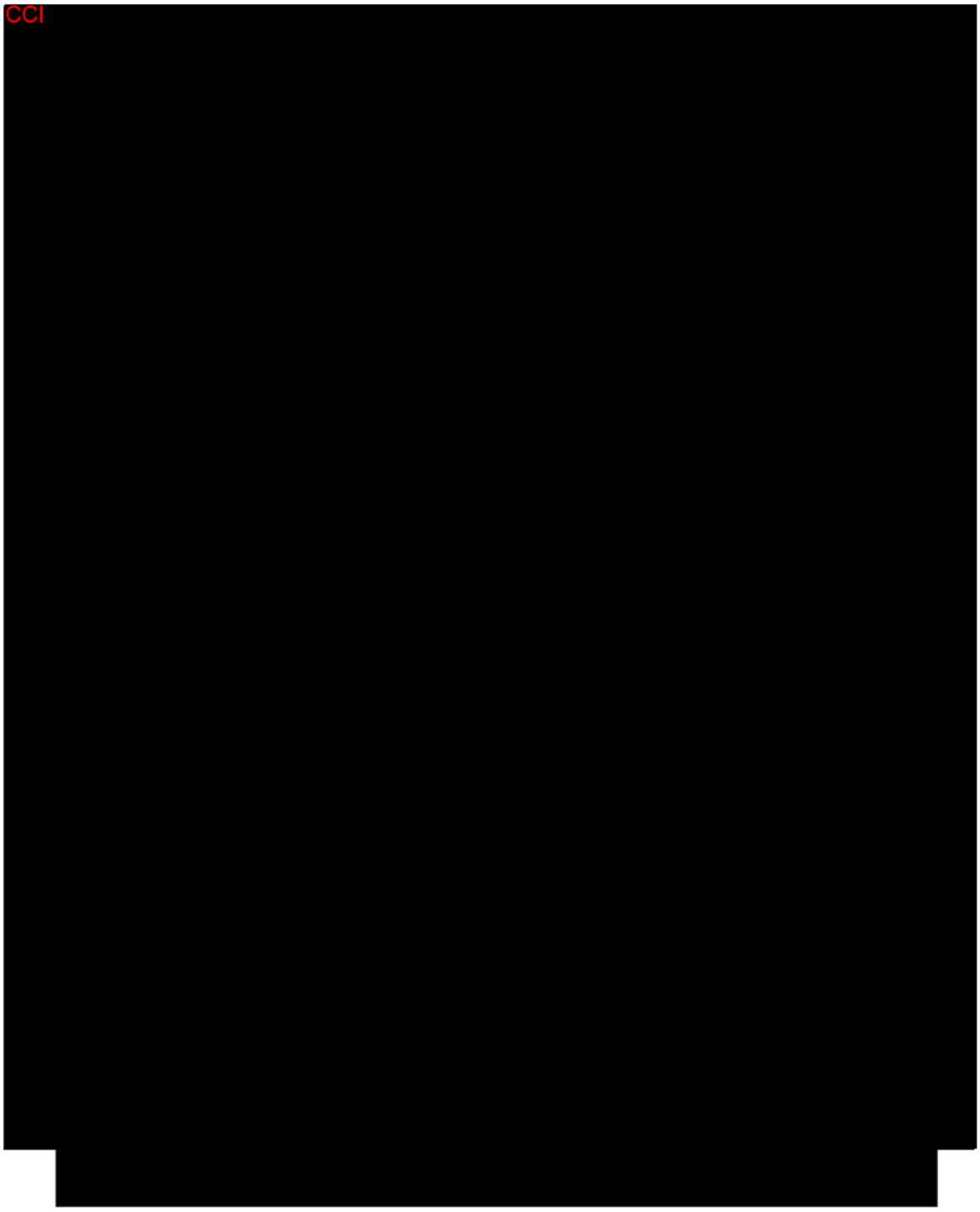
BASDAI - United States/English - Version of 26 Jul 10 - Mapi Research Institute.
ID5742 / BASDAI_T82.2_eng-US.doc

10.14. Appendix 14: Short Form 36 (SF-36)

CCI

[redacted]


CCI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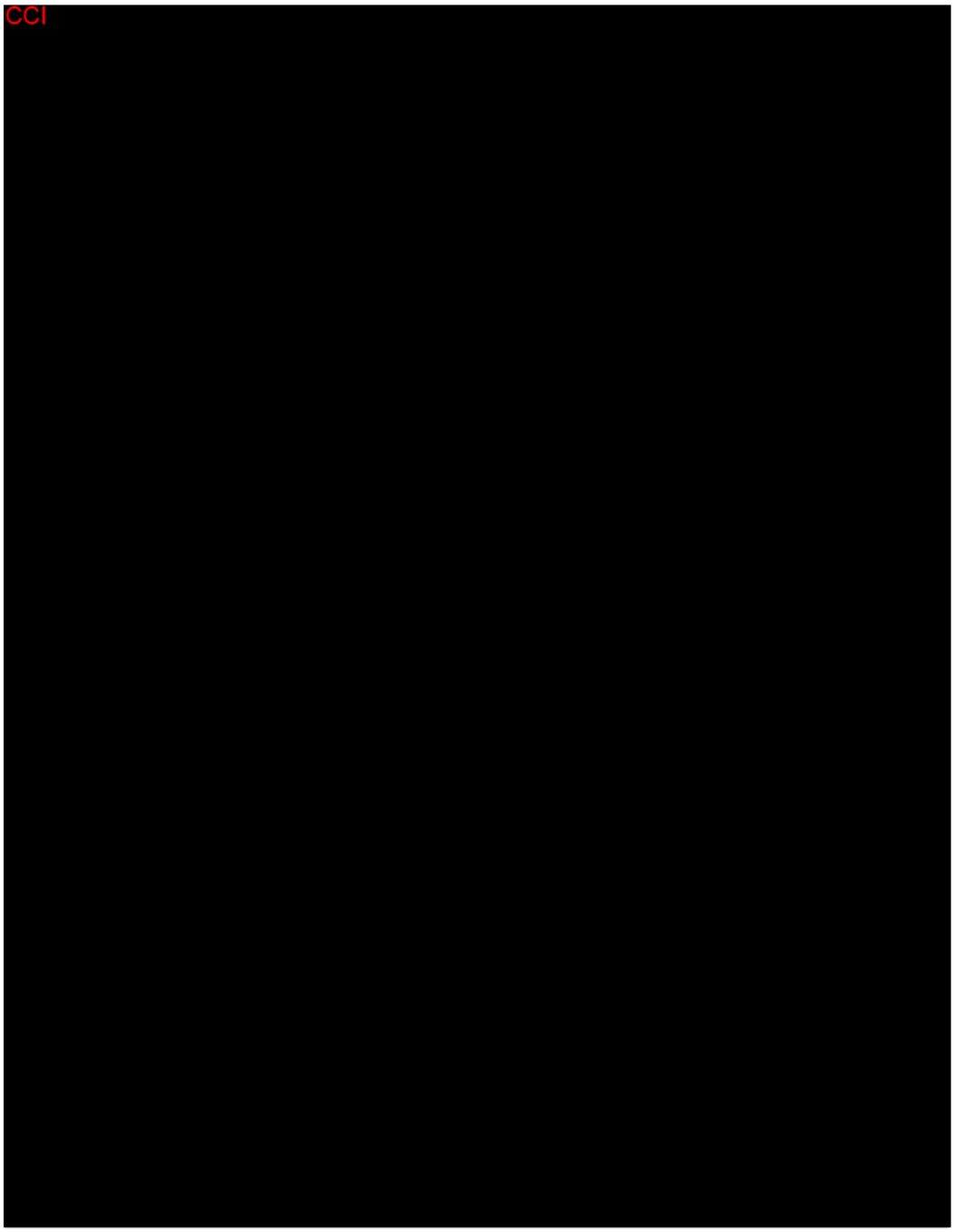
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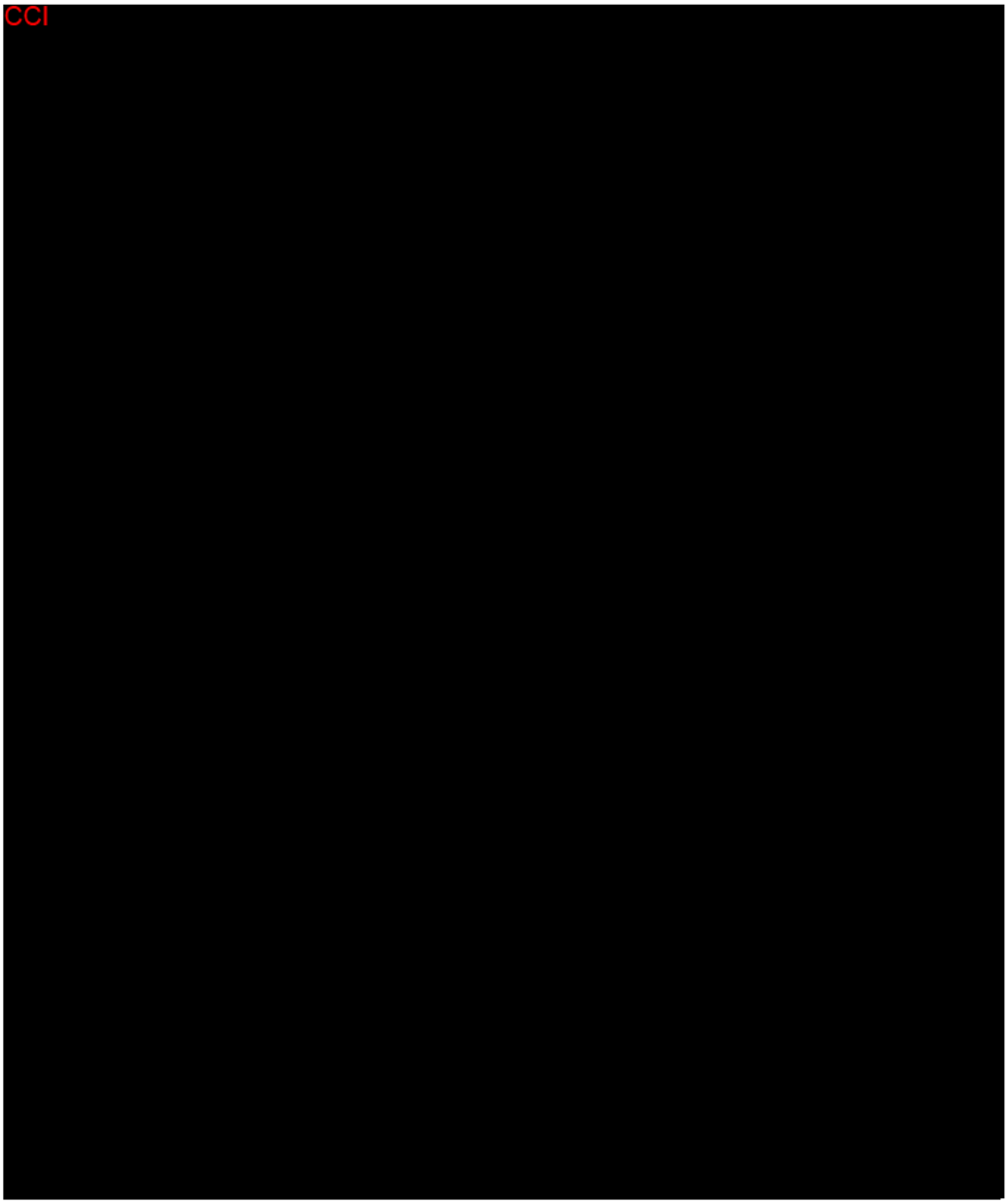
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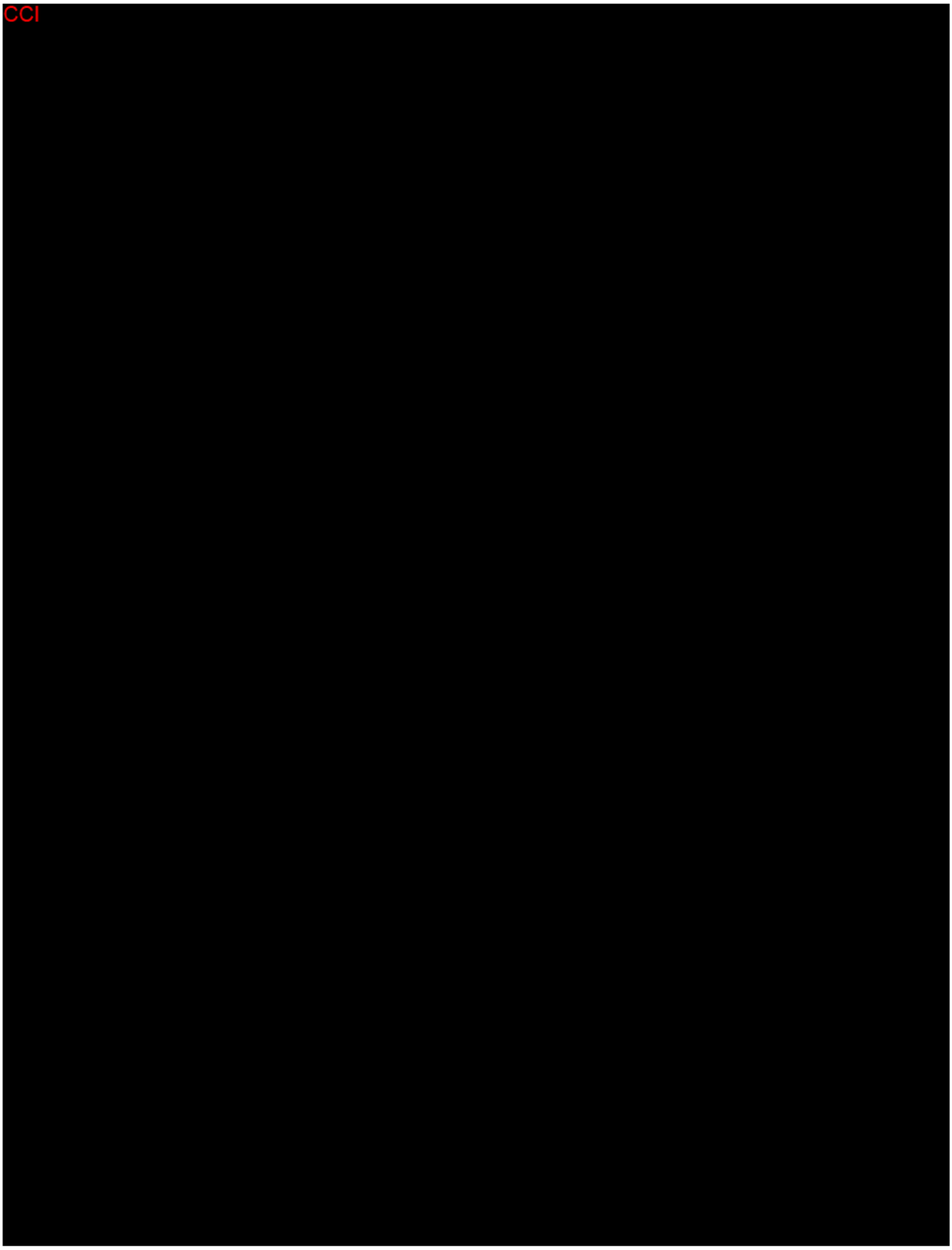
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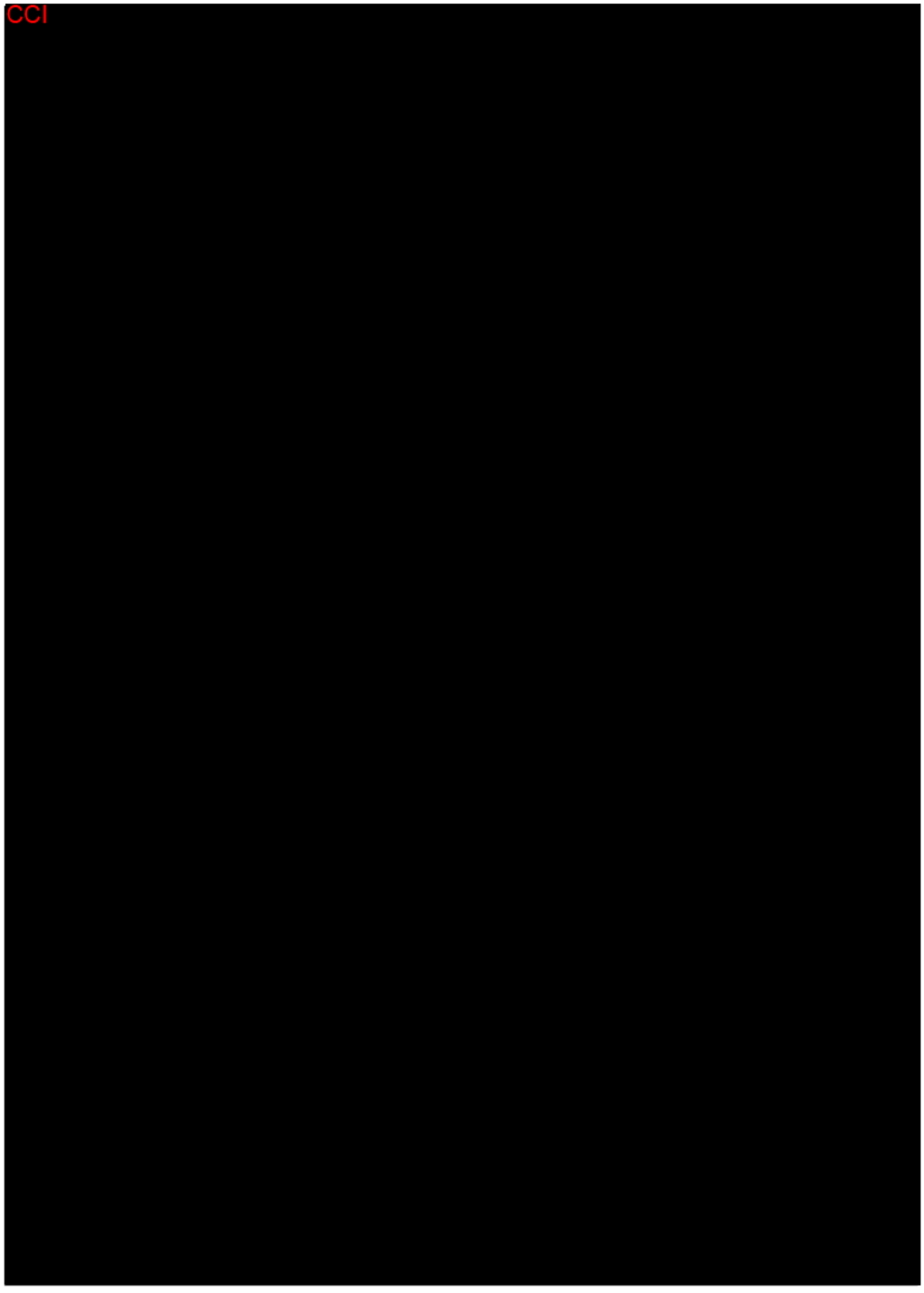
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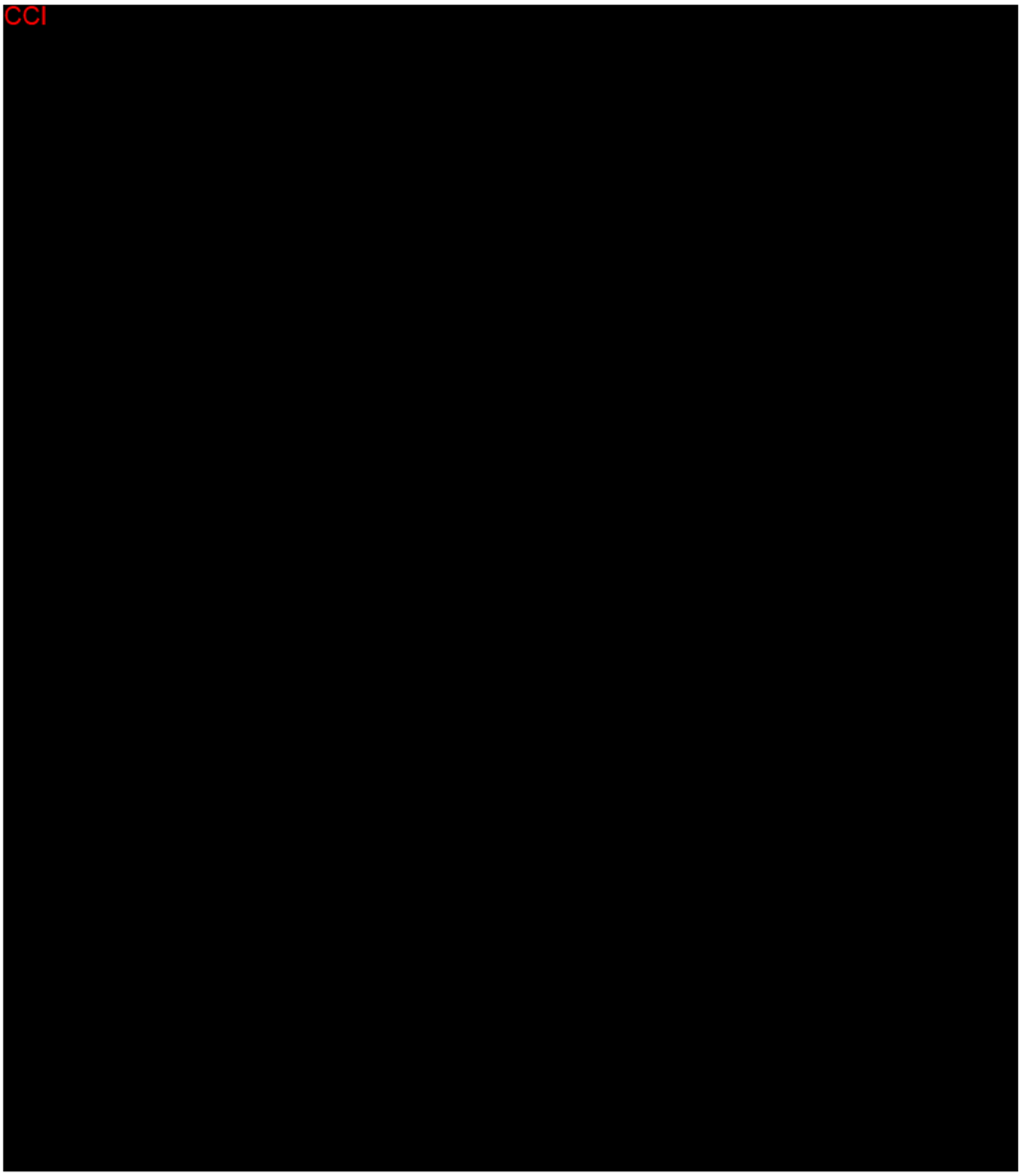
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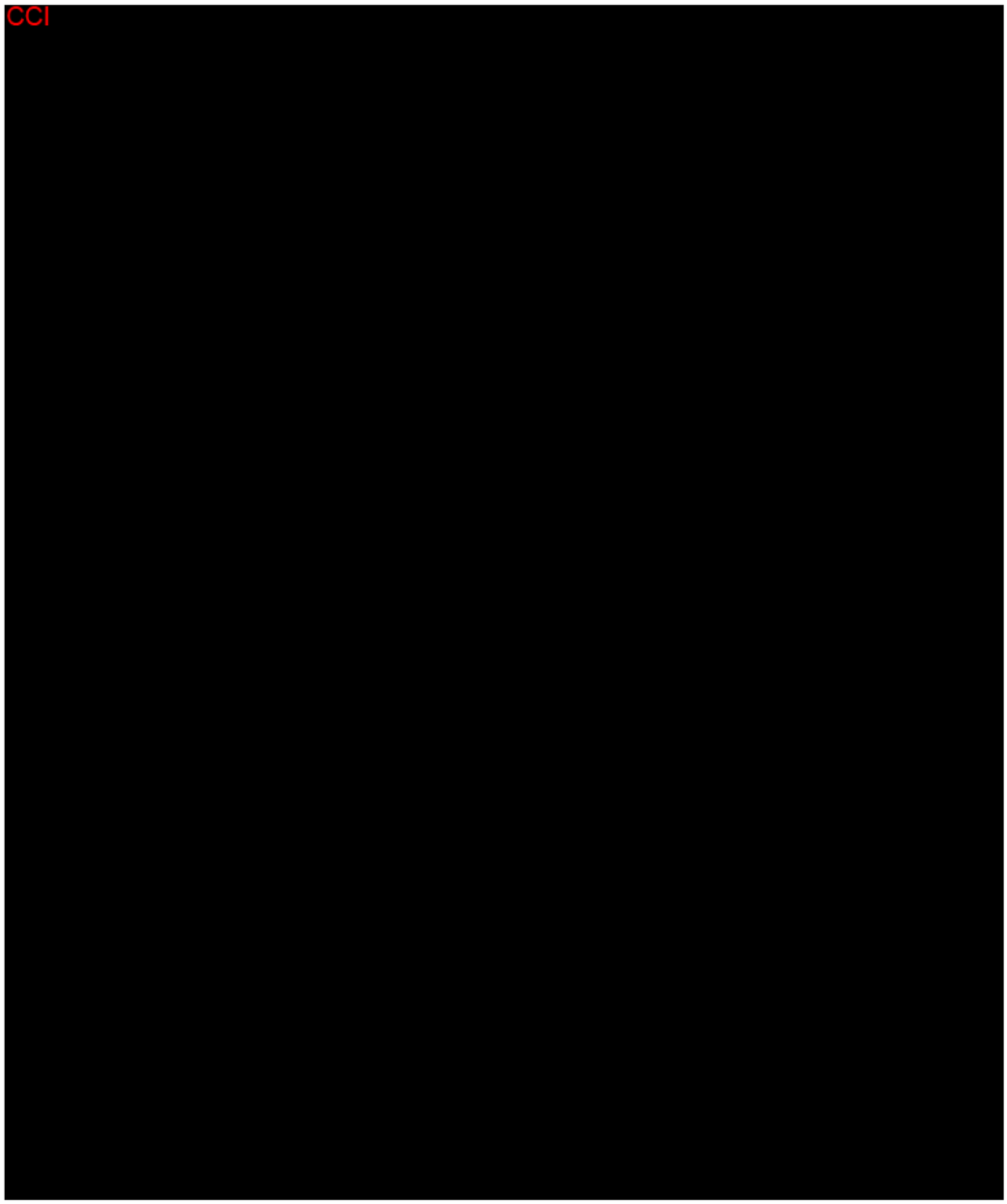
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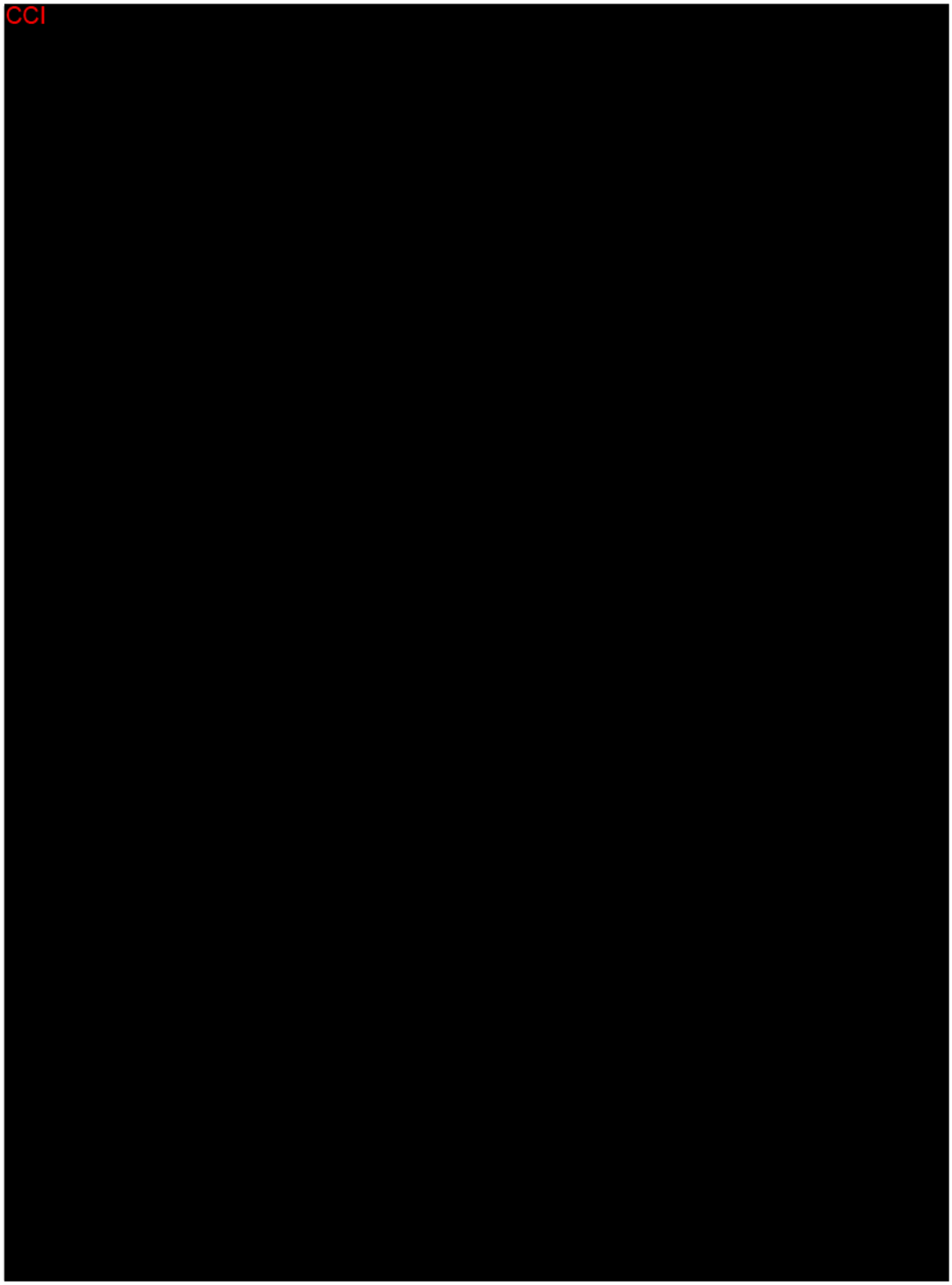
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10.15. Appendix 15: Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)

FACIT Fatigue Scale (Version 4)

English (Universal)

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10.16. Appendix 16: Patient-Reported Outcomes Measurement Information System 29 (PROMIS-29 v2.1)

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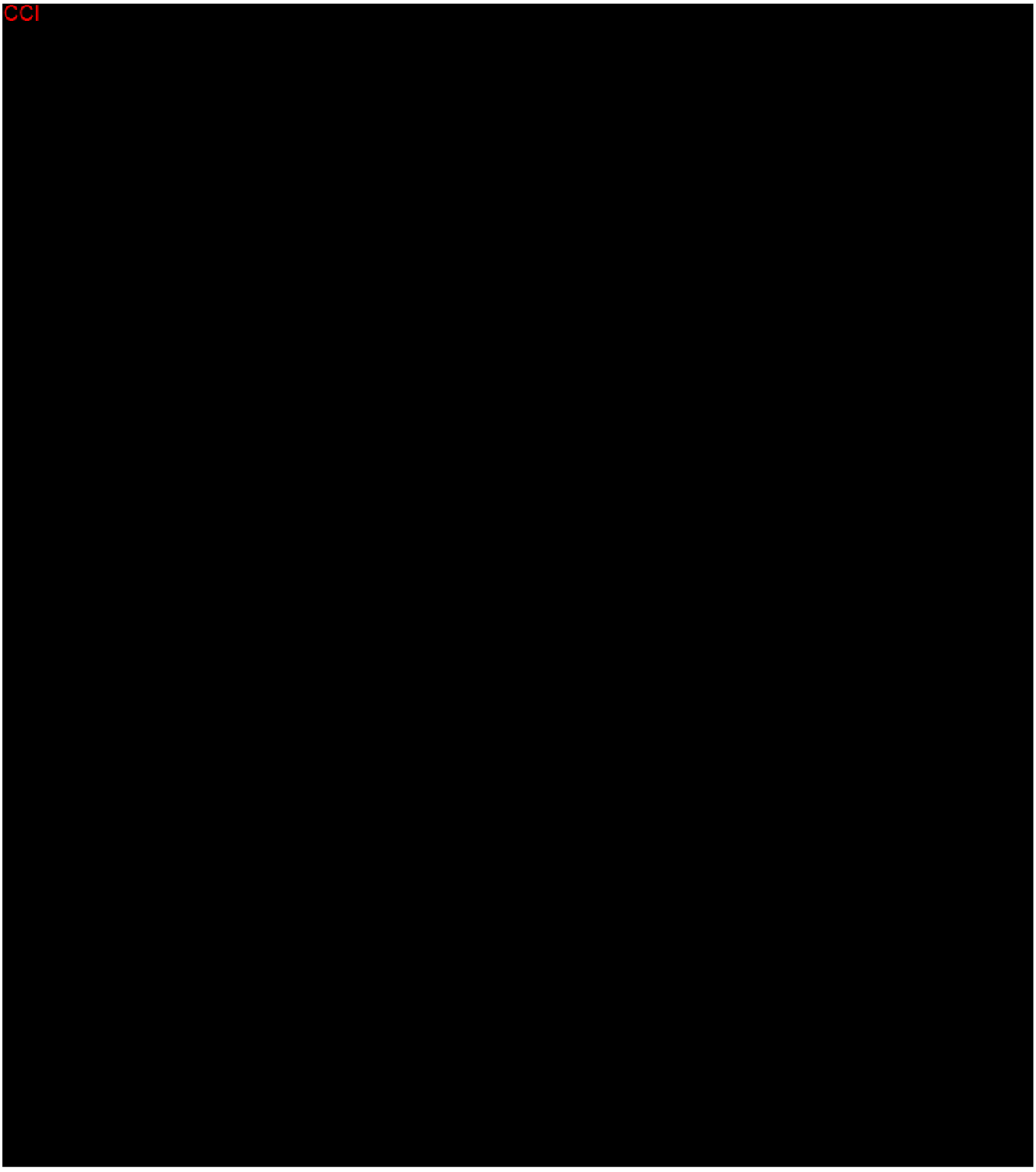

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PROMIS–29 Profile v2.1

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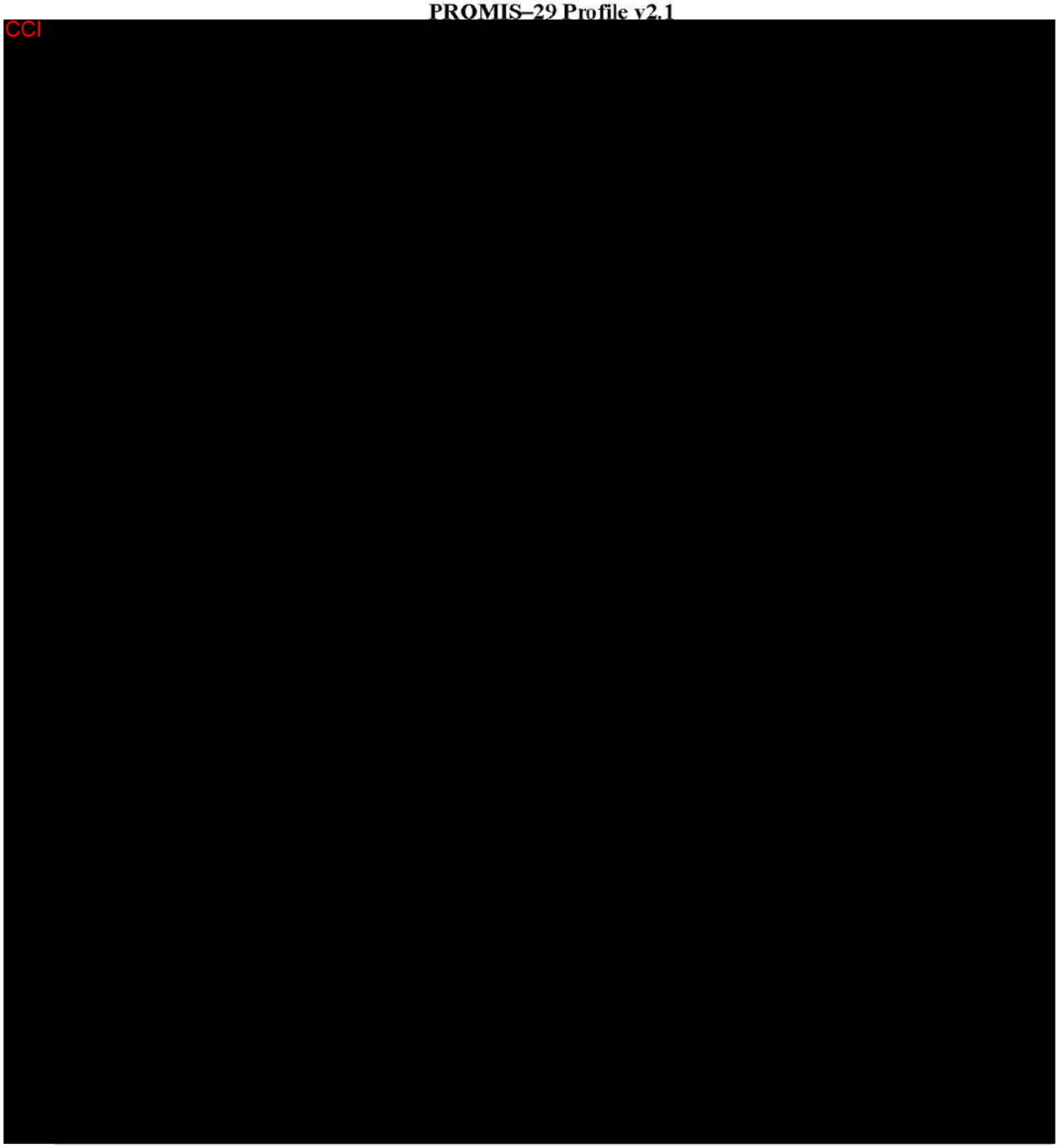

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10.17. Appendix 17: Definition of Intolerance, Inadequate Initial Response, and Loss of Response to anti-TNFα Therapy

The criteria for (I) intolerance, (II) inadequate initial response, and (III) loss of response to anti-TNFα therapy are described below.

I. Current or prior intolerance to therapy with infliximab, adalimumab, certolizumab pegol, etanercept, or their biosimilars.

Participants must satisfy criteria A and B.

A. Have had an adverse reaction that meets 1 of the following 3 criteria: 1) significant acute infusion/administration reaction; 2) significant delayed infusion/administration reaction (for example, delayed hypersensitivity or serum sickness-like reaction); or 3) significant injection-site reaction. Definitions of these 3 criteria are provided below. Adverse reactions also must have followed ≥1 dose of infliximab, adalimumab, certolizumab pegol, etanercept, or their biosimilars, and, in the treating physician's opinion, precluded continued use of the therapy.

1) A significant acute infusion/administration reaction is defined as an adverse reaction that was:

a) Manifested through ≥1 of the following symptoms:

- Fever >100°F (37.8°C)
- Chills or rigors
- Itching
- Rash
- Flushing
- Urticaria or angioedema
- Breathing difficulties (dyspnea, chest paint or tightness, shortness of breath, wheezing, stridor)
- Clinical hypotension (pallor, diaphoresis, faintness, syncope), blood pressure less than 90 mm Hg systolic and 60 mm Hg diastolic, or a systemic or orthostatic drop in systolic blood pressure of greater than 20 mm Hg

AND

b) Occurred ≤24 hours after infusion/administration of infliximab, adalimumab, certolizumab pegol, etanercept, or their biosimilars.

AND

c) Was considered related to the infusion/administration of infliximab, adalimumab, certolizumab pegol, etanercept, or their biosimilars.

2) A significant delayed infusion/administration reaction is defined as an adverse reaction that:

a) Was manifested through ≥1 of the following symptoms:

- Myalgias
- Arthralgias
- Fever >100°F (37.8°C)
- Malaise
- Rash

AND

b) Occurred >24 hours and <15 days after infusion/administration of infliximab, adalimumab, certolizumab pegol, etanercept, or their biosimilars.

AND

c) Was considered related to the infusion/administration of infliximab, adalimumab, certolizumab pegol, etanercept, or their biosimilars.

3) A significant injection-site reaction is defined as an adverse reaction that:

a) Was manifested through ≥1 of the following symptoms:

- Significant bruising
- Erythema
- Hemorrhage
- Irritation
- Pain
- Pruritus

AND

- Occurred ≤24 hours of an CC injection.

AND

- Was considered related to the injection.

B. Have documentation available to the investigator that meets the following 2 requirements:

1) Provides the date of discontinuation of adalimumab, certolizumab pegol, etanercept, or their biosimilars.

2) Documents that the participant had intolerance to adalimumab, certolizumab pegol, etanercept, or their biosimilars .

Examples of acceptable documents include medical records, letter provided by a referring physician, or other “reason for referral” documents (eg, insurance authorization form).

II. Inadequate initial response (primary nonresponse) to prior therapy with infliximab, adalimumab, certolizumab pegol, etanercept, or any biosimilar of these 4 therapies.

Eligible participants must satisfy criteria A and B.

A. Have received adequate dosing (including induction doses) for any of the following:

1) Infliximab or its biosimilar (≥14 weeks)

2) Adalimumab, certolizumab pegol, etanercept, or their biosimilars (≥12 weeks)

AND

Did not improve with at least 50% reduction in disease activity to these doses within 3 months and/or did not achieve target (ie, remission or low disease activity) within 6 months as assessed by a treating physician.

B. Have documentation available to the investigator that meets the following 2 requirements:

1) Provide the dates and doses of the failed infliximab, adalimumab, certolizumab pegol, etanercept, or biosimilar therapy.

2) Documents that the participant had persistence of disease activity following infliximab, adalimumab, certolizumab pegol, etanercept, or biosimilar therapy.

Examples of acceptable documents include medical records, letter provided by a referring physician, or other "reason for referral" documents (eg, insurance authorization form).

III. Initial response followed by loss of response (secondary nonresponse) to current or prior therapy with infliximab, adalimumab, certolizumab pegol, etanercept, or biosimilar.

Eligible participants must satisfy criteria A, B, and C.

A. Have received adequate dosing (including induction doses) for any of the following:

1) Infliximab or its biosimilar (≥14 weeks)

2) Adalimumab, certolizumab pegol, etanercept, or their biosimilars (≥12 weeks)

AND

Initially responded, that is improved with at least 50% reduction in disease activity within 3 months and achieved target (remission or low disease activity) within the first 6 months to therapy (including induction therapy).

B. Have or had at least 1 of the following signs or symptoms related to recurrence of psoriatic arthritis, as assessed by a treating physician:

1) Worsening in tender joint count

2) Worsening in swollen joint count

3) Worsening in psoriasis

4) Worsening in enthesitis

5) Worsening in dactylitis

6) Worsening in axial disease

7) Worsening in physical function

8) Worsening in disease activity

These signs and symptoms of psoriatic arthritis offered only as a benchmark of the minimally acceptable criteria required to designate a participant as having a loss of response to infliximab, adalimumab, certolizumab pegol, etanercept, or biosimilar therapy. It is acknowledged that previous treatment decisions could have been made based on evaluation of other measures that may be indicative of worsening disease (eg, elevations of inflammatory markers including but not limited to CRP and/or evidence of disease flare based on clinical imaging modalities including but not limited to CT and MRI). Under these circumstances, documentation of these specified measures of worsening disease activity can be accepted as evidence of IR to prior biologic treatment. However, investigators should note that participants must meet protocol-specified criteria for active disease during the current screening period as described in Section 5.1 to be eligible for enrollment.

C. Have documentation available to the investigator that meets the following 2 requirements:

1) Provide the dates and doses of the failed infliximab, adalimumab, certolizumab pegol, etanercept, or biosimilar maintenance therapy.

2) Documents that the participant had recurrence of disease activity despite infliximab, adalimumab, certolizumab pegol, etanercept, or biosimilar maintenance therapy. Examples of acceptable documents include medical records, letter provided by a referring physician, or other “reason for referral” documents (eg, insurance authorization form).

10.18. Appendix 18: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 (06 October 2021)

Overall Rationale for the Amendment: To address health authority feedback regarding washout periods for prohibited medications, provide further clarification on recurrent or chronic serious infections, testing for antibodies to both golimumab and guselkumab, and gadolinium administration.

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities; 8.1.1.9. Magnetic Resonance Imaging of the Hand and Foot; 10.2. Appendix 2, Clinical Laboratory Tests	Estimated glomerular filtration rate (eGFR) assessments were added (at Screening and Week 20).	Per Health Authority request. Due to the planned use of gadolinium contrast for these magnetic resonance imaging (MRI) assessments, an eGFR will be calculated prior to each MRI.
5.1. Inclusion Criteria, Inclusion Criterion 7; 6.8.4. Biologic Agents, Cytotoxic Drugs, JAK Inhibitors, or Investigational Agents	Clarified parameters around participant use of anti-tumor necrosis factor alpha (TNFα) agents, cytotoxic agents, JAK inhibitors, and biologic agents other than anti-TNFα agents.	Per Health Authority request.
7.1. Discontinuation of Study Intervention	Clarified definitions of recurrent and chronic serious infections.	Per Health Authority request.
Synopsis Statistical Methods; 8.7. Immunogenicity Assessments; 9.4.7. Other Analyses	Aligned these sections with previous sections, specifying that serum samples will be tested for antibodies to guselkumab and/or golimumab.	Per Health Authority request.
Synopsis Statistical Methods; 9.4.7. Other Analyses	Aligned these sections with previous sections, specifying that pharmacokinetics will be evaluated for guselkumab and/or golimumab.	Error was noted.
2.3.1. Risks for Study Participation	Aligned mitigation strategy for hypersensitivity or intolerance to include golimumab as already done in Section 5.2.	Error was noted.
8.1.1.9. Magnetic Resonance Imaging of the Hand and Foot	Clarified language regarding eligibility for MRI with gadolinium-based contrast agent (GBCA).	Provided clear criteria and safety screening procedures to determine which participants are not eligible to receive GBCA for MRI.
1.3. Schedule of Activities; 8.1.1.9. Magnetic Resonance Imaging of the Hand and Foot	Clarified timing of the MRI assessments.	To ensure that MRI assessments must be completed ≤14 days prior to the Week 0 and Week 24 visits and add a reminder that eGFR must be checked prior to the procedure.
5.2. Exclusion Criteria, Exclusion Criterion 1	Clarified eGFR threshold for renal insufficiency.	Potential participants with eGFR of <30 mL/min/1.73 m^2 are not eligible to participate in study.
5.2. Exclusion Criteria, Exclusion Criterion 25; 10.17. Appendix 17, Definition of	Provided definitions of intolerance, inadequate response, and loss of response to anti-TNFα therapy.	Provided investigator with detailed definitions for each term as they are key to study eligibility.

Section Number and Name	Description of Change	Brief Rationale
Intolerance, Inadequate Initial Response, and Loss of Response to anti-TNFα Therapy		
2. Introduction; 6.1. Study Interventions Administered; 6.1.1. Combination Products; 10.1. Appendix 1, Abbreviations	Clarified the language about the drug-device combination products to be used in this study.	Different drug-device combination products are used for the different interventions.
Synopsis Overall Design; 2. Introduction; 4.1. Overall Design; 6.1. Study Interventions Administered	Clarified the language about combination therapy and drug-device combination products.	Provided understanding that there are separate injections of study interventions via separate drug-device combination products.
Synopsis Overall Design; Synopsis Intervention Groups and Duration; Synopsis Statistical Methods; 1.2. Schema; 4.1. Overall Design; 6.1. Study Interventions Administered; 6.1.1. Combination Products; 9.4.2. Primary Endpoint	Changed “placebo” to “placebo 0.5 mL for golimumab.”	Aligned with the study site investigational product and procedures manual product description.
1.3. Schedule of Activities	Added note and cross-reference to Section 10.2, which lists laboratory tests.	Enabled study personnel to easily access components of individual clinical laboratory assessments via cross-reference.
2.3.3. Benefit-Risk Assessment for Study Participation; 5.1. Inclusion Criteria, Inclusion Criterion 2; 8.2.4. Electrocardiograms	Changed 12-lead electrocardiogram (ECG) to be at Week 0 visit to align with Schedule of Activities; ECG was therefore removed from Inclusion Criterion 2 as it will not be assessed at screening.	Error was noted.
6.3. Measures to Minimize Bias	Clarified language regarding unblinding in relation to the database locks (DBLs).	Data that are potentially unblinding will be handled with special care until the final DBL, not the first DBL at Week 24.
1.2. Schema	Added bracket denoting double-blind phase, replaced bracket for safety follow-up with a final safety visit label at Week 36.	Clarified that the double-blind phase lasts until the final efficacy visit.

Section Number and Name	Description of Change	Brief Rationale
4.2. Scientific Rationale for Study Design	Clarified safety follow-up interval.	Provided understanding that the final safety visit will be approximately 16 weeks after the last dose of study intervention administration at Week 20.
4.1. Overall Design	Clarified the language about when the interim analysis will be performed.	Minor error: Interim analysis is planned when 60 participants reach Week 24.
4.2. Scientific Rationale for Study Design	Split the subheadings for DNA Collection and Biomarker Collection.	Clarified that genetic testing is not being performed on biomarker samples.
Synopsis Intervention Groups and Duration; 4.1. Overall Design; 9.4. Statistical Analyses	Added text describing the Week 24 and Week 36 DBLs.	Provided a clear statement about when the DBLs are scheduled.
Synopsis Efficacy Evaluations	Clarifications to planned efficacy evaluations.	Language added for completeness.
9.4. Statistical Analyses	Clarified the timing of Statistical Analysis Plan (SAP) finalization.	Provided a clear statement on SAP timing.
Synopsis Statistical Methods; 9.4.1. General Considerations; 9.4.2. Primary Endpoint	Minor clarifications to planned statistical analyses.	Minor errors were noted and language added for completeness. Added another statistical method that potentially will be applicable.
8.2.5. Clinical Safety Laboratory Assessments	Removed “urine sample for urinalysis.”	Should not have been included and is not in the Schedule of Activities or Clinical Laboratory Tests in Section 10.2.
6.1. Study Interventions Administered	Removed text with injection directions for site staff.	This text belongs in the study site investigational product and procedures manual.
10.3.6. Appendix 3, Regulatory, Ethical, and Study Oversight Considerations, Committees Structure	Corrected language regarding Data Monitoring Committee (DMC) responsibility.	The DMC will not review efficacy data for this study.
5.2. Exclusion Criteria	Combined previous subheadings “Prior/Concurrent Clinical Study Experience,” “Diagnostic Assessments,” and “Other Exclusions” into 1 subheading titled “Other Exclusions”.	Error was noted.
5.2. Exclusion Criteria, Exclusion Criterion 22	Updated language regarding severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)/Coronavirus Disease 2019 (COVID-19) testing and infection.	Aligned with update to Janssen COVID-19 guidance.
5.3. Lifestyle Considerations, Criterion 1	Updated language regarding vaccination history.	Aligned with update to Janssen COVID-19 guidance.
6.8.7. Vaccines	Updated language regarding COVID-19 vaccination.	Aligned with update to Janssen COVID-19 guidance.
10.7. Appendix 7, Guidance on Study Conduct During the COVID-19 Pandemic	Updated language regarding study conduct and COVID-19.	Aligned with update to Janssen COVID-19 guidance.

Section Number and Name	Description of Change	Brief Rationale
10.3.6. Appendix 3, Regulatory, Ethical, and Study Oversight Considerations, Committees Structure	Changed "Sponsor Committee" to "sponsor."	Minor errors were noted.
10.18. Appendix 18, Protocol Amendment History	Updated text to direct to the Protocol Amendment Summary of Changes Table.	This is an amendment and no longer an original protocol.
10.1. Appendix 1, Abbreviations	Updated abbreviations table.	Aligned with changes to the rest of the protocol.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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INVESTIGATOR AGREEMENT

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

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

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: 19 August 2022

(Day Month Year)

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

Signature

User	Date	Reason
PPD	19-Aug-2022 23:29:57 (GMT)	Document Approval

Janssen Research & Development *

Clinical Protocol

GUIDANCE ON STUDY CONDUCT DURING MAJOR DISRUPTION

Protocol Title

A Phase 2a, Multicenter, Randomized, Double-blind Study Evaluating the Efficacy and Safety of Subcutaneously Administered Guselkumab and Golimumab Combination Therapy in Participants with Active Psoriatic Arthritis

AFFINITY

Subcutaneously Administered Guselkumab and Golimumab Combination Therapy in Active Psoriatic Arthritis

Protocol CNTO1959PSA2003 ; Phase 2a

CNTO1959 (guselkumab) CNTO148

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

EudraCT NUMBER: 2021-002012-31

Status: Approved

Date: 2 May 2022

Prepared by: Janssen Research & Development, LLC; Janssen Research & Development,

EDMS number: EDMS-RIM-722549, 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

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

Study Conduct During a Major Disruption

GUIDANCE ON STUDY CONDUCT DURING A MAJOR DISRUPTION

It is recognized that the major disruption involving Ukraine, Russia, and neighboring countries/territories may have an impact on the conduct of this clinical study due to, for example, isolation or quarantine of participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or reassigned to critical tasks.

The sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's travel to the study site is considered to be dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study intervention will be followed.

If, as a result of the major disruption involving Ukraine, Russia, and neighboring countries/territories scheduled visits cannot be conducted in person at the study site, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted after consultation with the participant, investigator, and the sponsor.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. Modifications made to the study conduct as a result of the major disruption involving Ukraine, Russia, and neighboring countries/territories should be summarized in the clinical study report.

- Certain protocol-mandated visits to the study site may not be possible during the major disruption involving Ukraine, Russia, and neighboring countries/territories. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of patient care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:
  - remote (eg, by phone telemedicine) or in person, off-site (eg, in-home) interactions between site staff (or designees) and participants for study procedures (eg, those related to safety monitoring/efficacy evaluation/study intervention storage and administration [including training where pertinent]).

  - study intervention administration may take place outside of the scheduled visit window due to disruption of study intervention shipment to the site.
  - laboratory assessments using a suitably accredited local laboratory; the sponsor should be consulted when determining if any laboratory assessments may be conducted from home.

- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented in the eCRF.
  - other relevant study data elements impacted by the major disruption involving Ukraine, Russia, and neighboring countries/territories should also be documented in eCRFs and/or other study systems, as directed by detailed sponsor guidance. These may include missed/delayed/modified study visits/assessments/dosing, and instances where temporary measures such as those above are implemented.
- The sponsor will evaluate the totality of impact of the major disruption involving Ukraine, Russia, and neighboring countries/territories on collection of key study data.
  - if needed additional data analyses will be outlined in study SAP(s).

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 intervention, 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): PPD

Institution: Janssen Research & Development

Signature: [electronic signature appended at the end of the protocol] Date: _____
(Day Month Year)

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

Signature

User	Date	Reason
PPD	02-May-2022 18:02:25 (GMT)	Document Approval