Janssen Research & Development *

Clinical Protocol

A Phase 2, Multicenter, Randomized, Placebo-controlled, Double-blind, Proof-of-Concept Study to Evaluate Guselkumab for the Treatment of Participants with New-onset or Relapsing Giant Cell Arteritis

THEIA

A Proof-of-Concept Study of Guselkumab in the Treatment of Subjects with New-onset or Relapsing Giant Cell Arteritis

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Protocol CNTO1959GCA2001; Phase 2
Amendment 5
Guselkumab (CNTO1959)

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

Regulatory Agency Identifier Number(s)

Registry	**ID**
EudraCT	2020-000622-26

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EDMS Number:	EDMS-ERI-204602737, 7.0

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

Confidentiality Statement

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 5	25 May 2022
Amendment 4	17 Sep 2021
Amendment 3	09 Jul 2021
Amendment 2	18 Dec 2020
Amendment 1	09 Jul 2020
Original Protocol	12 May 2020

Overall Rationale for the Amendment: The sponsor decided to no longer pursue a treatment regimen that includes IV induction doses. Newly enrolled participants will now be treated with a full subcutaneous (SC) dosing regimen. Sample size reduced while maintaining sufficient statistical power. Updated inclusion/exclusion criteria.

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis; 1.2. Schema. 1.3. Schedule of activities (SoA); 4.1.Overall Design; 4.2. Scientific Rationale for Study Design; 4.3 Justification of Dose; 6.1. Study interventions administered; 6.2. Preparation/Handling/Storage/Accountability; 6.4. Study Intervention Compliance	Change in treatment regimen: removal of IV induction dosing of study intervention. Newly enrolled participants will receive SC dosing of study intervention throughout the study. Added rationale for SC only treatment regimen. Updated Figure 1 (Schematic Overview of Main Study) Updated Schedule of Activities Removed Section 4.3.1. Induction Dose Regimen, and 4.3.2. Maintenance Dose Regimen	As dose regimen for newly enrolled participants is guided by scientific rationale and based on emerging data, IV induction dosing followed by SC maintenance dosing is no longer being pursued as a dosing regimen for GCA. SC only treatment regimen is also more convenient for participants.
1.1. Synopsis; 4.1. Overall design; 6.3. Measures to Minimize Bias: Randomization and Blinding; ; 9.2. Sample size determination; 9.5. Interim Analyses	Sample size reduced from approximately 60 to approximately 51. Removal of Interim analyses.	Sample size was reduced to ensure timely completion of the study while maintaining sufficient statistical power. Reduction of sample size to 51 negates the need for interim analysis at n=45 participants to inform the future development planning of guselkumab for the treatment of GCA. Data from the week 28 DBL will be used instead.
1.3. Schedule of Activities ; 8.9. Exploratory FDG-PET/CT Imaging	Added clarification on utilization of FDGPET/CT scan as exploratory endpoint.	Protocol clarification.
2.2. Background; 2.3.3. Benefit-Risk Assessment for Study Participation	Updated paragraph on clinical studies with guselkumab. Removed content related to IV dosing.	Update with current available information.

Section Number and Name	Description of Change	Brief Rationale
4.1. Overall Design	Clarifying that Flare visit can be combined with a regular visit and that PET/CT scan can be performed on another day.	Protocol clarification.
5.1. Inclusion criteria	Criterion 4 modified to also allow GCA confirmation by angiography or cross-sectional imaging (ultrasound, MRI, CT, PET).	Based on feedback from investigators, EULAR recommendations and ACR/VF guidelines for management of GCA.
5.1. Inclusion criteria	Criterion 14: Updated TB screening criteria.	New sponsor standard.
5.2. Exclusion criteria	Criterion 4 and 19 expanded to exclude individuals with high risk of venous thromboembolism (VTE).	GCA is associated with an increased risk of VTE. Two participants in this study reported venous thromboembolisms during the IV induction period. Both participants had individual risk factors that may have contributed to their risk of venous thrombosis.
5.4. Screen failures	Clarified that for participants that are rescreened, PET/CT scans obtained during the first screening do not have to be repeated if performed in a reasonable period of time before randomization after consultation with the sponsor. Added that individuals who were screen fails due to a trial suspension may be rescreened a second time with sponsor approval.	Protocol clarification.
6.8.1. Permitted therapy; 8. Study Assessments and Procedures	Modified language to clarify when to start tapering glucocorticoids.	Protocol clarification to increase compliance to protocol-defined GC taper regimen.
7.1. Discontinuation of Study Intervention	Added that study assessments may be reduced if participants discontinue treatment and continue in the study.	Protocol clarification to avoid oversampling and collection of data that is not in the interest of the study or the participant.
8. Study Assessments and Procedures	Removed details related to sample collection for PK analysis. Diagnostic confirmation of GCA: Editorial changes and cross-referred to inclusion criterion 4	Protocol clarification
8.2.2. Vital signs	Added language that bilateral measurement of blood pressure and pulse is required for the first measurement only per visit. Subsequent measurements can be performed on a single arm (unilateral).	Protocol clarifications to reduce burden on the participants.

Section Number and Name	Description of Change	Brief Rationale
8.2.9. Adverse Events Temporally Associated with Infusion	Removed Section.	Study agent is not administered through IV infusion anymore.
8.3.7. Adverse event of special interest	Added Venous thromboembolism (VTE) as AESI.	Expedite reporting of VTE.
8.4. Pharmacokinetics (8.4.1. Evaluations)	Removed that PK samples should be drawn from a different arm than the IV infusion line if study agent is administered at that visit.	Study agent is not administered through IV infusion anymore.
9.3. Analysis Sets	Updated population definition for immunogenicity analysis set.	Protocol clarification
9.4.5. Safety analyses	The number and proportion of participants with injection-site reactions by treatment intervention will be analysed for all visits at which participants received SC injections.	Modified due to change in dosing regimen.
Title page; Appendix 3: Regulatory, Ethical, and Study Oversight Considerations (Investigator Responsibilities; Regulatory Approval/Notification; Country/Territory Selection; Privacy of Personal Data)	Updated “country” to “country/territory”	To align with the latest template per Asia Pacific (APAC) Market Referencing Guidance
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 2, Multicenter, Randomized, Placebo-controlled, Double-blind, Proof-of-Concept Study to Evaluate Guselkumab for the Treatment of Participants with New-onset or Relapsing Giant Cell Arteritis

DESCRIPTION OF COMPOUND

Guselkumab (CNTO1959) is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that binds to human interleukin (IL)-23 with high specificity and affinity.

OBJECTIVES AND ENDPOINTS

Primary objectives:

- To evaluate the efficacy of guselkumab compared to placebo, in combination with a 26-week glucocorticoid (GC) taper regimen, in adult participants with new-onset or relapsing giant cell arteritis (GCA).

Secondary Objectives:

- To evaluate the efficacy of guselkumab compared to placebo, in combination with a 26-week GC taper regimen, in adult participants with new-onset or relapsing GCA as measured by alternative definitions of GC free remission, GC-sparing effects, and prevention of disease flares.
- To evaluate the safety of guselkumab, in combination with a 26-week GC taper regimen, in adult participants with new-onset or relapsing GCA.
- To evaluate the pharmacokinetics (PK) and immunogenicity of guselkumab, in combination with a 26-week GC taper regimen, in adult participants with new-onset or relapsing GCA.

Exploratory objectives:

- To explore the longer-term efficacy of guselkumab compared to placebo, in combination with a 26-week GC taper regimen, in adult participants with new-onset or relapsing GCA.
- To evaluate the changes in immune-markers to guselkumab compared to placebo, in combination with a 26-week GC taper regimen, in adult participants with new-onset or relapsing GCA.
- To explore the changes in pharmacodynamic markers and arterial vessel wall inflammation following administration of guselkumab in adult participants with new-onset or relapsing GCA.
- To explore changes in participant reported Clinical Outcome Assessments, pain and fatigue, and physician reported outcomes and digital health parameters following administration of guselkumab in adult participants with new-onset or relapsing GCA.

Exploratory objectives for the Long-Term Extension (LTE) Period:

- To evaluate long-term efficacy of guselkumab in adult participants with new-onset or relapsing GCA.
- To evaluate the continued safety of guselkumab in adult participants with new-onset or relapsing GCA.
- To evaluate the PK and immunogenicity of guselkumab, in adult participants with new-onset or relapsing GCA.
- To explore the changes in pharmacodynamic (PD) markers and arterial vessel wall inflammation following administration of guselkumab in adult participants with new-onset or relapsing GCA in the LTE period.

- To explore changes in participant reported Clinical Outcome Assessments, pain and fatigue, and physician reported outcomes following administration of guselkumab in adult participants with new-onset or relapsing GCA in the LTE period.

HYPOTHESIS

The primary hypothesis is that guselkumab treatment with a 26-week GC taper is superior to placebo with a 26-week GC taper in participants with new-onset or relapsing GCA as assessed by the proportion of participants achieving GC-free remission at Week 28.

OVERALL DESIGN

This is a randomized, double-blind, placebo-controlled, parallel, multicenter, interventional Phase 2 Proof-of-Concept study evaluating the efficacy, safety, PK, and immunogenicity of guselkumab for the treatment of active new-onset or relapsing GCA in adult participants.

NUMBER OF PARTICIPANTS

A target of approximately 51 participants will be enrolled in this study. Participants will be randomly assigned into 2 treatment groups in a 2:1 ratio for guselkumab versus placebo.

INTERVENTION GROUPS AND DURATION

Participants in the study will be on background GC, supplied by the clinical study site.

In addition to remaining on the standard-of-care noted above, participants will be randomized with a 2:1 ratio to 1 of 2 treatment groups as described below:

- Guselkumab: Participants will receive guselkumab 200 mg SC every 4 weeks from Week 0 through Week 48.
- Placebo: Participants will receive placebo SC every 4 weeks from Week 0 through Week 48.

Participants who complete the Week 52 visit and are assessed to be in GC-free remission, may have the option to participate in the LTE period of the study for up to 12 months.

Participants of the LTE period will continue to receive SC injections every 4 weeks (either active or placebo) starting at Week 52 (LTE Week 0) through Week 100 (LTE Week 48) or until the participants have a GCA flare, or the participants discontinues treatment due to unblinding after the Week 60 DBL for the Main study, or until a decision is made not to continue clinical development in this GCA population, whichever occurs first.

EFFICACY EVALUATIONS

Investigator assessments and patient-reported outcomes of efficacy include the following:

- GCA disease signs and symptoms
- Physician’s global assessment of disease activity
- C-reactive protein and erythrocyte sedimentation rate
- Patient’s global assessment of disease activity
- Pain assessment
- Functional assessment of chronic illness therapy-fatigue
- Short form 36

PHARMACOKINETIC EVALUATIONS

Venous blood samples will be collected for measurement of serum concentrations of guselkumab and antibodies to guselkumab (Section 8.7) at the timepoints shown in the Schedule of Activities (SoA, Section 1.3).

Venous blood samples will be collected, and each serum sample will be divided into 3 aliquots (1 each for PK, anti-guselkumab antibodies, and a back-up).

IMMUNOGENICITY EVALUATIONS

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

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

BIOMARKER EVALUATIONS

Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to guselkumab treatment, GCs and GCA, where local regulations permit. Assessments will include the evaluation of relevant biomarkers in serum, whole blood, and peripheral blood mononuclear cells collected as specified in the SoA, where local regulations permit.

PHARMACOGENOMIC (DEOXYRIBONUCLEIC ACID [DNA]) EVALUATIONS

Participation in pharmacogenomic research is optional. A pharmacogenomic (DNA) blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, where local regulations permit.

SAFETY EVALUATIONS

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

STATISTICAL METHODS

Approximately 51 participants are planned to be enrolled into the study. The assumptions for the sample size and power calculation were based on the data from the Actemra Phase 3 GCA study. The GC-free remission rates at Week 28 are assumed to be 40% for placebo and 80% for guselkumab treatment arm. Based on these assumptions, 51 participants are planned to be randomized in a 2:1 ratio to either the guselkumab group or the placebo group. These sample sizes provide the study with 82% power to detect a difference in the primary endpoint between the 2 treatment groups.

For purposes of analysis, the following populations are defined:

- Enrolled: All participants who signed the informed consent form.
- Full Analyses Set: All participants who were randomized in the study and received at least one administration of study intervention.
- Safety Analysis Set: All participants who received at least one dose of study intervention.
- Immunogenicity Analysis Set: All participants who received at least 1 administration of guselkumab and have at least one sample obtained after their first dose of guselkumab.

- PK Analysis Set: All participants who received at least 1 administration of guselkumab and have at least one valid blood sample drawn for PK analysis.
- PD Analysis Set: All participants who received at least 1 administration of study intervention and have at least one post-dose sample collection.

Data primarily will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, standard deviation, median, interquartile range, minimum and maximum, as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate. Median time will be reported for time to event variables. In addition, graphical data displays (eg, line plots) and participant listings may also be used to summarize/present the data.

For continuous endpoints, Mixed-Effect Model Repeated Measure model and Analysis of Covariance will be used for analysis. For binary endpoints, a Cochran-Mantel-Haenszel test stratified by new-onset and relapsing GCA, and the baseline prednisone dose (≤30 mg/day or >30 mg/day) will be used to analyze data. For time to first event data, Kaplan-Meier curves and Cox proportional hazards regression will be used to analyze the data. In addition, treatment differences and their associated 90% confidence intervals will be presented.

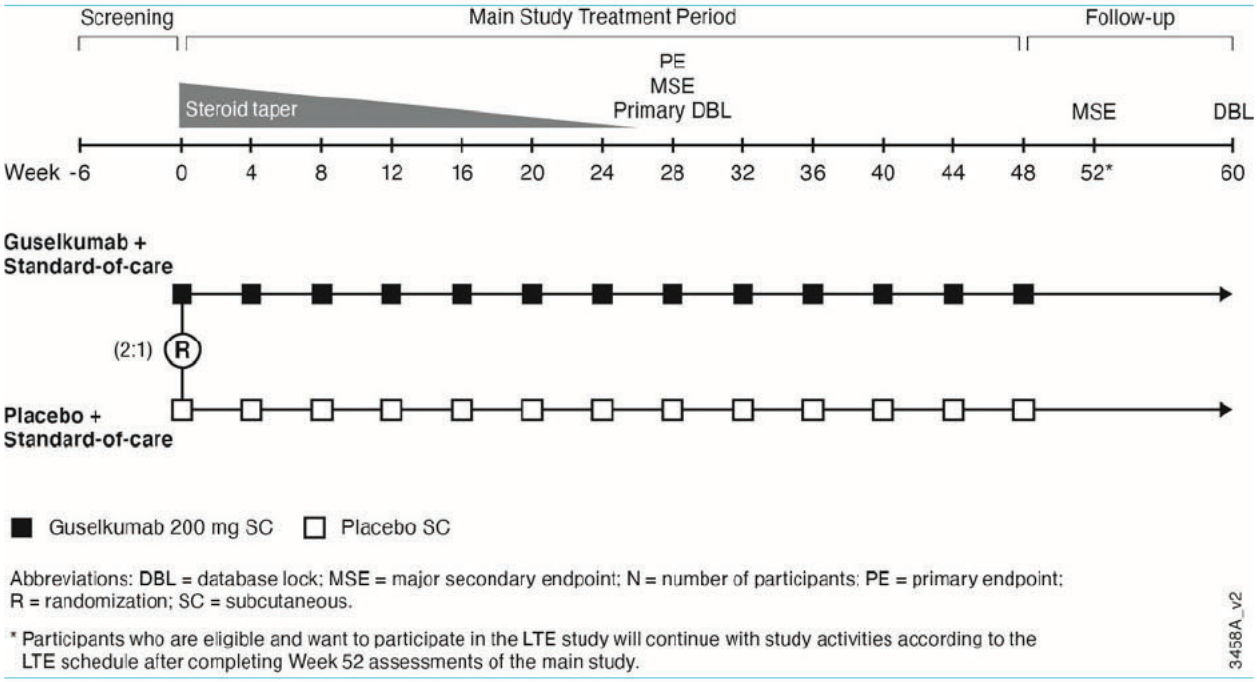
In general, all statistical tests will be performed at a 2-sided significance level of α=0.10. No multiplicity adjustment will be made for the secondary endpoints being tested and nominal p values will be reported.

1.2. Schema

An overview of the main study design is presented in Figure 1. Participants in glucocorticoid (GC)-free remission at Week 52 of the main study have the option to continue treatment in the LTE period. The Week 52 visit of the main study will be Week 0 of the LTE period.

An overview of the long-term extension (LTE) period is presented in Figure 2.

Figure 1: Schematic Overview of Main Study



Abbreviations: DBL = database lock; MSE = major secondary endpoint; N = number of participants; PE = primary endpoint; R = randomization; SC = subcutaneous.

* Participants who are eligible and want to participate in the LTE study will continue with study activities according to the LTE schedule after completing Week 52 assessments of the main study.

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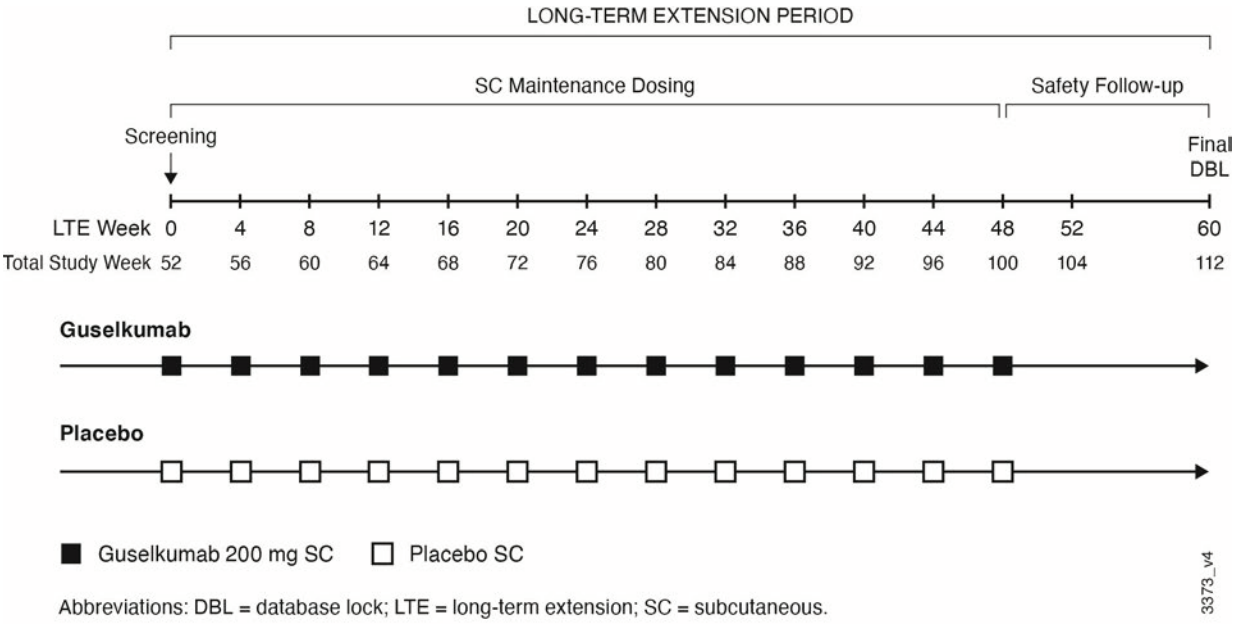
Figure 2: Schematic Overview of the Long-Term Extension (LTE) Period



1.3. Schedule of Activities (SoA)

Schedule of Activities From Screening through Week 60																		
Period	**Screening[a]**	**Blinded Active Treatment Period**													**Safety Follow-up**			
Study Week	**-6 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52[g]**	**60**	**Flare Visit[q]**	**Early Termination Visit[b]**
Study Day (post D1 window ±7 days)	**-42 to -1**	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**420**		
Study Procedure[c]																		
Screening/Administrative																		
Informed consent	X																	
Medical history and demographics	X																	
Inclusion/ exclusion criteria	X	X[n]																
Study Intervention Administration																		
Randomization		X																
Study intervention SC administration		X	X	X	X	X	X	X	X	X	X	X	X	X				
Predefined GC taper[p]		X----------→Week 26																
Rollover into LTE[g]															X[g]			
Safety Assessments																		
Physical examination	X														X	X		X
Height	X																	
12-lead ECG	X																	
Weight	X	X							X						X			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tuberculosis evaluation	X	X---------- X															X	X
Chest radiograph[i]	X																	
Urine Pregnancy Test[o]	X	X														X		X
C-SSRS[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Injection-site reaction evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X				

Schedule of Activities From Screening through Week 60																		
Period	**Screening[a]**	**Blinded Active Treatment Period**													**Safety Follow-up**			
Study Week	**-6 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52[g]**	**60**	**Flare Visit[q]**	**Early Termination Visit[b]**
Study Day (post D1 window ±7 days)	**-42 to -1**	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**420**		
Study Procedure[c]																		
Concomitant therapy		X----------																X
Adverse events		X----------																X
Efficacy Assessments																		
Clinical Assessor's GCA Disease Assessment S&S[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Physician's Global Assessment of Disease Activity (PhGA)		X							X						X		X	
Patient's Global Assessment of Disease Activity (PGA)[d]		X							X						X		X	
Pain Assessment[d]		X							X						X		X	
FACIT-Fatigue[d]		X							X						X		X	
SF-36[d]		X							X						X		X	
Clinical Laboratory Assessment																		
QuantiFERON®-TB test[r]	X																	
HIV, Hepatitis B and C serology	X																	
Coagulation	X																	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ESR/CRP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Pharmacokinetics and Immunogenicity[e]																		
Serum guselkumab		X	X	X	X	X			X						X		X	X

Schedule of Activities From Screening through Week 60

Period	Screening[a]	Blinded Active Treatment Period													Safety Follow-up			
Study Week	-6 to -1	0	4	8	12	16	20	24	28	32	36	40	44	48	52[g]	60	Flare Visit[q]	Early Termination Visit[b]
Study Day (post D1 window ±7 days)	-42 to -1	1	28	56	84	112	140	168	196	224	252	280	308	336	364	420		
Study Procedure[c]																		
Concentration																		
Antibodies to guselkumab		X	X	X	X				X						X		X	X
Pharmacogenomic (DNA)																		
Optional pharmaco-genomic sample[m]		X																
Biomarkers																		
Serum biomarkers[c,l]		X							X						X		X	
PBMC (cryopreserved) [c,l]		X							X									
Whole blood (PAXgene) [c,l]		X							X						X		X	
FDG-PET/CT Imaging[h]	X[h]														X[h]		X[h]	
Actigraphy watch	X[k]	----------X															X	X

Footnotes:

a. The screening visit should occur no more than 6 weeks before the Week 0 visit.
b. Participants who discontinue study intervention (but have not terminated study participation) before receiving the last planned dose, will continue for their planned visits but without study intervention administration. Participants who terminate their study participation before final planned study visit, should receive an early termination visit approximately 12 weeks after the last administration of study intervention (unless consent is withdrawn).
c. All study procedures and evaluations are to be completed before study intervention is administered except where otherwise indicated.
d. PGA, Pain assessment, FACIT F and SF 36 should be performed before any laboratory/safety tests, procedures, or other evaluations (PhGA and assessment of GCA disease signs and symptoms). Event driven patient reported outcomes will be applicable for participants developing a GCA flare.
e. For all visits where study intervention will be administrated, one blood sample should be collected prior to study intervention administration for evaluation of serum concentration of guselkumab and/or antibodies to guselkumab
f. Clinical Assessor's assessment of GCA signs and symptoms at every visit as specified in Section 8.1.1.
g. Participants who are eligible to participate in the LTE study and have consented will continue with LTE Week 0 activities after completing Week 52 assessments and follow SoA for LTE for subsequent visits. Participants who are not eligible or do not want to participate in the LTE study will continue to Week 60 visit in the main study for final safety follow up assessments.
h. FDG PET/CT is to be performed during screening prior to Week 0, and at Week 52 (or timepoint of flare if earlier). If a participant has a GCA flare prior to Week 52, an attempt will be made to perform the FDG PET/CT imaging at that flare timepoint instead of Week 52, preferably within 1 week from identification of GCA flare by the principal investigator. If FDG PET/CT scan is used for diagnosis this may be used as the study baseline image but requires sponsor pre approval. This is to avoid exposure of the participant

Schedule of Activities From Screening through Week 60																		
Period	**Screening[a]**	**Blinded Active Treatment Period**													**Safety Follow-up**			
Study Week	**-6 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52[g]**	**60**	**Flare Visit[q]**	**Early Termination Visit[b]**
Study Day (post D1 window ±7 days)	**-42 to -1**	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**420**		
Study Procedure[c]																		

to excess radiation. FDG PET/CT scan is being obtained as part of exploratory endpoint and results should not be used in determining disease status at the associated week 52 visit.

i. Chest radiograph (posterior anterior and lateral views, or per country regulations where applicable) must be obtained within 12 weeks before the Week 0 visit. Note: A chest CT scan is also acceptable if obtained instead of a chest radiograph outside of the protocol.
j. At the screening visit, the C 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 C SSRS should be completed after all PROs and before any other tests, procedures, or other consultations. In this study, the C SSRS is a physician administered questionnaire and should be administered by certified, trained, and delegated principal investigator or subinvestigator only.
k. At screening participants will be provided with an Actigraphy watch to be able to capture a baseline profile. Participants who will not prove eligible will return their Actigraphy watch to the study site. Participants may decline actigraphy measurements in case the participant is at risk for withdrawal of consent or if this assessment is a reason for participant not wanting to join the study.
l. Every attempt should be made to collect biomarker samples (as per schedule) during a flare but before a GC dose increase.
m. An optional whole blood pharmacogenomic (DNA) sample will be collected from those participants who sign a separate consent form (where local regulations permit). The pharmacogenomic sample should be collected at the specified time point, however if necessary, it may be collected at a later time point without constituting a protocol deviation.
n. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documentation in Section 10.3. Check clinical status again before first dose of study medication
o. Urine pregnancy testing is required for female participants of childbearing potential only (Section 8.2.5). If more frequent pregnancy testing is required by local regulations, these are allowed to be taken locally.
p. Investigators/site staff are recommended to contact the participant by telephone weekly to verify that correct steroid dose is taken.
q. In case a participant is diagnosed as having a flare during a study visit or shortly before a planned study visit, the Flare visit and regular visit can be combined. Overlapping procedures and assessments need only be performed once. The FDG PET/CT scan can be scheduled separately from other assessments.
r. 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.

Abbreviations: CRP=C reactive protein; CT=computed tomography; C SSRS=Columbia Suicide Severity Rating Scale; D1=Day 1; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ESR=erythrocyte sedimentation rate; FACIT=Functional Assessment of Chronic Illness Therapy; FDG=fluorodeoxyglucose; GC=glucocorticoid; GCA=Giant cell arteritis; HIV=human immunodeficiency virus; LTE=long term extension; PBMC=peripheral blood mononuclear cell; PET=positron emission tomography; PGA=Patient's Global Assessment of Disease Activity; PhGA=Physician's Global Assessment of Disease Activity; PRO=patient reported outcome; SF 36=short form 36; SC=subcutaneous; TB=tuberculosis; Term= termination.

1.4. Schedule of Activities (SoA) – Long-Term Extension

Schedule of Activities from Week 52 Main Study until End of LTE Period																	
Period	**LTE Treatment Period**													**LTE Safety Follow-up**			
Study Week	**52[k]**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**112**	**LTE Flare Visit[m]**	**LTE Early Termination Visit[a]**
LTE Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**60**		
Study Day (window ±7 days)	**364**	**392**	**420**	**448**	**476**	**504**	**532**	**560**	**588**	**616**	**644**	**672**	**700**	**728**	**784**		
Study Procedure[b]																	
Screening/Administrative																	
Informed consent review[j]	X																
Inclusion/ exclusion criteria for LTE period	X[g]																
Study Intervention Administration																	
Study intervention SC administration[c]	X	X	X	X	X	X	X	X	X	X	X	X	X				
Safety Assessments																	
Physical examination														X	X		X
Weight							X							X			
Vital signs				X			X			X				X	X	X	X
Tuberculosis evaluation		X----------													X	X	X
Urine Pregnancy Test[h]															X		X
C-SSRS[f]				X			X			X				X			
Injection-site reaction evaluation (self-reported)	X	X	X	X	X	X	X	X	X	X	X	X	X				
Concomitant therapy		X----------							X							X	X
Adverse Events		X----------							X							X	X
Efficacy Assessments																	

Schedule of Activities from Week 52 Main Study until End of LTE Period																	
Period	**LTE Treatment Period**													**LTE Safety Follow-up**			
Study Week	**52[k]**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**112**	**LTE Flare Visit[m]**	**LTE Early Termination Visit[a]**
LTE Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**60**		
Study Day (window ±7 days)	**364**	**392**	**420**	**448**	**476**	**504**	**532**	**560**	**588**	**616**	**644**	**672**	**700**	**728**	**784**		
Clinical Assessor's GCA Disease Assessment S&S[d]				X			X			X				X		X	
Physician's Global Assessment of Disease Activity (PhGA)							X							X		X	
Patient's Global Assessment of Disease Activity (PGA)[l]							X							X		X	
Pain Assessment[l]							X							X		X	
FACIT-Fatigue[l]							X							X		X	
SF-36[l]							X							X		X	
Clinical laboratory assessments																	
Hematology				X			X			X				X	X	X	X
Chemistry				X			X			X				X	X	X	X
ESR/CRP				X			X			X				X		X	
Pharmacokinetics and Immunogenicity																	
Serum guselkumab concentration[i]							X							X		X	X
Antibodies to guselkumab[i]							X							X		X	X
Biomarkers																	
FDG-PET/CT Imaging[e]														X		X	

Footnotes:

a. Participants who discontinue study participation before final planned study visit, should receive an early termination visit approximately 12 weeks after the last administration of study intervention (unless consent is withdrawn).
b. All study procedures and evaluations are to be completed before study intervention is administered except where otherwise indicated.
c. SC injections every 4 weeks from LTE Weeks 0 through 48 or until the participants have a GCA flare, or the participants discontinues treatment due to unblinding after the Week 60 DBL for main study, or until a decision is made not to continue clinical development in this GCA population, whichever occurs first.

Schedule of Activities from Week 52 Main Study until End of LTE Period																	
Period	**LTE Treatment Period**													**LTE Safety Follow-up**			
Study Week	**52[k]**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**112**	**LTE Flare Visit[m]**	**LTE Early Termination Visit[a]**
LTE Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**60**		
Study Day (window ±7 days)	**364**	**392**	**420**	**448**	**476**	**504**	**532**	**560**	**588**	**616**	**644**	**672**	**700**	**728**	**784**		

d. Clinical Assessor's assessment of GCA signs and symptoms as specified in Section 8.1.1.
e. FDG PET/CT scan in the LTE is to be performed at Study Week 104 (LTE Week 52) or timepoint of flare if earlier. If a participant has a GCA flare prior to Study Week 104 (LTE Week 52), an attempt should be made to perform the FDG PET/CT imaging within 1 week from identification of GCA flare by the principal investigator during the LTE period. If a participant has a GCA flare within 1 month (or other timeframe in accordance with local country regulations) of FDG PET/CT imaging for the Study Week 52 timepoint of the main study, the FDG PET/CT scan should not be performed. Participants may decline to obtain the LTE FDG PET/CT. FDG PET/CT scan is being obtained as part of exploratory endpoint and results should not be used in determining disease status at the associated Study Week 104 (LTE Week 52) visit.
f. In this study, the C SSRS is a physician administered questionnaire and should be administered by the certified, trained, and delegated principal investigator or subinvestigator only.
g. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documentation in Section 10.3. Check clinical status again before first dose of study medication
h. Urine pregnancy testing is required for female participants of childbearing potential only (Section 8.2.5). If more frequent pregnancy testing is required by local regulations, these are allowed to be taken locally.
i. For visits where study intervention will be administered, 1 blood sample should be collected prior to study intervention administration, if applicable, for evaluation of serum concentration of guselkumab and/or antibodies to guselkumab.
j. The investigator is expected to re review the informed consent with the participant to ensure that the participant understands the purpose of, as well as the study procedures and required visits associated with the LTE period.
k. Participants who are eligible and willing to participate in the LTE study will continue with LTE Week 0 activities after completing Week 52 assessments of the main study.
l. PGA, Pain assessment, FACIT Fatigue, and SF 36 should be performed before any laboratory/safety tests, procedures, or other evaluations (PhGA and assessment of GCA disease signs and symptoms). Event driven PROs will be applicable for participants developing a GCA flare. C SSRS should be completed after all PROs and before any other tests, procedures, or other consultations.
m. In case a participant is diagnosed as having a flare during a study visit or shortly before a planned study visit the Flare visit and regular visit can be combined. Overlapping procedures and assessments need only be performed once. The FDG PET/CT scan can be scheduled separately from other assessments.

Abbreviations: CRP=C reactive protein; CT=computed tomography; C SSRS=Columbia Suicide Severity Rating Scale; ESR=erythrocyte sedimentation rate; FDG=fluorodeoxyglucose; GC=glucocorticoid; GCA=Giant cell arteritis; LTE=long term extension; PET=positron emission tomography; PRO=patient reported outcome. SC=subcutaneous.

2. INTRODUCTION

Guselkumab (CNTO1959) is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that binds to human interleukin (IL)-23 with high specificity and affinity. The binding of guselkumab to the IL-23p19 subunit blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23-specific intracellular signaling and subsequent activation and cytokine production. In this manner, guselkumab inhibits the biological activity of IL-23 in all in vitro assays examined.

Guselkumab has been approved for the treatment of adults with moderate to severe plaque psoriasis (PsO) in the United States (US), European Union, Canada, Japan and several other countries worldwide. In addition, guselkumab has been approved for the treatment of psoriatic arthritis (PsA), generalized pustular PsO, erythrodermic PsO, and palmoplantar pustulosis in Japan.

Guselkumab is currently being developed in other diseases including for the treatment of patients with PsA, hidradenitis suppurativa (HS), familial adenomatous polyposis, Crohn's disease, Lupus Nephritis (LN) and ulcerative colitis (UC). Phase 3 studies in PsA, a Phase 2/3 program in Crohn's disease, a Phase 2b/3 study in UC, and Phase 2 studies in HS and LN are currently ongoing or planned globally.

For the most comprehensive nonclinical and clinical information regarding guselkumab, refer to the latest version of the Investigator's Brochure (IB) and Addenda for guselkumab.

The term "study intervention" throughout the protocol, refers to study drug, as defined in Section 6.1, Study Interventions Administered.

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.

2.1. Study Rationale

Giant cell arteritis (GCA) is a non-necrotizing granulomatous systemic vasculitis of unknown etiology affecting medium-sized and large arteries usually accompanied or preceded by systemic inflammation. GCA has 2 disease components: vessel wall inflammation inducing arterial stenosis/occlusion and a systemic inflammation leading to polymyalgias, anemia, failure-to-thrive, and malaise (Weyand 2003). Prototypic vessel wall inflammation preferentially affects the upper extremity and extracranial branches of the aorta causing blindness, stroke, aortic arch syndrome, aortic aneurysm, or dissection (Weyand 2003; Evans 1995). Histologically, GCA is characterized by an infiltration of the media with lymphocytes, macrophages, and giant cells (Ciccia 2017). Inflammation may show a segmental infestation pattern in which inflammatory and non-inflammatory vascular segments are located side by side. It is the most common primary form of vasculitis in the US and Europe and occurs predominantly in individuals aged 50 years or over with the mean age of onset of approximately 70 years of age (Salvarani 2004). The onset of GCA symptoms may be abrupt, but in most instances, symptoms develop gradually over a period of several weeks. Women are affected 2-3 times as often as men (Nesher 2014; Waldman 2013).

Clinically, patients with GCA suffer from symptoms including headaches, scalp tenderness or pain, jaw/tongue/limb claudication, symptoms of polymyalgia rheumatica (PMR) and visual impairment. In many patients a systemic inflammatory response may also occur with symptoms including fever, weight loss and fatigue (González-Gay 2019). Typically C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are increased, and anemia, thrombocytosis and mild transaminitis are common features of GCA. Establishing a firm early diagnosis for GCA can be challenging, as patients present with a variety of symptoms and there are no conclusive diagnostic markers for GCA. Histological analysis of temporal artery biopsy tissue and temporal artery ultrasound are used to confirm GCA diagnosis. Delayed diagnosis and treatment can lead to significant complications including permanent visual loss due to anterior optic ischemic neuropathy or retinal artery occlusion. Other serious GCA complications include cerebrovascular strokes, infarction of the tongue and scalp necrosis (Waldman 2013).

Glucocorticoids (GCs) are the treatment of choice starting with an initial high dose of prednisone at 40-60 mg/day for most cases followed by a tapered lowering of dose. Glucocorticoid treatment with intravenous (IV) methylprednisolone 500 to 1000 mg/day for 3 days may be considered in patients with vision loss (transient or permanent), diplopia, transient ischemic attacks, or stroke.

2.1.1. Unmet Need in Giant Cell Arteritis

Major unmet needs in GCA include non-invasive diagnostic tests, optimization of GC use to avoid GC related complications, identification of more targeted treatments, and identification of prognostic factors.

Despite an often-rapid improvement of symptoms following initial GC treatment, most patients develop serious adverse side effects related to long-term use of GCs, including GC-induced diabetes, arterial hypertension, osteoporosis, cataracts, infection, and psychosis (Baig 2019). In fact, an estimated 86% of patients treated with long-term GC therapy suffered from these GC-related complications within 10 years (Ness 2013).

Glucocorticoid tapering is typically started when symptomatology resolves and inflammatory markers normalize, with the goal to reduce the risks of long-term GC use. Tapering can result in either complete weaning off of GC or finding a low stable maintenance dose, however disease relapse is common (50% to 80%) during GC taper (Hachulla 2001; Weyand 2000). While the general view is that GC treatment can be reasonably stopped after 2 years, patients oftentimes require GC therapy for much longer (Hayreh 1997). Furthermore, a significant proportion (~25%) of patients do not achieve permanent remission (Proven 2003).

Due to the frequent complications of prolonged GC treatment, there is a need to develop GC-sparing maintenance therapies for GCA.

Tocilizumab (anti-IL6) is the only biologic approved for GCA. Its use is often limited to patients who fail GCs due to limited efficacy or safety concerns. Additionally, IL-6 receptor blockade with tocilizumab abrogates the hepatic synthesis of acute-phase reactants and renders CRP and ESR measurement unreliable for the purpose of monitoring disease activity in GCA in clinical practice (Prieto-González 2017).

Significant opportunity remains for the development of new treatment options for GCA that provide greater sustained GC-free remission with a favorable safety profile in newly diagnosed and relapsing GCA patients. A safe and efficacious alternative to GCs is an urgent unmet need in GCA and is a niche that guselkumab may fill given its well-characterized safety profile and durable responses in other indications where it has been shown to be effective.

2.1.2. Rationale for Targeting IL-23 in Giant Cell Arteritis

IL-23 responses occur mainly in two types of tissue: microbiome rich barrier surfaces (gut and skin) (Furie 2009) and sterile interfaces subject to dynamic biomechanical loading. The latter is directly relevant to GCA as sites include the aorta (as well as entheses and eye). In contrast to adaptive immune responses, resident IL-23R+ cells are present within tissue in the resting, healthy state. In animal models and/or explants from human tissues, exposure to IL-23 results in immediate activation of these cells and a robust onset of tissue inflammation which exactly phenocopies the pathognomonic anatomical specificity of human disease in conditions such as aortitis, PsO, PsA/enthesitis, uveitis and (with additional manipulations) inflammatory bowel disease (Hayreh 1997; Baig 2019). These insights have underscored the clinical success of guselkumab in several disease areas.

Aortitis is therefore within the domain of broader systemic inflammatory disorders in which IL-23 is known to be important. This is further emphasized by the observation that enthesopathic arthritis is associated with aortitis. Enthesopathic arthritis is also associated with both clinical and subclinical intestinal inflammation, whilst aortitis (specifically, Takayasu's arteritis) has been reported to associate with inflammatory bowel disease (Deng 2010). Strong evidence of the role of IL-23 in aortitis comes from its ability to directly drive aortic root inflammation upon experimental expression of the cytokine where it acts on local IL-23 responsive cells resident in this structure (Hayreh 1997). This understanding of aortitis is consistent with the role of IL-23 at other sites of high biomechanical stress, such as the entheseal structures where similar IL-23 responsive cells are present. Furthermore, the IL-23 driven aortic inflammation bears strong histopathological resemblance to Takayasu's Arteritis (a large vessel vasculitis predominantly affecting the aorta). Despite GCA having a different phenotype than Takayasu's, it can also be associated with a widespread aortitis and there is even a diagnostic entity of "large vessel GCA" (Hachulla 2001; Evans 1995; Conway 2018). Whereas both the precise location of IL-23R+ cells and the exact location of skeletal enthesitis is related to the presence of tensile collagenous fibers, GCA is well known to develop in the part of the artery which has an internal elastic lamina. This may reflect an analogous predilection for IL-23 responses to be focused upon such biomechanical fibers as well as the lamina being a potential target for adaptive immune responses. In GCA, the temporal artery is also IL-23 responsive, and IL-23 is expressed by local inflammatory cells (Ciccia 2017).

As well as these anatomical and structural implications, further evidence for the involvement of IL-23 comes from the presence of IL-23 driven Th17 cells in GCA. These cells are expanded in GCA and cytokines in the IL-23 pathway, including IL-17, IL-6, IL-21 are elevated. Indeed pro-inflammatory cytokines including IL-6 and IL-23 that induce Th17 cells are elevated in GCA. T cell lines from GCA patients have been tested for their inflammation-inducing capacity and a T

cell subset analysis revealed a strong bias towards the enrichment of Th17 and Th17/Th1 cells (Deng 1995), including the detection of IL-17+ T cells in the vascular tissue of GCA patients. The relevance of these cells is further highlighted by the effects of therapeutics on this biology. Currently, GCs are the standard of care for GCA and are highly effective in normalizing pro-inflammatory cytokines including IL-6, IL-17, IL-23 and Th17 cell levels in blood and lesional tissue, providing rationale for testing guselkumab in GCA (Weyand 2011). The pathogenesis of GCA is incompletely understood and clinical trials with targeted therapies provide an opportunity to test the relevance of specific pathways that may be driving vascular inflammation, including IL-23.

Taken together, these observations supply firm scientific evidence to suggest a role for IL-23 in driving the pathogenesis of large vessel vasculitides such as GCA. These results suggest that reducing IL-23-mediated inflammation with guselkumab may improve the signs and symptoms of new-onset and relapsing GCA.

2.2. Background

Nonclinical Studies

A full nonclinical development program was conducted with guselkumab in support of initial global submissions and approvals. This program included general toxicology and toxicokinetic studies in support of first-in-human dosing, studies in support of Phase 2 and Phase 3 clinical development, and developmental and reproductive toxicology studies. A comprehensive overview of nonclinical data is presented in Section 3 of the guselkumab IB.

This section provides a summary of the sponsor's assessment of how the overall nonclinical data support the safety of the proposed dosing for guselkumab in this Phase 2 clinical study in GCA. Details regarding the proposed dose regimen and dose rationale are described in Section 4.3 of this protocol.

To place the selected clinical dosing for guselkumab in GCA patients into perspective relative to the existing preclinical data, the predicted human exposure at steady-state (based on the dose tested in this protocol, ie, 200 mg SC every 4 weeks) was compared with the exposure at the NOAEL in cynomolgus monkeys following weekly SC administration in the 24-week arm of the subchronic toxicology study. These data are presented in Table 1.

Table 1: Predicted Guselkumab Exposure Margins for the Dosing Regimen to be Evaluated in the Study

Guselkumab Predicted Exposure Margins at 200 mg SC Dosing		
Parameters	**Mean C_{max} (µg/mL)**	**Mean AUC (µg.day/mL)**
Cynomolgus Monkey Exposure at the NOAEL (50 mg/kg/week) Following 24 Weekly SC Doses	993[a]	5412[b]

Table 1: Predicted Guselkumab Exposure Margins for the Dosing Regimen to be Evaluated in the Study

Human Predicted SC Exposure	30[c]	134[d]
Predicted Exposure Margin[e]	33.1	40.4

Abbreviations: AUC=area under the curve; C_{max}=maximum serum concentration; NOAEL=no observed adverse effect level; SC=subcutaneous

a. Highest observed concentration following the twenty fourth 50 mg/kg dose (SC)
b. AUC from Day 161 through 168 (1 week after the last 50 mg/kg dose).
c. Highest predicted concentration at steady state following SC administration.
d. Predicted human AUC at steady state following 200 mg SC every 4 weeks administration. Each value was divided by 4 to obtain the AUC over one week, which in turn corresponds to the AUC interval for cynomolgus monkeys. Simulation of human pharmacokinetic exposure was based on a body weight of 70 kg.
e. Exposure margins represent the ratio between guselkumab exposure metrics in the cynomolgus monkey compared with those predicted in humans.

From a nonclinical perspective, the risk to GCA patients at the selected guselkumab dose regimen is considered low based on no adverse findings observed in cynomolgus monkeys. As shown in Table 1, the predicted exposure margins for the selected SC dose (200 mg SC every 4 weeks) relative to the exposures at the NOAEL in cynomolgus monkeys are approximately 33- to 40-fold for mean area under the curve and mean C_{max}, respectively, which is considered adequate to support the long-term SC dosing in the guselkumab GCA Phase 2 study. Further supportive clinical data for the selected guselkumab doses in terms of safety are described in Section 4.3.

Clinical Studies

Guselkumab has demonstrated efficacy in PsO and has received marketing approval in several countries and regions globally for the treatment of adults with moderate to severe plaque PsO, including in the US, Canada, European Union, Latin America, and the Asia Pacific region. The approved guselkumab dose for PsO is 100 mg by SC injection at Weeks 0, 4, and every 8 weeks thereafter. In addition, guselkumab has been approved for the treatment of PsA in multiple countries, and for generalized pustular PsO, erythrodermic PsO, and palmoplantar pustulosis in Japan.

This protocol represents the first study of guselkumab in participants with GCA.

Phase 3 development is ongoing globally in PsA, and a seamless global Phase 2/3 clinical program is ongoing in Crohn's disease, a global Phase 2b/3 program is ongoing in ulcerative colitis, and there are several Phase 2 studies with guselkumab in other indications.

- The Phase 2 study of the Phase 2/3 guselkumab Crohn's disease program evaluated the induction dose regimens up to a maximum dose of 1200 mg IV every 4 weeks given 3 times.
- The ongoing Phase 3 studies of the Phase 2/3 guselkumab Crohn's disease program are evaluating an induction dose of 200 mg IV every 4 weeks given 3 times and a maintenance dose of 100 mg SC every 8 weeks or 200 mg SC every 4 weeks.

- In the Phase 2b/3 guselkumab UC program induction doses up to 400 mg IV every 4 weeks and maintenance doses up to 200 mg SC every 4 weeks were evaluated. For the Phase 3 induction part of the study, 200 mg IV at Week 0, 4, and 8 was chosen for induction regimen.
- A Phase 2 HS study evaluated the induction dose regimen of 1200 mg IV every 4 weeks given 3 times, as well as a maintenance dose range from 100 mg SC every 8 weeks to 200 mg SC every 4 weeks.
- In a Phase 2 LN study and Phase 2 systemic Sclerosis study, guselkumab doses of 400 mg IV at Weeks 0, 4, and 8 followed by guselkumab 200 mg SC every 4 weeks are being evaluated.
- A Phase 2a proof-of-concept study with a guselkumab and golimumab combination in UC which includes a guselkumab monotherapy arm (guselkumab 200 mg IV at Weeks 0, 4, and 8 followed by guselkumab 100 mg SC every 8 weeks) has been completed.

Details about these guselkumab clinical development programs across various indications are provided in Section 4 of the latest version of the guselkumab IB.

Through the IB cutoff date of 12 July 2021, an estimated 703 healthy participants, 4,068 participants with PsO, 109 participants with rheumatoid arthritis (RA), 1,471 participants with PsA, 182 participants with palmoplantar pustulosis, 230 participants with Crohn's disease, 175 participants with HS, 540 participants with UC, and 51 participants with familial adenomatous polyposis have been exposed to guselkumab. Overall, an estimated 7,827 participants have been exposed to guselkumab in the clinical development program.

The largest clinical experience to date with guselkumab has been in plaque PsO. The safety profile of guselkumab in participants with moderate to severe plaque PsO is based on data from the Phase 2 study CNTO1959PSO2001 and Phase 3 studies CNTO1959PSO3001, CNTO1959PSO3002, CNTO1959PSO3003, CNTO1959PSO3006, and CNTO1959PSO3009. Of the 2,711 guselkumab treated participants, 2,255 participants were exposed for at least 1 year, 1,516 were exposed for at least 2 years, and 692 participants were exposed for 3 years. The Phase 2 and 3 plaque PsO studies included a substantial proportion of participants ≥45 years of age. Out of 2,711 participants, a total of 1,174 (43.3%) patients between the age of 45 and <65 years and 165 (6.1%) patients ≥65 years of age received guselkumab. No overall differences in safety or efficacy were observed between older and younger patients who received guselkumab in clinical studies.

2.3. Benefit/Risk

2.3.1. Risks for Study Participation

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Risks Due to Study Intervention Guselkumab		
Clinical worsening of GCA related to rapid GC taper	The benefit-risk of guselkumab in treatment of GCA has not been established.	Participants are receiving investigational agent with standard-of-care GCs that are tapered down (Section 6.5). Participants that are unable to taper

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
		GCs (GC dependent) for their GCA will not be permitted to participate in the study (Section 5.2). Participants that experience a flare will be allowed to use rescue GCs as needed (Section 6.8.3). Participants may discontinue study intervention if it is not in their best interest or if they need to initiate certain protocol-prohibited medications in Section 6.8 and Section 7.1).
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.	Participants with a history of, or ongoing, chronic, or recurrent infectious disease, evidence of active or untreated latent opportunistic infections including tuberculosis (TB), will be excluded from the study (Section 5.2). Participants receiving a live viral or bacterial vaccination within 12 weeks of first study intervention 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 12 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 (Sections 8.2.10 and 8.2.10). A participant's study intervention must be discontinued if an opportunistic infection including TB develops, and study intervention must be interrupted if the participant develops a serious infection, including but not limited to sepsis or pneumonia, and continuation or discontinuation of study intervention should be discussed and decided with the medical monitor or designee (Section 7.1).
Hypersensitivity reactions, including serious hypersensitivity reactions.	Serious hypersensitivity reactions including anaphylaxis have been reported in postmarketing experience with guselkumab in PsO patients. Hypersensitivity, including anaphylaxis, urticaria	Participants with known allergy, hypersensitivity, or intolerance to guselkumab or its excipients will be excluded from the study. Sites are instructed that before any administration of study intervention, appropriately trained

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
	and rash have been identified as ADRs for guselkumab.	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 8.2.8). Any participant who develops a serious hypersensitivity reaction such as anaphylaxis must discontinue study intervention (Section 7.1).
Malignancy	The preponderance of preclinical data suggests that blockade of endogenous IL-23 would not be detrimental and may in fact be beneficial in tumor immunosurveillance and host protection; however, a risk of malignancy cannot be excluded.	Participants with a current malignancy or a history of malignancy within 5 years prior to screening (with exceptions noted in Section 5.2) will be excluded from the study. 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 labs and inquiring of any adverse events (AEs) to assess for 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 cancers that are treated with no evidence of recurrence or residual disease) will be discontinued from study intervention (Section 7.1).
Liver injury	A serious adverse event (SAE) of 'toxic hepatitis' was reported in the ongoing Phase 2/3 guselkumab Crohn's disease program in a participant who received guselkumab 1200 mg IV at Weeks 0, 4, and 8, and 200 mg SC at Week 12. Based on the hepatocellular pattern of injury,	During the conduct of the study, liver function tests will be monitored at regular intervals in accordance with regulatory guidance (Section 10.9) (FDA 2009). In addition, the induction doses in this study will be lower and will not exceed 400 mg IV. Participants with marked liver enzyme elevations or symptoms or signs of liver dysfunction (eg,

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
	temporal relationship of the event to guselkumab exposure, and the exclusion of alternative etiologies, this event may represent drug-induced liver injury possibly related to guselkumab. 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 every 4 weeks compared to100 mg every 8 weeks.	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).
Immunosuppression	Although guselkumab has been studied with other immunosuppressives in other diseases, there may be an increased risk of infection or malignancy.	In order to minimize the theoretical increased risk of infection or malignancy with the combination of guselkumab with immunosuppressive therapy, the baseline dose of oral GCs on study entry is limited to ≤60 mg/day prednisone or equivalent, which must be tapered starting at Week 1. Additionally, participants are also excluded from the study if they have received a variety of immunomodulatory therapies if received within a protocol defined timeframe from first study intervention (Section 5.1 and 5.2).
Risks Due to Study Procedures		
Risks associated with fluorodeoxyglucose (FDG)- positron emission tomography (PET)/computed tomography (CT) imaging include radiation exposure and risk of allergic reaction to the tracer.	These risks are well recognized, with radiation exposure for a PET/CT scan being lower than if both scans were to be done separately, and the risk of serious complications like an allergic reaction is very rare.	Trained and experienced physicians will be performing the procedure during this study, participant preparation and precautionary measures will be taken to reduce tracer uptake in normal tissues (fasting, well pre-hydrated, limited activity and kept warm). A low-dose protocol will be used for fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scanning which results in an estimated average effective radiation dose between 9 and 15 mSv when a full body CT (approximately 2-8 mSv) is used and a fixed dose of 10mCi* of FDG (approximately 7 mSv) is administered. All participants will be limited to two FDG-PET/CT scans over the course of the main study (Grayson 2018; Willowson 2012).

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
		In the long-term extension (LTE) period, 1 additional FDG-PET/CT scan will be performed at Week 104 (LTE Week 52) or if a participant has a flare. If a participant has a GCA flare prior to LTE Week 52, an attempt should be made to perform the FDG-PET/CT imaging within 1 week from identification of GCA flare by the principal investigator during the LTE period. In case of a flare occurring within 1 month of the Week 52 main study FDG-PET/CT scan (or other timeframe in accordance with local country regulations), the FDG-PET/CT scan will not be performed.

* In countries where local regulations require adjustment of the dose this should be done in consultation with the sponsor.

More detailed information about the known and expected benefits and risks of guselkumab may be found in the IB.

2.3.2. Benefits for Study Participation

There is no established benefit to participants of receiving study intervention. There is evidence that inflammation associated with increased IL-17 pathway activity mediated by IL-23 may be involved in the pathogenesis of GCA. Given the scientific rationale for IL-23 blockade and that ustekinumab may provide benefit in the treatment of GCA (Section 2.1.2), participants may experience an improvement in disease status during treatment with guselkumab. Participants in the study will also help in furthering development of this drug to treat GCA and increased understanding of GCA. Thus, the knowledge gained from this study has the potential to benefit many more patients suffering with GCA, and thus offers potential public health benefits.

Participants may also experience some benefit from the participation in a clinical study irrespective of receiving study treatment, due to regular visits and assessments monitoring their overall health.

2.3.3. Benefit-Risk Assessment for Study Participation

Guselkumab has undergone extensive nonclinical and clinical development as summarized in the latest version of the IB and described briefly in Section 2.2. The collective efficacy and safety results of the Phase 1, Phase 2, and Phase 3 clinical studies in healthy volunteers and patients with plaque PsO and PsA established a favorable benefit-risk profile for guselkumab in the treatment of plaque PsO and PsA. There is a global regulatory approval for the plaque PsO and PsA indications. In Japan, guselkumab has also been studied and received regulatory approval for the treatment of erythrodermic PsO, generalized pustular PsO, and palmoplantar pustulosis. This clinical experience provided support for the ongoing development of guselkumab in other inflammatory diseases such as Crohn's disease, UC, lupus nephritis and systemic sclerosis.

Although at present there are no clinical results for guselkumab in the treatment of GCA, current available scientific data suggests IL-23 may play an important role in the pathogenesis of GCA (Section 2.1.2) and inhibition of IL-23 cytokines will be helpful in controlling GCA while being able to taper GCs. In addition, a phase 2 study evaluating secukinumab in GCA (Venhoff 2021), provided evidence that targeting IL-17 is efficacious. The secukinumab data is particularly relevant for guselkumab since secukinumab targets IL-17 which is connected with the IL-23 pathway that is targeted by guselkumab. A 26-week GC taper is considered the standard in clinical trials in GCA, and combined with a rescue GC therapy option provides an appropriate mitigation for potential GCA flares.

The guselkumab dose to be evaluated (ie, 200 mg SC every 4 weeks) in this protocol is higher than the approved dose regimen of guselkumab in PsO and PsA. Based on the data from nonclinical toxicology studies (Section 2.2), the predicted exposure margins during the treatment period relative to the exposure at the NOAEL identified in cynomolgus monkey are adequate to support the proposed clinical doses (Section 4.3).

The guselkumab dose to be evaluated in this protocol is 200 mg SC every 4 weeks from Week 0 to Week 48 for the main study (see Sections 4.2, Scientific Rationale for Study Design and Section 4.3, Justification for Dose). Based on a population pharmacokinetics (PK) analyses in patients with PsO or PsA, age (≥65 years) was not found to have significant impact on guselkumab apparent clearance following SC administration; therefore, guselkumab PK exposure in elderly participants is not expected to be substantially different from the non-elderly.

Potential risks of guselkumab, including those of serious infection and malignancy, and the risk of tapering participants of GCs are being addressed via judicious inclusion/exclusion criteria, frequent study visits to allow for close monitoring of patient safety, guidelines for participant management (including monitoring of clinical laboratory tests and treatment discontinuation criteria), detailed description of allowed and prohibited concomitant medications, and comprehensive medical monitoring of data by the sponsor during the conduct of the studies. In addition, a comprehensive safety monitoring plan with oversight from an independent Data Monitoring Committee (DMC) will be implemented to ensure the safety of guselkumab in participants with new-onset or relapsing GCA (Section 9.6).

In summary, the collective preclinical and clinical evidence for the anti-IL-23 mechanism of action in GCA, and the benefit-risk profile of guselkumab established to date in PsO and other immune mediated diseases, provide a strong scientific and clinical rationale for pursuing development of guselkumab in patients with GCA and for the investigation of guselkumab in this Phase 2 program. Taking into account the measures taken to minimize risk to participants in this study, the potential risks associated with guselkumab are justified by the potential benefits that may be provided to participants with GCA.

3. OBJECTIVE AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the efficacy of guselkumab compared to placebo, in combination with a 26-week glucocorticoid (GC) taper regimen, in adult participants with new-onset or relapsing giant cell arteritis (GCA).	The proportion of participants achieving GC-free remission at Week 28
Secondary	
To evaluate the efficacy of guselkumab compared to placebo, in combination with a 26-week GC taper regimen, in adult participants with new-onset or relapsing GCA as measured by alternative definitions of GC free remission, GC-sparing effects, and prevention of disease flares.	The proportion of participants achieving GC-free remission from Week 28 by visit through Week 52 The proportion of participants achieving GC-free remission and normalization of erythrocyte sedimentation rate (ESR) at Week 28 and by visit through Week 52 The proportion of participants achieving GC-free remission and normalization of C-reactive protein (CRP) at Week 28 and by visit through Week 52 The proportion of participants achieving GC-free remission and normalization of both ESR and CRP at Week 28 and by visit through Week 52 The cumulative GC dose through week 28 and through Week 52 The time to first GCA disease flare or discontinuation of study intervention due to AE of worsening of GCA through Week 28 and through Week 52 The number of GCA disease flares or discontinuation of study intervention due to AE of worsening of GCA through Week 28 and through Week 52
To evaluate the safety of guselkumab, in combination with a 26-week GC taper	Number/proportion of participants with treatment-emergent adverse events (TEAEs) through Week 60

Objectives	Endpoints
regimen, in adult participants with new-onset or relapsing GCA.	Number/proportion of participants with TEAEs by system organ class with a frequency threshold of 5% or more through Week 60 Number/proportion of participants with treatment-emergent serious adverse events (SAEs) through Week 60 Number/proportion of participants with clinically significant abnormalities in vital signs, laboratory safety tests through Week 60
To evaluate the PK and immunogenicity of guselkumab, in combination with a 26-week GC taper regimen, in adult participants with new-onset or relapsing GCA.	Mean (standard deviation [SD]) serum concentrations of guselkumab through Week 52 in participants receiving active study intervention. Number/proportion of participants with antibodies to guselkumab in participants receiving active study intervention.
Exploratory	
To explore the longer-term efficacy of guselkumab compared to placebo, in combination with a 26-week GC taper regimen, in adult participants with new-onset or relapsing GCA.	Proportion of participants in sustained remission through Week 52
To evaluate the changes in immune-markers to guselkumab compared to placebo, in combination with a 26-week GC taper regimen, in adult participants with new-onset or relapsing GCA.	Change from baseline in CRP through Week 52 Change from baseline in ESR through Week 52
To explore the changes in pharmacodynamic (PD) markers and arterial vessel wall inflammation following administration of guselkumab in adult participants with new-onset or relapsing GCA.	Assessment of IL-23 pathway related and disease related biomarkers in serum, whole blood, and peripheral blood mononuclear cell (PBMC) through Week 52. Large-Vessel Imaging (fluorodeoxyglucose positron emission tomography/computed tomography [FDG-PET/CT]) changes from baseline at Week 52 (or flare)

Objectives	Endpoints
To explore changes in participant reported Clinical Outcome Assessments, pain and fatigue, and physician reported outcomes and digital health parameters following administration of guselkumab in adult participants with new-onset or relapsing GCA.	Change from baseline on electronic patient-reported outcome (ePRO): Patient's Global Assessment of Disease Activity (PGA), Pain Assessment, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue and short form-36 (SF-36) by visit through Week 52 Change from baseline on clinician reported outcome: Physician's Global Assessment of Disease Activity (PhGA) by visit through Week 52 Change from baseline in Actigraphy Watch collected continuous data on physical activity, mobility, and sleep by visit through Week 52
Exploratory Objectives for the Long-Term Extension (LTE) period	
To evaluate long-term efficacy of guselkumab in adult participants with new-onset or relapsing GCA	The proportion of participants achieving GC-free remission from Week 52 (LTE Week 0) through Week 104 by visit (LTE Week 52) The time to first GCA disease flare from Week 52 (LTE week 0) through Week 104 (LTE Week 52).
To evaluate the continued safety of guselkumab in adult participants with new-onset or relapsing GCA.	Number/proportion of participants with TEAEs or SAEs from Week 52 (LTE Week 0) through Week 112 (LTE Week 60) Number/proportion of participants with clinically significant abnormalities in vital signs and laboratory safety tests from Week 52 (LTE Week 0) through Week 112 (LTE Week 60)
To evaluate the PK and immunogenicity of guselkumab, in adult participants with new-onset or relapsing GCA.	Mean (SD) serum concentrations of guselkumab from Week 52 through Week 104 (LTE Week 52) in participants receiving active study intervention. Number/proportion of participants with antibodies to guselkumab in participants receiving active study intervention

Objectives	Endpoints
To explore the changes in PD markers and arterial vessel wall inflammation following administration of guselkumab in adult participants with new-onset or relapsing GCA in the LTE period.	Assessment of IL-23 pathway related and disease related biomarkers in serum and whole blood at Week 104 (LTE Week 52) Large-Vessel Imaging (FDG-PET/CT) changes from baseline and Week 52 at Week 104 (LTE Week 52) or flare
To explore changes in participant reported Clinical Outcome Assessments, pain and fatigue, and physician reported outcomes following administration of guselkumab in adult participants with new-onset or relapsing GCA in the LTE period.	Change from baseline on electronic patient-reported outcome (ePRO): Patient's Global Assessment of Disease Activity (PGA), Pain Assessment, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue and short form-36 (SF-36) at Week 76 (LTE Week 24), Week 104 (LTE Week 52) or Flare visit. Change from baseline on clinician reported outcome: Physician's Global Assessment of Disease Activity (PhGA) at Week 76 (LTE Week 24) Week 104 (LTE Week 52) or Flare visit.

Refer to Section 8 for evaluations related to endpoints.

Definitions of Efficacy Endpoints:

Remission of GCA: No signs or symptoms of GCA and adherence to the 26-week taper without GCA flare.

GCA Flare: For participants in GCA remission, flare is defined as the recurrence of signs and symptoms of GCA, with or without elevation of inflammatory markers, and the necessity for an increase in GC dose for GCA.

Having CRP/ESR elevations in isolation without clinical signs and symptoms attributable to GCA, does not qualify as flare, unless the investigator decided to increase the GC dose (see Section 6.8.3).

Sustained remission of GCA: No signs and symptoms of GCA through Week 52, and completion of the protocol defined GC taper, and not having required GC rescue therapy at any time by Week 52.

HYPOTHESIS

The primary hypothesis is that guselkumab treatment with a 26-week GC taper is superior to placebo with a 26-week GC taper in participants with new-onset or relapsing GCA as assessed by the proportion of participants achieving GC-free remission at Week 28.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, parallel, multicenter, interventional Phase 2 Proof-of-Concept study evaluating the efficacy, safety, PK, and immunogenicity of guselkumab for the treatment of active new-onset or relapsing GCA in adult participants.

A target of approximately 51 participants will be enrolled in this study. Participants will be randomly assigned into 2 treatment groups in a 2:1 ratio of guselkumab versus placebo.

- **Group 1: Guselkumab (200 mg SC every 4 weeks)**

  Participants will receive guselkumab 200 mg SC every 4 weeks at Week 0 through Week 48.

- **Group 2: Placebo**

  Participants will receive placebo SC every 4 weeks at Week 0 through Week 48.

Participant randomization will be stratified by new-onset and relapsing GCA (relapsing preferentially limited to 70% to ensure some enrollment of new-onset GCA but may be increased depending on the rate of enrollment of relapsing versus new-onset GCA), and by baseline GC dose (≤30 mg/day or >30 mg/day).

The placebo comparator (in addition to standard-of-care background therapy of GCs) will be used in this study through Week 48 of the Main study to allow for blinded, placebo-controlled evaluation of the long-term efficacy and safety of guselkumab in participants with GCA. Participants on placebo that continue into the LTE will continue to receive placebo until the participant reaches Week 100 (LTE Week 48) or experiences a GCA flare, or until unblinding of the study due to completion of the main study, whichever occurs first.

The total duration of the study is up to 66 weeks for the main study: a screening period of ≤ 6 weeks, a 48-week main study treatment period, and a 12-week safety follow-up period after the last dose (a final efficacy visit 4 weeks after the last dose and a safety follow-up visit 12 weeks after the last dose). Participants that continue in the LTE period may continue in the study for a total duration of 112 weeks.

Participants that experience a flare should have a Flare visit with assessments performed according to the SoA preferably within 1 week of having the flare. In case a participant is diagnosed as having a flare during a study visit or shortly before a planned study visit, the Flare visit and regular visit can be combined. Overlapping procedures and assessments need only be performed once. The

FDG-PET/CT scan can be scheduled separately from other assessments. In case of subsequent flares, a Flare visit should be performed according to the SoA with the exception of the FDG-PET/CT scan. Depending on the circumstances, reduced assessments may be considered in consultation with the sponsor.

Efficacy, safety, PK, immunogenicity, and biomarkers will be assessed according to the Schedule of Activities (SoA; Section 1.3). An optional pharmacogenomic blood sample will be collected from participants who consent to the collection of these samples (where local regulations permit).

The primary efficacy analysis will be performed after all participants have completed Week 28 efficacy assessments (or discontinued). Additional secondary endpoints will be completed at Week 28 and Week 52. Three planned database locks (DBLs) will occur, at Week 28 and at Week 60 for the main study and a final DBL lock when the last participant completes last visit in the LTE period. The study will be double-blind until all participants have completed the main study and associated Week 60 DBL has occurred.

An independent DMC will be commissioned for this study. Refer to Sections 9.6 (Data Monitoring Committee) and for the Committees Structure in Section 10.3.

Long-term Extension Treatment Period (Week 52 to Week 112; optional for eligible participants)

Participants who complete the Week 52 visit and are assessed to be in GC-free remission, may have the option to participate in the LTE period of the study.

If a participant is in GC-free remission at Week 48, the participant will be informed of the possibility to participate in the LTE period and continue to receive study intervention. Study intervention will continue to be blinded, meaning that a participant will continue to receive the treatment that had been allocated to that participant (placebo or guselkumab) in the main study. After the Week 52 evaluations, if the participant is eligible and has consented for the LTE, the participants will continue to receive SC study intervention every 4 weeks starting at Week 52 (LTE Week 0) under this protocol's study extension until participants reach Week 100 (LTE Week 48) or until a participant experiences a GCA flare, or the participants discontinues treatment due to unblinding after the Week 60 DBL for the Main study, or until the Sponsor makes a decision not to continue this study, whichever occurs first. Participants who continue treatment as part of the study extension will be intermittently evaluated per the protocol for efficacy, PK, and safety. The LTE period is followed by a 12-week safety follow-up period after the last dose (a final efficacy visit 4 weeks after the last dose and a safety follow-up visit 12 weeks after the last dose). Participants that experience a flare should have have a Flare visit with assessments performed according to the SoA preferably within 1 week of having the flare and an early termination visit approximately 12 weeks after the last dose. In case a participant is diagnosed as having a flare during a study visit or shortly before a planned study visit, the Flare visit and regular visit can be combined. Overlapping procedures and assessments need only be performed once. The FDG-PET/CT scan can be scheduled separately from other assessments.

After the Week 60 DBL, the study will be unblinded to treatment. Any participants in the LTE that are on placebo will be informed and administration of study intervention will be discontinued. The participants may still continue in the study until Week 112 or until the end of the safety follow-up period in case they experienced a GCA flare.

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

4.2. Scientific Rationale for Study Design

A double-blind, placebo-controlled study was selected where participants would be randomized to guselkumab or placebo in addition to the standard-of-care background therapy. This study design was selected as a true placebo comparator group is unethical for this serious disease condition. Therefore, placebo and experimental treatments will be added to a standard-of-care regimen of GCs.

With this standard-of-care regimen, participants will enter on GCs (not exceeding 60 mg/day prednisone or its equivalent) and will be tapered off their GCs by Week 26 to minimize confounding treatment effects of GCs on efficacy endpoints and to determine GC-sparing effects of study intervention in order to reduce the risks of long-term GC use. Similar GC tapering regimens have been used in some recent GCA studies (Unizony 2013; Stone 2017), and are currently used in ongoing investigational studies for GCA.

For participants who will be treated with guselkumab, an IV induction dose regimen of guselkumab was originally chosen, followed by SC doses as this follows the typical induction-maintenance treatment paradigm, that has been used to treat multiple immune-mediated disease under investigation with guselkumab including CD, HS, UC, and LN. This was expected to ensure target inhibition of IL-23 in the large vessel walls in this proof-of-relevance study. New insights based on results from these ongoing internal studies as well as data from external studies with therapeutics that have been evaluated for treatment of GCA, suggest that IV induction dose regimens may not be needed and that SC only dose regimens are expected to be sufficient to ensure target inhibition of IL-23 in GCA (discussed in section 4.3). Per Amendment 5, newly enrolled participants will start study intervention on a SC dose regimen.

Additional details on doses and dose justification are described in Section 4.3.

Blinding, Control, Study Phase/Periods, Intervention Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Deoxyribonucleic acid (DNA) and Biomarker 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 DNA to allow the identification of genetic factors that may influence the PK, PD, efficacy, safety, or tolerability of guselkumab and to identify genetic factors associated with GCA or the response to guselkumab treatment.

Biomarker samples (where local regulations permit) will be collected to evaluate cellular and molecular mechanism of action of guselkumab or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to a treatment. The goal of the biomarker analyses is to further define the mechanism of action of selective blockade of IL-23 with guselkumab in GCA and aid in evaluating the intervention-clinical response relationship. 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. Participant Input into Design

An advisory board of GCA patients and several GCA patient interviews were used to consult patients on the study design and conduct. Participants provided insights on the protocol design, where they perceived barriers to participation, and how the clinical study experience could be improved for patients. In particular, feedback was received about preference of repeat imaging over repeat temporal artery biopsy for GCA, there were reservations about a 1:1 randomization ratio versus a 2:1 ratio, and the highest-ranking patient concerns were continued fatigue affecting their daily lives and the fear of losing sight. Additionally, there was feedback on some of the inclusion/exclusion criteria and the SoA.

Improvements to willingness to participate likely to impact recruitment strategy included provision of logistical support with study site visits (transportation, home study visits) and access to the medication after the trial, which were considered to make trial participation more attractive.

4.2.2. 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 the medication has shown to have efficacy in humans in other diseases, efficacy has not been shown in GCA, and response to medication in GCA is theoretical at this time.

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

4.3. Justification for Dose

The dose regimen of 200 mg SC every 4 weeks will be evaluated for this Phase 2 POC study in participants with active new-onset or relapsing GCA.

This dose regimen was selected based on the objective of determining the maximum efficacy of guselkumab for treatment of GCA, the approved dose regimen for PsO and PsA, the ongoing investigation for induction and maintenance therapy in Crohn's disease, UC, LN, and systemic sclerosis, the available safety information from relevant preclinical and clinical studies and the results from clinical studies from other approved and/or emerging GCA therapeutics.

In previous versions of the protocol (prior to amendment 5), a guselkumab dose regimen consisting of an IV induction regimen (400 mg at weeks 0, 4 and 8) followed by a SC maintenance regimen of 200 mg every 4 weeks starting from Week 12 had been chosen for this POC study based on evidence available at time of initial protocol development and outlined in protocol versions 1-4. Based on scientific rationale and emerging data, it is now considered that an IV induction dose regimen of guselkumab would not be necessary for the treatment of GCA. The dose regimen of 200 mg SC every 4 weeks starting at Week 0 is anticipated to provide sufficient drug exposure to treat GCA. Results from a Phase 2 trial with secukinumab, an anti-IL-17A monoclonal antibody, reveal that a SC regimen targeting IL-17 can be effective at treating GCA (Venhoff 2021). These data are particularly relevant since IL-17 is an inflammatory cytokine within the IL-23 pathway. The SC dose regimen in this study is also supported by the results of the phase 3 tocilizumab data (Stone 2017), which demonstrated that a beneficial effect on GCA can be obtained without the use of an IV induction dose regimen and at doses that are similar to those utilized for inflammatory arthritis.

Furthermore, the lowest IV induction dose regimen (200 mg of guselkumab at Week 0, 4 and 8) was shown to be efficacious in Phase 2 dose ranging studies for Crohn's disease (GALAXI [Sandborn 2022]) and Ulcerative Colitis (QUASAR [Dignass 2022]). This lowest IV dose regimen was therefore selected for further evaluation in the ongoing Phase 3 studies for these two IBD populations (see also Section 2.2). In addition, the CRP reduction associated with guselkumab was not found to be dose dependent in these trials (Sandborn 2022). This is pertinent for GCA as systemic markers of inflammation, CRP and ESR, are utilized to follow disease activity in GCA. These data suggest that an IV induction regimen would not add incremental value to the treatment of GCA with guselkumab.

In population PK analyses for guselkumab PsA or PsO studies, age was not found to have significant impact on guselkumab apparent clearance following SC administration in participants with PsA (range: 19 to 74 years; 38 [5.1%] participants ≥65 years old and 13 [1.74%] participants

≥70 years old) or PsO (range: 18-82 years; 70 [4.8%] participants ≥65 years old and 4 [0.3%] participants ≥75 years old) (Population Pharmacokinetics Analysis 2016; Population Pharmacokinetics Analysis 2019). As a monoclonal antibody, guselkumab PK exposure in elderly participants is not expected to be substantially higher than that in the non-elderly.

With respect to safety of the SC dose regimens, the predicted exposure margins for the 200 mg SC every 4 weeks dose regimen relative to the NOAEL of 50 mg/kg/week in cynomolgus monkeys are approximately 33 to 40, as shown in Table 1, which are considered adequate to support the long-term SC dosing (for chronic maintenance) in the guselkumab GCA clinical development programs. Guselkumab is approved for the treatment of plaque PsO and PsA with a good long-term clinical safety profile (with data generated primarily at 100 mg SC every 8 weeks), and dose regimens up to 200 mg SC every 4 weeks are being investigated in clinical trials with no new safety concerns identified to date.

The available clinical safety data, along with acceptable safety margins and other studies evaluating similar dose regimens, make it reasonable to study GCA with this dose regimen of 200 mg of guselkumab SC every 4 weeks. This dose regimen is anticipated to provide sufficient drug exposure for the treatment of GCA. In addition, the SC administration will be more convenient for study participants.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last visit for the 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 main study if the participant has completed study treatment through Week 48 of the main study phase, and the 12-week safety follow-up for the main study (Week 60) or, if a participant continued onto the LTE period, has completed main study Week 52 visit. For the LTE period, a participant will be considered having completed the study if the participant has completed study treatment through Week 100 (LTE Week 48) and the 12-week safety follow-up for the LTE period (Week 112 [LTE Week 60]).

5. STUDY POPULATION

Screening for eligible participants will be performed within 6 weeks before administration of the study intervention. Refer to Section 5.4 for conditions under which the repeat of any screening procedures is 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. The inclusion and exclusion criteria will be evaluated by the sponsor prior to enrollment of participants.

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

5.1. Inclusion Criteria

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

1. Male or female (according to their reproductive organs and functions assigned by chromosomal complement)

2. At least 50 years of age, inclusive

3. Diagnosis of GCA according to the revised American College of Rheumatology criteria (Salehi-Abari 2016):

   Age at onset of disease ≥50 years, AND
   No criteria excluding GCA (ENT and eye inflammation, kidney, skin and peripheral nervous system involvement, lung infiltration, lymphadenopathies, stiff neck and digital gangrene or ulceration), AND
   Presence of 3 points (p) or more out of 11 with at least one point from domain I

   Domain I criteria:
   - new onset localized headache (1p)
   - sudden onset of visual disturbances (1p)
   - unequivocal symptoms of PMR defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness (2p)
   - jaw claudication (1p)
   - abnormal temporal artery (up to 2p)

   Domain II criteria:
   - Unexplained fever and/or anemia (1p)
   - History or current ESR ≥50 mm/hour* (1p)
   - GCA compatible pathology (vascular and/or perivascular fibrinoid necrosis along with leucocyte infiltration (1p) /and granuloma (1p)

   * If historic ESR is unavailable, a history of CRP ≥ 24.5 mg/L (2.45 mg/dL) is required. The CRP value was derived from published data both from GCA and RA patients (Hayreh 1997; Paulus 1999; Wolfe 1997).

4. 4.1 Criterion modified per Amendment 1

4.2 Criterion modified per Amendment 4

4.3 Criterion modified per Amendment 5.

Temporal artery biopsy revealing features of GCA either at time of diagnosis or at other timepoint during disease history

OR,

Evidence of cranial GCA either at time of diagnosis or at other timepoint during disease history by cranial doppler-ultrasound, cranial Magnetic Resonance Imaging or Magnetic Resonance Angiography, or other imaging modality upon agreement with the sponsor.

OR

Evidence of GCA by angiography or cross-sectional imaging (ultrasound, MRI, CT, PET).

5. Have new onset or relapsing GCA

New onset: diagnosis of GCA within 6 weeks of first study intervention*

Relapsing GCA: diagnosis of GCA >6 weeks before first study intervention and in the meantime achieved remission (absence of signs and symptoms attributable to GCA and normalization of ESR (<30 mm/hr) and CRP (<10 mg/L or <1 mg/dL) included) including previous treatment with ≥40 mg/day prednisolone (or equivalent) for ≥2 weeks.

* The 6-week time window must be calculated from the date of suspected GCA diagnosis. Suspected diagnosis is defined as the date when GC therapy was initiated to treat suspected GCA.

6. Criterion modified per Amendment 2

6.1. Have active GCA within 6 weeks of first study intervention

Active GCA: presence of signs and symptoms of GCA (Domain I, see Section 10.5) and elevated ESR ≥ 30 mm/hr, or CRP ≥ 10 mg/L (or 1 mg/dL), attributed to active GCA.

ESR ≥ 30 mm/hour or CRP ≥ 10 mg/L (or 1 mg/dL) is not required if active GCA has been confirmed by a positive temporal artery biopsy or ultrasound or other imaging modality (see inclusion criterion 4) within 6 weeks of first study intervention

Concomitant or previous medical therapies received

7. At screening, receiving oral GC treatment with a minimum dose of 20 mg/day and maximum dose of 60 mg/day (prednisone or equivalent) for the treatment of active GCA.

8. Clinically stable GCA disease on a GC dose between 20 and 60 mg/day (prednisone or equivalent) at randomization such that the participant is able to safely participate in the protocol defined prednisone taper regimen, in the opinion of the investigator.

Contraception

9. A woman must be:

   Not of childbearing potential

   OR

   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 12 weeks after last dose - the end of relevant systemic exposure.

   Definitions of childbearing potential and examples of highly effective methods of contraception are located in Section 10.7.

10. A woman of childbearing potential must have a negative urine pregnancy test at screening and at Week 0 prior to administration of study intervention.

11. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 12 weeks after receiving the last administration of study intervention.

12. A man who is sexually active with a woman of childbearing potential and who has not had a vasectomy must agree to use a barrier method of birth control, eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository during the study and for at least 12 weeks after receiving the last administration of study intervention.

13. A male participant must agree not to donate sperm for the purpose of reproduction or plan to father a child during the study and for a minimum of 12 weeks after receiving the last dose of study intervention.

14. Criterion modified per Amendment 5

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

a) Have no history active TB before screening.
b) have no history of untreated latent TB. An exception is made for participants who satisfy one of the following criteria:
   - are currently receiving treatment for latent TB,
     OR
   - will initiate treatment for latent TB before the first administration of study intervention,

Note: For participants with a history of treated latent TB, there must be documentation of having completed appropriate treatment prior to the first administration of study intervention. It is the responsibility of the investigator to verify the adequacy of previous anti-TB treatment and provide appropriate documentation.

c) Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
d) Have had no recent close contact with a person with active TB. An exception is made if such participants are referred to a physician specializing in TB to determine if treatment is warranted or not. This evaluation must be adequately documented and, if treatment is recommended, the participant must be receiving appropriate treatment prior to the first administration of study intervention.
e) Within 2 months before the first administration of study intervention, have a negative QuantiFERON-TB test result, or have a newly identified positive QuantiFERON-TB test result (see Laboratory Manual) 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. Within 2 months before the first administration of study intervention, a negative tuberculin skin test, or a newly identified positive tuberculin skin test 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, is additionally required if the QuantiFERON-TB test is not approved/registered in that country or the tuberculin skin test is mandated by local health authorities.

A suspected false-positive initial QuantiFERON-TB test must be repeated. If repeat testing is NOT positive, the participant must be referred to a physician specializing in TB to determine if the initial test can be considered a false-positive. This evaluation must be adequately documented prior to the first administration of study intervention. If repeat testing is positive, however, it will be considered a true-positive and the participant is only eligible if active TB has been ruled out and appropriate treatment for latent TB has been initiated as described above.

A participant whose first QuantiFERON-TB test result is indeterminate should have the test repeated. If 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 medical monitor and recorded in the participant's source documents and initialed by the investigator.

NOTE: The QuantiFERON-TB test and the tuberculin skin test are not required at screening for participants with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment as described above; participants with documentation of having completed adequate treatment as described above are not required to initiate additional treatment for latent TB.

f) Have a chest radiograph (both posterior-anterior and lateral views, or per country regulations where applicable), taken within 3 months before the first administration of study intervention and read by a qualified radiologist (or pulmonologist in accordance with local regulations), with no evidence of current, active TB or old, inactive TB. A chest CT scan is also acceptable if obtained instead of a chest radiograph outside of the protocol.

15. Have screening laboratory test results within the following parameters, if one or more of the laboratory parameters is out of range, a single retest of laboratory values is permitted:

a. Hemoglobin	≥9 g/dL	SI:≥90 mmol/L
b. White blood cells	$\geq 3.0 \times 10^3/\mu L$	SI: ≥3.0 GI/L
c. Neutrophils	$\geq 1.5 \times 10^3/\mu L$	SI: ≥1.5 GI/L
d. Platelets	$\geq 100 \times 10^3/\mu L$	SI: ≥100 GI/L
e. Serum creatinine	≤1.8 mg/dL	SI:≤159 μmol/L
f. Aspartate aminotransferase (AST)	≤3 × ULN*	
g. Alanine aminotransferase (ALT)	≤3 × ULN*	

*For ALT/AST values >2 upper limit of normal (ULN) participants can only be included if bilirubin is normal.

General

16. Criterion modified per Amendment 3

16.1. 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.

17. Criterion modified per Amendment 3

17.1. Must sign a separate ICF if the participant agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample does not exclude a participant from participation in the study.

18. Must be willing and able to adhere to all specified requirements, including but not limited to completion of the required assessments, adherence to the visit schedule, and compliance with the lifestyle restrictions as specified in this protocol.

Inclusion criterion for LTE period

19. Participants are eligible for participation in the LTE period of the study if the participant:

    1. Has completed Week 52 visit of the main study, AND

       has no signs and symptoms of active GCA, AND

       completed treatment study intervention according to the protocol, AND

       completed 26-week protocol defined GC-taper without the need to use rescue medication for GCA, AND

       has not experienced a GCA flare through Week 52

    2. Has not had any study intervention-related SAE or severe AE
    3. Is able and willing to continue (blinded) treatment with study intervention

5.2. Exclusion Criteria

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

Coexisting Medical Conditions or Past Medical History

1. Has any known severe or uncontrolled GCA complications (aortic, thoracic or abdominal aneurysm, history of myocardial infarction or stroke due to GCA, significant or permanent and complete visual loss in at least 1 eye due to GCA)

2. Criterion modified per Amendment 3

   Has any rheumatic disease other than GCA such as Takayasu's Arteritis, granulomatosis with polyangiitis (Wegener's), RA, systemic lupus erythematosus that could interfere with assessment of GCA

3. Has a current diagnosis or signs or symptoms of severe, progressive, or uncontrolled renal, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances, (or, in the investigators opinion, has any other concomitant medical condition that places the participant at risk by participating in this study).

4. Criterion modified per Amendment 5:

4.1a. Has or has had any major ischemic event, within 12 weeks of first study intervention

4.1b. Has a personal history of arterial thrombosis or venous thromboembolism (including deep venous thrombosis [DVT] and Pulmonary Embolism [PE])

5. 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

6. Has any comorbidities requiring 3 or more courses of systemic GCs within 12 months of first study intervention, AND,

- inability, in the opinion of the investigator, to withdraw GC therapy through protocol-defined taper regimen due to suspected or established adrenal insufficiency,

OR,

- currently on systemic chronic GC therapy for reasons other than GCA and be GC dependent and have the potential to flare due to GC tapering (eg, unstable asthma, unstable COPD)

7. Has a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection (eg, bronchiectasis), recurrent urinary tract infection (recurrent pyelonephritis or chronic non remitting cystitis), fungal infection (eg, mucocutaneous candidiasis, but excluding fungal infections of the nail beds), or open, draining, or infected skin wounds or ulcers

8. Has or has had a serious infection (eg, sepsis, pneumonia, or pyelonephritis), or has been hospitalized or received IV antibiotics for an infection during the 2 months before first study intervention

9. A potential participant with the following features will be excluded from participating in the study protocol

   During the 6 weeks prior to baseline, have had ANY of (a) confirmed SARS-CoV-2 (Coronavirus Disease 2019; COVID-19) infection (test positive), OR (b) suspected SARS-CoV-2 infection (clinical features 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

- NOTES on COVID-related exclusion:
  1. If a participant is excluded due to recent COVID-19-related features, the reason for screen failure should be documented in the case report form under the exclusion criterion of having a condition for which participation would not be in the participant's interest or could confound study assessments.

  2. 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.

10. Has or has had a nontuberculous mycobacterial infection or clinically significant opportunistic infection (eg, cytomegalovirus, pneumocystosis, invasive aspergillosis)

11. Has a history of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening. Refer to inclusion criterion 14 for information regarding eligibility with a history of latent TB

12. Has a history of an infected joint prosthesis or has received antibiotics for a suspected infection of a joint prosthesis within 6 months of first study intervention, if that prosthesis has not been removed or replaced

13. Has a history of or is infected with human immunodeficiency virus (HIV [positive serology for HIV antibody]); tests positive for hepatitis B virus (HBV) infection (refer to Section 10.6); has antibodies to hepatitis C virus (HCV) at screening

14. Has experienced a recent single dermatomal herpes zoster eruption within the past 4 months. Has ever had multi-dermatomal herpes zoster (defined as appearance of lesion outside the primary or adjacent dermatome) or central nervous system zoster infection

15. Currently has a malignancy or has a history of malignancy within 5 years before screening (with the exception of a non-melanoma skin cancer that has been adequately treated with no evidence of recurrence for at least 3 months before the first study intervention administration or cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 3 months before the first study intervention)

    Note: premalignant lesions should be discussed with the sponsor medical monitor

16. Has a transplanted organ (with exception of a corneal transplant >3 months before the first study intervention)

17. Has unstable suicidal ideation or suicidal behavior in the last 6 months, that may be defined as a Columbia-Suicide Severity Rating Scale (C-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.

In addition, participants with C-SSRS ratings of Ideation level 1 3 (ie, Wish to be Dead, Non-Specific Active Suicidal Thoughts, Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act), or non-suicidal self-injurious behavior who are determined to be at risk by the investigator may also not be randomized.

18. Has known allergies, hypersensitivity, or intolerance to guselkumab or its excipients

19. Criterion modified per Amendment 5

19.1. Has had a fracture of the hip or leg, major trauma or spinal cord injury, hip or knee replacement within 8 weeks before screening; had major surgery (eg, requiring general anesthesia and hospitalization), within 8 weeks before screening, or has not fully recovered from major surgery, or has major surgery planned during the time the participant is expected to participate in the study (48 weeks). Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate

20. Has a history of drug or alcohol abuse according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, within 1 year before screening

Concomitant or previous medical therapies received

21. Criterion modified per Amendment 1

21.1. Has received within 90 days, or 5 half-lives (whichever is greater), or failed treatment with any investigational or approved biologic agent or Janus kinase inhibitor prior to first study intervention, including but not limited to:

- IL-23 inhibitor therapy (including but not limited to guselkumab, risankizumab, tildrakizumab, brazikumab, mirikizumab, ustekinumab)
- tocilizumab (Actemra)
- sirukumab, sarilumab, mavrilimumab, abatacept, belimumab
- TNFα-inhibitors (including infliximab, adalimumab, etanercept, certolizumab, golimumab)
- IL-12/23 inhibitors (ustekinumab)
- IL-17 inhibitors (secukinumab, ixekizumab, brodalumab)
- JAK-inhibitors (including tofacitinib, baricitinib, upadacitinib)

OR,

Received the following therapy within 6 months, or 5 half-lives (whichever is greater):

- natalizumab, visilizumab

OR,

Received the following therapy within 12 months, or 5 half-lives (whichever is greater):

- rituximab, alemtuzumab

Note: Not listed biologic agents should be discussed and agreed with the sponsor medical monitor

22. Criterion modified per Amendment 2

22.1. Has been treated with:

Within 6 months of study intervention:

- Any cytotoxic agents (cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents)
- Intravenous immunoglobulin (IVIG), apheresis therapy (plasmapheresis or leukopheresis)

Within 3 months of first study intervention or at least 5 half-lives (whichever is greater):

- Hydroxychloroquine, cyclosporine A, azathioprine, tacrolimus, sirolimus, sulfasalazine, leflunomide with cholestyramine washout or mycophenolate mofetil/mycophenolic acid

Within 6 weeks of first study intervention:

- Intramuscular, intra-articular, intrabursal, epidural, intra-lesional or IV GCs
- Any complementary therapies, including traditional/Chinese medicines, herbs, ointments, or procedures (eg, acupuncture), that have the potential to activate (eg, echinacea) or inhibit (eg, *Tripterygium wilfordii* Hook F) the immune system
- Any complementary therapies, including traditional/Chinese medicines and herbs, that have the potential to interact with antithrombotic agents (eg, St. John's Wort) in those taking antithrombotic agents

Any questions or concerns with the use of these therapies should be discussed with the study sponsor and/or medical monitor.

23. Criterion modified per Amendment 4

23.1. Has started Methotrexate (MTX) within 12 weeks of first study intervention. If started MTX >12 weeks prior to first study intervention MTX must have been at a stable dose for minimally 4 weeks and must not be receiving more than 25 mg oral or SC MTX per week

24. Has chronic continuous use of systemic GCs for >4 years or inability, in the opinion of the investigator, to withdraw GC treatment through protocol-defined taper regimen due to suspected or established adrenal insufficiency

25. Has received an investigational intervention (including investigational vaccines) within 3 months or 5 half-lives (whichever is longer) or used an invasive investigational medical device within 3 months of the first study intervention or is currently enrolled in an investigational study

26. Bacille Calmette-Guérin (BCG) vaccination within 12 months or any other live bacterial or live viral vaccination within 12 weeks of randomization

27. Has taken any prohibited or restricted medications as noted in Section 6.8, Concomitant Therapy before the first study intervention

General

28. Has donated blood (volume ≥450 mL) within 60 days prior to screening

29. Is unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins

30. Lives in an institution on court or authority order

31. Currently participating or intends to participate in any other study using an investigational agent or procedure during the conduct of this study

32. 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 describes options for retesting. The required source documentation to support meeting the enrollment criteria is noted in Section 10.3.

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. Refer to Section 6.8 for details regarding prohibited and restricted therapy during the study

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. Must agree not to receive a live virus or live bacterial vaccination during the study and for 12 weeks after receiving the last dose of study intervention

4. Must agree not to receive a BCG vaccination during the study and for 12 months after receiving the last dose of study intervention

5. Must not receive guselkumab outside of this protocol or participate in any other clinical study with an investigational agent while in this study and must terminate study participation if they do. A participant who intends to participate in any other clinical study with an investigational agent should complete the appropriate visit(s) as described in Section 1.3 before the participant terminates study participation

6. Must be willing and able to complete study related questionnaires and document clinical symptoms, AEs, etc

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.

Retesting

Retesting of abnormal laboratory values that may lead to exclusion will be allowed once. Retesting can occur at an unscheduled visit during the screening phase, as long as this is done within the specified screening window of up to 6 weeks. In such cases, the first abnormal test result will not constitute a screen failure. If a laboratory abnormality occurs, the site is encouraged to wait for all laboratory tests to be completed to ensure other laboratory tests do not need to be repeated, as only 1 retest of laboratory tests is allowed. A screening laboratory test(s) analyzed by the central laboratory may be repeated more than once in the event of suspected error in sample collection or analysis as long as the result is obtained within the screening period.

Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time. Rescreened participants will be assigned a new participant number, undergo the informed consent process, and then start a new screening phase. Previous TB evaluation results (including the QuantiFERON-TB test and chest radiograph) from the first screening event may be used if they meet the specified protocol criteria as described in Section 5.1. Medical Monitor approval is required prior to the study site obtaining a new informed consent for rescreening. In addition, individuals who were screen fails due to a trial suspension may be rescreened a second time with sponsor approval.

FDG-PET/CT results from the first screening event do not have to be repeated when performed within a reasonable period of time before randomization and after consultation of the Sponsor.

5.5. Criteria for Temporarily Delaying [Enrollment/Randomization/Administration of Study Intervention Administration]

This section is not applicable for this protocol.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Interventions Administered

Participants in the study will be on background GC (see also Section 5.1, inclusion criterion 7 and inclusion criterion 8), supplied by the clinical study site. The GC dose tapering is described in Section 6.8.1 and a tapering schedule is provided in Section 10.8.

In addition to remaining on the standard-of-care noted above, participants will be randomized with a 2:1 ratio to 1 of 2 treatment groups as described below:

- Guselkumab: Participants will receive guselkumab 200 mg SC every 4 weeks, Week 0 through Week 48.
- Placebo: Participants will receive placebo SC every 4 weeks Week 0 through Week 48.

Participants will remain on their assigned treatment through Week 48. Participants will receive 2 SC injections (either active or placebo) at each SC dosing visit. Participants of the LTE period will continue to receive SC injections every 4 weeks (either active or placebo) starting at Week 52 (LTE Week 0) through Week 100 (LTE Week 48) or until the participants have a GCA flare or the participants discontinues treatment due to unblinding after the Week 60 DBL for the Main study, or until a decision is made not to continue clinical development in this GCA population, whichever occurs first.

Since multiple SC injections are administered at visits, each injection of study intervention should be given at a different location of the body.

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

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

Detailed instructions on the administration of study intervention will be provided in the Site Investigational Product Procedures Manual (sIPPM).

For details on rescue medications, refer to Section 6.8.3. For a definition of study intervention overdose, refer to Section 6.7.

6.1.1. Combination Products

- For this protocol, the term combination product refers to the single integral drug-device combination
- The sponsor-manufactured combination product for use in this study is the PFS assembled with an UltraSafe Plus™ Passive Needle Guard (PFS-U). Additional details on the PFS-U are provided in Section 6.2 and the guselkumab IB
- All 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 using a combination product, these deficiencies will be reported as product quality complaints (PQC) (see Section 10.4 in Appendix 10: 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

For SC administrations, guselkumab will be supplied as a 100 mg/mL sterile solution in a single-use prefilled syringe (PFS) assembled in an UltraSafe Plus™ Passive Needle Guard (PFS-U). For SC administration, placebo for guselkumab will be supplied as a 1 mL sterile solution in a single-use PFS assembled in a PFS-U.

Guselkumab and placebo for guselkumab should be clear and colorless to light yellow solution that may contain small translucent particles. Do not use guselkumab or placebo for guselkumab if the liquid is cloudy or discolored or has large particles. Protection from light is not required during the preparation and administration of the study intervention material but avoid direct exposure to sunlight. Aseptic technique must be used during the preparation and administration of the study intervention material.

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 drug accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study.

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 ampules, needles, syringes, and vials containing hazardous liquids, 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

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by new-onset and relapsing GCA and baseline GC use (≤30 mg/day or >30 mg/day). The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

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 conditions. 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.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the intervention assignment (ie, study intervention serum concentrations, anti-guselkumab antibodies, study intervention preparation/accountability data, intervention allocation, biomarker, 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 until the time of DBL and unblinding.

Under normal circumstances, the blind should not be broken until all participants have completed the Main study and the Week 60 database is finalized. Otherwise, the blind should be broken only if specific emergency intervention/course of action would be dictated by knowing the intervention status of the participant. In such cases, the investigator may, in an emergency, determine the identity of the intervention by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible, to discuss the particular situation, before breaking the blind.

Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the CRF and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded should continue to return for scheduled evaluations.

In general, randomization codes will be disclosed fully only if the study is completed, and the clinical database is closed. However, as a DBL at Week 28 is specified, the randomization codes and, if required, the translation of randomization codes into intervention and control groups will be disclosed to those authorized. At the Week 28 DBL, the data will be unblinded for analysis to limited sponsor personnel while participants are still participating in the study. Identification of sponsor personnel who will have access to the unblinded participant-level data will be documented prior to unblinding. Investigative study sites and participants will remain blinded to initial treatment assignment until after the Week 60 database is locked.

6.4. Study Intervention Compliance

When study intervention is administered by qualified staff, the details of each administration will be recorded in the eCRF. For SC injections, this will include date and time of SC injection.

Compliance with the treatment schedule is strongly encouraged.

6.5. Dose Modification

No study intervention dose adjustment will be permitted through the study.

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

Local regulations on continued access will always take precedence. Plans for continued access stated in this protocol may change if new information on the benefit-risk profile of guselkumab becomes available during the study or program.

At the end of their participation in the main study, participants who have completed the study and are benefiting from the study intervention, as determined by being in GC-free remission for GCA at Week 52, may be offered the opportunity to enter the LTE period to continue treatment for up to 12 months.

If analyses performed prior to the first participant’s entry into the LTE or during the LTE demonstrate an unfavorable benefit: risk profile or safety concerns arise, the study (and LTE) may be stopped.

6.7. Treatment of Overdose

For this study, any dose of guselkumab greater than 10% above the dose at a single dosing visit specified in this protocol will be considered an overdose. The sponsor does not recommend

specific treatment for an overdose. In the event of overdosage, monitor the participant for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately.

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

- Contact the medical monitor immediately
- Closely monitor the participant for AE/SAE and laboratory abnormalities
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF
- Discuss with the medical monitor if one or additional serum sample for PK analysis will be required and at what timepoints

Decisions regarding dose interruptions will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

Prestudy therapies including specific GCA therapies administered up to 60 days before first dose of study intervention must be recorded at screening.

Concomitant therapies including specific GCA therapies must be recorded throughout the study beginning with start of the screening to the final safety follow-up visit. Concomitant therapies should also be recorded beyond the final safety follow-up visit only in conjunction with SAEs that meet the criteria outlined in SAEs that meet the criteria outlined in Section 8.3.1.

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. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a participant into the study.

Any questions or concerns with the use of concomitant therapies should be discussed with the study sponsor and/or medical monitor. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.8.1. Permitted Therapy

Therapy to Prevent and Treat GC-Induced Osteopenia/Osteoporosis

Participants are recommended to receive oral calcium and 25-hydroxy vitamin D supplementation unless contraindicated (calcium 1000 to 1200 mg and vitamin D 600 800 IU daily in divided doses). Unless contraindicated, bisphosphonate therapy (eg, alendronate 70 mg weekly or zoledronate 5 mg annually) may also be administered at the discretion of the investigator for the prevention of GC-induced osteoporosis (Buckley 2017). Participants with documented

osteoporosis will be treated with approved drugs for osteoporosis according to local practice or clinical guidelines (eg, National Osteoporosis Foundation).

Methotrexate

Methotrexate may be used if started >12 weeks prior to the first study administration, but the dose must remain stable for minimally 4 weeks prior to study agent administration and not exceed 25 mg/week of oral or SC MTX. During the study the MTX dose should stay stable, but may be reduced or discontinued if necessary for safety reasons or if, in the opinion of the investigator, it is no longer required to treat the participant's GCA after Week 28. Folic acid should be taken concomitantly with MTX according to the local practice.

Anti-Platelet or Anti-Coagulation Therapy

Participants may be treated with anti-platelet therapy (including but not limited to aspirin, clopidogrel, ticlopidine) or anti-coagulation therapy (including but not limited to warfarin) according to the local practice at the discretion of the investigator.

Lipid Lowering Therapy

Use of lipid-lowering agents in participants with elevated lipids is strongly encouraged at any time during the study in conjunction with the investigator's clinical judgment and any applicable professional treatment guidelines.

Anti-Hypertensive Therapy

Participants are permitted to receive stable doses (>2 weeks prior to first study agent administration) of anti-hypertensive treatment according to the local practice at the discretion of the investigator. Participants should not initiate anti-hypertensive therapy between randomization and 4 weeks after the last dose of study intervention, unless discussed and agreed with the sponsor medical monitor.

Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) and other regularly administered analgesics should not be adjusted for at least 2 weeks prior to the first administration of the study intervention and through 4 weeks after the last dose of study intervention, and they may be changed only if the participant develops unacceptable side effects. Participants are permitted to receive the usual marketed doses approved in the country in which the study is being conducted. NSAIDs, including aspirin or selective cyclooxygenase-2 (COX-2) inhibitors, and other analgesics (including injectable NSAIDs, analgesics or other pain-relieving agents) that are used on an "as needed" basis would generally not be considered to constitute stable dosing. Participants using them in specific situations (eg, prior to an activity) may be considered stable but these situations should be discussed with the medical monitor or sponsor prior to enrollment into the study.

Topical Medications

Regular use of topical medications is permitted. "As needed" use of topical NSAIDs, analgesics, or other pain-relieving agents is permitted, but not within 48 hours prior to study visit. "As needed"

use of topical GCs is permitted if involving a limited BSA (≤20%), but not within 48 hours prior to a study visit.

Oral Glucocorticoids and Protocol-Defined 26-Week Taper for GCA

Participants must be receiving this medication at screening and be on a stable dose equivalent to an average daily dose between 20 and 60 mg/day prednisone (or equivalent), for at least 2 weeks prior to the first study intervention dose. Participants that are on GC other than prednisone or prednisolone during screening should preferably be switched to prednisone or prednisolone to follow the GC taper in Section 10.8. If the participant continues on GC other than prednisone or prednisolone, the Investigator should contact the Sponsor to ensure that the taper is appropriately adjusted for the GC equivalency compared with prednisone (see Section 10.10). Participants are required to be receiving at least 20 mg/day prednisone (or equivalent) at screening and randomization.

A protocol specified 26-Week open-label GC tapering schedule is provided in Section 10.8. Adherence to this schedule is required. Participants will remain on the GC dose they were on at baseline for one week (Week 0). Participant should adhere to the tapering schedule that corresponds to their entry dose of glucocorticoid (section 10.8) through Week 26 unless they require use of rescue GC therapy for GCA disease flare. Reason(s) for not tapering GCs should be documented.

Additional considerations of oral GC use during the study are as follows:

- If a participant is unable to follow the protocol specified GC taper due to worsening GCA disease activity requiring an increase in GC dose (GCA flare), further GC dose decreases will be suspended, and/or their oral GC dose may be temporarily increased (ie, GC rescue, see section 6.8.3) if deemed necessary by the investigator
- If a participant is receiving rescue GCs, and thus no longer follows the protocol specified GC tapering schedule, Investigators are to continue to provide GC as per standard medical care for GCA
- It is recommended that participants be educated about and monitored for symptoms of GC adrenal insufficiency/deficiency (eg, Addisonian symptoms such as fatigue, muscle weakness, decreased appetite, nausea, vomiting, joint and muscle pain) by study staff during periods of GC tapering, as appropriate. Investigators should monitor participants at the regular study visits for any signs and symptoms of Addisonian crisis
- If a participant is unable to follow the protocol specified GC taper due to requirement for increased GC for management of adrenal insufficiency, the participant can make use of the rescue GC therapy (see Section 6.8.3).

Glucocorticoids for Conditions Other than GCA

Glucocorticoids administered by bronchial or nasal inhalation for treatment of stable concomitant respiratory conditions may be given as needed. Otic, ocular, topical or other routes of mucosal delivery of GCs are allowed throughout the study.

Non-live vaccines, including COVID-19 vaccines

It is recommended that participants are up-to-date on age-appropriate vaccinations prior to screening as per routine local medical guidelines. When considering use of locally-approved COVID-19 vaccines in study participants, follow applicable local labelling, guidelines, and standards of care for patients receiving immune-targeted therapy.

For study participants receiving a locally-approved 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 drug be administered on different days, separated by as large an interval as is practical within the protocol.

6.8.2. Prohibited Therapies

Use of additional investigational or approved biologic or non-biologic immunosuppressant or immunomodulatory agents, other than those explicitly allowed in the inclusion/exclusion criteria (see Sections 5.1 and 5.2), are prohibited including but not limited to, the following:

- biologic agents (eg, Actemra or other anti-IL-6(R), anti-IL-23, anti-IL-12, anti-IL-17, anti-TNF therapy, mavrilimumab)
- Janus kinase inhibitors (eg, tofacitinib, upadacitinib)
- cell-depleting therapies (eg, abatacept, rituximab, alemtuzumab)
- cytotoxic alkylating agents (eg, chlorambucil, cyclophosphamide)
- new start of MTX
- IV immunoglobulin
- apheresis therapy
- other investigational agents

Oral Glucocorticoids

Use of oral GCs for GCA other than for the protocol-defined taper, is prohibited during the study, with the exception of use for GC rescue therapy (see Section 6.8.3).

The use of oral GCs (or other systemic GCs) for indications other than GCA during the study should be limited to only situations for which, in the opinion of the treating physician, there are no adequate alternatives. This should be discussed with the medical monitor or designee prior to providing these and may require discontinuation of study drug.

Intramuscular, Intra-articular, Intrabursal, Epidural, Intra-lesional or IV Glucocorticoids

Intramuscular, intra-articular, intrabursal, epidural, intra-lesional, or IV GCs are prohibited from 6 weeks prior to first study intervention until end of study and are also prohibited when used as chronic continuous systemic GCs for >4 years.

Complementary Therapies

The use of complementary therapies (eg, herbs, ointments, traditional Chinese medicine, acupuncture) that have the potential to activate or inhibit the immune system is prohibited (see Section 5.2). In addition, use of complementary therapies that have the potential to interact with antithrombotic agents is prohibited in those taking antithrombotic agents.

The use of other complementary therapies is strongly discouraged; in individual cases, use may be permitted following discussion with the study sponsor and/or medical monitor.

As these lists cannot be exhaustive, please consult the medical monitor to discuss prior to starting any new therapies not specifically mentioned in inclusion or exclusion criteria or the list of permitted medications.

6.8.3. Rescue Medication

The study site will supply GC rescue medication that will be obtained locally.

Participants who develop a GCA flare or are unable to adhere to the protocol-defined 26-week open-label GC tapering regimen because of ongoing disease activity should stop the protocol-defined GC taper and be given open-label rescue therapy with GCs at the discretion of the investigator. When considering use of rescue GC, a careful assessment should be made by the investigator whether the symptoms are related to a GCA flare (failure of taper) or are more likely due to non-inflammatory symptoms which could represent adrenal insufficiency or other comorbidities.

The participant may continue to receive blinded study agent administrations and continue in the study if it is in the best interest for the participant in the opinion of the investigator. Treatment with GC and/or other GCA medication will be at the discretion of the investigator for the further duration of the study. If other GCA medication is required, the medical monitor or designee should be contacted and treatment with study intervention should be discontinued. A wash-out period of 12 weeks is recommended before starting treatment with biologic therapies.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

Participants who require rescue therapy for their GCA disease during the protocol-defined GC taper and up to Week 28 will be deemed non-responders in the primary endpoint analysis.

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 within the study period (see Section 10.7)
- The participant develops an opportunistic infection (this does not include candidiasis that is limited to the mouth)
- The participant becomes 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 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), unless active TB can be ruled out and appropriate treatment for latent TB can be initiated prior to the next study intervention administration and continued to completion (see also Section 8.2.11). Indeterminate QuantiFERON-TB test results should be handled as described in Section 8.2.11. Participants with persistently indeterminate QuantiFERON-TB test results may continue without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the medical monitor or designee and recorded in the participant's source documents and initialed by the investigator

  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 related to an injection resulting in bronchospasm with wheezing and/or dyspnea that requires ventilatory support OR that results in symptomatic hypotension with a decrease in systolic blood pressure >40 mm Hg or blood pressure <90/60 mm Hg
- 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
- Participant requires dialysis
- Noncompliance with study drug administration defined as multiple episodes of missing the window in which to receive study intervention
- The participant has severe liver test abnormalities that are not transient and are not explained by other etiologies, as described in Section 10.9.
- In the LTE period, the study intervention must be discontinued if a participant experiences a GCA flare. Participants that experience a flare should have a Flare visit with assessments performed according to the SoA preferably within 1 week of having the flare and an early termination visit approximately 12 weeks after the last dose.
- After the study has been unblinded at the Week 60 DBL, participants in the LTE will be unblinded to treatment. Study treatment of participants on placebo will be discontinued. They may continue in the study for their planned visits as per the schedule of events until Week 112 or, in case of a GCA flare, until the early termination visit.

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

- Worsening of GCA based on visual symptoms related to GCA
- If the participant initiates treatment with prohibited therapies for GCA, the medical monitor or designee should be contacted to discuss possible discontinuation of study intervention
- The participant develops a serious infection, including but not limited to sepsis or pneumonia
- Note: Any serious infection should be discussed with the medical monitor or designee, and study intervention should be withheld until the clinical assessment is complete.
- Discontinuation of study treatment 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) C-SSRS assessment. If a participant can be adequately treated with psychotherapy and/or pharmacotherapy based on an evaluation by a mental health professional, then the participant, at the discretion of the investigator, may continue with treatment if agreed to by the medical monitor or designee. Discussion of such participants with the medical monitor or designee is required
- The participant develops a severe injection-site reaction, but not meeting criteria specified above.

A participant will not be automatically withdrawn from the study if he or she must discontinue treatment before the end of the treatment regimen. If a participant discontinues study intervention for any reason before the end of the main study phase, they may continue for their planned visits as per the schedule of events, but without study intervention administration. Depending on the reason for study treatment discontinuation, assessments may be reduced in consultation with the

Sponsor. Study intervention assigned to the participant who discontinued study intervention may not be assigned to another 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 CRF and in the source document. Participants who terminate their study participation before final planned study visit, should receive an early termination visit approximately 12 weeks after the last administration of study intervention (unless consent is withdrawn) as specified in the SoA (Sections 1.3 and 1.4). If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

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.

Prior to a participant withdrawing consent for follow-up, the investigator should offer the participant an opportunity for one of the alternative reduced follow-up mechanisms described below as well as the opportunity to decline actigraphy assessment described in Section 8.10. 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.

Circumstances for Reduced Follow-up

In the situation where a participant may be at risk for withdrawal of consent and is unable to return for scheduled visits at the protocol-defined frequency, the investigator may consider options for reduced follow-up. These may include (as local regulations permit):

Less frequent clinical visits

- Telephone, email, letter, social media, fax, or other contact with:
  - participant
  - relatives of the participant
  - participant's physicians (general or specialist)
- Review of any available medical records

Details regarding these contacts must be properly documented in source records including responses by participants.

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 samples:

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

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

The participant may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples 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 Section 10.3). 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 summarizes the frequency and timing of efficacy, PK, immunogenicity, biomarker/PD, pharmacogenomic, and safety measurements applicable to this study.

All visit-specific PRO assessments should be conducted/completed before any tests, procedures, or other consultations (only exception is urine pregnancy test) to prevent influencing participant perceptions. All PROs should be completed independently by study participants. It is recommended that PROs be completed in the following sequence: PGA, pain assessment, SF-36, FACIT-fatigue and C-SSRS (except at screening where the C-SSRS is performed as first assessment after signing informed consent). It is recommended that clinician-reported outcome procedures be performed in the following sequence: GCA signs and symptoms assessment and PhGA. Clinician-reported outcome assessments should be performed by an adequately trained assessor (see Section 8.1 for details).

Laboratory samples: All samples (including for safety, efficacy, and PD/biomarkers) should be obtained after the PRO assessments but prior to study intervention administration.

Screening Phase

The screening phase is up to 6 weeks duration before randomization. After written informed consent has been obtained, all screening evaluations (eg, laboratory test results, medical history, clinical data, and concomitant medication data) that establish participant eligibility will be performed by the principal investigator or designee to confirm that the participant satisfies all inclusion criteria and does not violate any exclusion criteria. The C-SSRS should be completed as the first assessment after signing informed consent and before any other tests, procedures, or other consultations. Participants who meet all the inclusion and none of the exclusion criteria can be enrolled in the study. Every effort should be made to adhere to the SoA (Sections 1.3 and 1.4) for each participant. The collection of AEs will start at the time informed consent is obtained.

Participants must undergo testing for TB 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 (Section 8.2.11). Procedures conducted as part of the participant's routine clinical management (eg, chest radiograph taken up to 3 months prior to baseline) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria.

All screening evaluations establishing participant eligibility will be performed and reviewed by the investigator before a participant can be randomized.

A diagnostic confirmation of GCA according to inclusion criterion 4 is required, if one has not been done this must be performed prior to allowing the participant to complete the full screening. A de-identified copy of the pathology or imaging report will be required to be provided for study entry confirmation.

Documentation (historical or local laboratory testing) of unequivocally positive biochemical test values (as defined in the laboratory's reference range) should be provided for the following: CRP and ESR by Westergren.

All participants should be receiving GC treatment at screening between 20 and 60 mg/day prednisone or equivalent. GC treatment must be initiated at screening for new-onset or relapsing GCA participants not currently receiving treatment, and with a dose based upon investigator clinical decision. An increase in GC dose during screening may be required for some participants to stabilize their disease activity prior to randomization. Participants are required to have clinically stable GCA disease at randomization and be able to participate in the GC taper regimen in the opinion of the investigator. At Baseline (Randomization), doses must be within 20-60 mg prednisone or equivalent for the starting dose when the protocol-specified GC taper is initiated. At Week 0 participants will remain on their baseline GC dose that week, and will follow the GC protocol defined taper regimen from Week 1 as described in Section 6.8.1 and in Section 10.8.

The total blood volume to be collected from each participant will not exceed 300 mL. In addition, repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

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 (Sections 1.3 and 1.4) 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:

- Investigator Site File (includes clinical study protocol and guselkumab IB)
- Study sIPPM
- Sample ICFs

- Laboratory Manual and Laboratory kits
- IWRS Manual
- eCRF completion instructions
- ePRO equipment (tablet device questionnaires, completion instructions)
- Imaging manual
- Actigraphy watch and instruction for use
- Patient recruitment materials

8.1. Efficacy Assessments

Investigator assessments, inflammatory PD markers, physician's global assessment and PROs of efficacy are included in this section. Specific assessments will be collected as noted in Sections 1.3 and 1.4.

- The PRO instruments will be provided in the local language in accordance with local guidelines
- The PRO instruments must be available for regulators and for IRB/ERC submissions
- The PRO and adverse event data will not be reconciled with one another

If a participant develops a GCA flare (as per Investigator clinical decision and in accordance with the GCA Flare definition), the participant should be further assessed by the investigator following the Flare Visit assessments as noted in Sections 1.3 and 1.4.

If a participant has a GCA flare, an attempt will be made to collect event-driven PRO assessments, preferably before a GC dose increase, if possible.

8.1.1. GCA Disease Signs and Symptoms

Efficacy of guselkumab in GCA will be assessed from the presence of GCA activity including investigator assessment of signs and symptoms of GCA.

Evaluation of clinical signs and symptoms by the dedicated Clinical Assessor at every study visit according to the SoA will include the following (Hellmich 2020).

Key symptoms

- Persistent localized headache, often in the temporal area, consistent with GCA
- Constitutional symptoms (eg, fatigue/malaise) could be considered features of a flare only if they occur in combination with elevated ESR and/or CRP.
- Jaw and/or tongue claudication
- Acute visual symptoms such as amaurosis fugax, acute visual loss, diplopia

- Symptoms of PMR such as recent discreet proximal musculoskeletal symptoms including aching and stiffness about the upper arms, posterior neck, pelvic girdle, and/or lumbar region often associated with morning stiffness, gelling, and/or functional limitations
- Limb claudication, myocardial and cerebrovascular symptoms

Key signs on clinical examination

- Tenderness and / or thickening of the superficial temporal arteries with or without reduced pulsation
- Scalp tenderness
- Bruits (particularly in the axilla)
- Reduced pulses/blood pressure of the upper limbs
- Pathological findings during ophthalmologic examination including anterior ischemic optic neuropathy, oculomotor cranial nerve palsy/palsies, central retinal artery occlusion, branch retinal artery occlusion and/or choroidal ischemia.

8.1.2. Physician's Global Assessment of Disease Activity (PhGA)

The physician's global assessment independent of participants' assessment of the patients GCA activity is recorded on a 10-cm visual analog scale (VAS) with verbal anchors "No GCA" on the far-left side of the scale and "Very severe GCA" on the far right of the scale. The baseline measurement for the PhGA is defined as the closest measurement taken prior to the initiation of the Week 0 administration.

8.1.3. C-Reactive Protein and Erythrocyte Sedimentation Rate

C-reactive protein and ESR have been demonstrated to be useful as a marker of inflammation in participants with GCA. In participants with GCA, elevated CRP and ESR have been associated with more active disease (van der Geest 2015).

Samples for the measurement of CRP and ESR will be collected from all participants at visits indicated in the SoA (Sections 1.3 and 1.4). C-reactive protein will be assayed using a validated, CRP assay and ESR will be assessed using the Westergren method.

8.1.4. Patient's Global Assessment of Disease Activity (PGA)

The patient's global assessment of their GCA disease activity is recorded on a 10-cm VAS with verbal anchors on how their GCA feels today are "very poor" on the far-left side of the scale and "very well" on the far right of the scale. The baseline measurement for the PGA is defined as the closest measurement taken prior to the initiation of the Week 0 administration.

8.1.5. Pain Assessment

Participants will be asked to rate the severity of their average pain now on 10-cm VAS with anchors ranging from 0, "no pain" to 10, "the worst pain imaginable". The baseline measurement for the pain assessment is defined as the closest measurement taken prior to the initiation of the Week 0 administration.

8.1.6. FACIT-fatigue

The FACIT-fatigue version 4.0 is a 13-item questionnaire formatted for self-administration that assesses patient-reported fatigue and its impact upon daily activities and function over the past 7 days. Participants will be asked to answer each question using a 5-point Likert-type scale (0 Not at all; 1 A little bit; 2 Somewhat; 3 Quite a bit; and 4 Very much). The interpretation of FACIT-fatigue scores is such that a higher score indicates less fatigue, with a range of possible scores of 0-52, with 0 being the worst possible score and 52 the best (Lai 2011).

8.1.7. Short Form 36 (SF-36)

The Medical Outcome Study health measure entitled the 36-item Short-Form Version 2 acute (SF-36v2 acute) health survey questionnaire was developed as part of the Rand Health Insurance Experiment and consists of 8 multi-item scales.

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

These scales are scored from 0 to 100 with higher scores indicating better health. Another algorithm yields 2 summary scores, the Physical Component Score and Mental Component Score. These summary scores are also scaled with higher scores indicating better health) (Ware 1994). The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments) (Ware 1992).

8.2. Safety Assessments

Details regarding the Independent DMC are provided in Committees Structure in Section 9.6.

Adverse events will be reported and followed by the investigator as specified in Section 8.3 and Section 10.4.

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 (Sections 1.3 and 1.4).

8.2.1. Physical Examinations

Physical Examination

Physical examinations will be performed by the investigator or designated physician, nurse practitioner or physician assistant as specified in the SoA (Sections 1.3 and 1.4). Any new, clinically significant finding (in the opinion of the investigator) must be captured as an AE. In addition, resolution of any abnormal findings during the study will be noted in the source document and in the eCRF.

The full physical examination will be performed including: the head and neck, chest, abdomen, and extremities, as well as including examinations based on the individual's medical history and manifestations of GCA.

Specific assessment of GCA related signs and symptoms will be performed by a clinical assessor as described in Section 8.1.1 and at timepoints specified in the SoA (Section 1.3 and 1.4).

Assessment of the participants for safety may require some physical examination by an investigator.

Height and Weight

Height and weight will be measured as specified in the SoA (Sections 1.3 and 1.4 [only weight]). Participants will be instructed to remove shoes and outdoor apparel and gear prior to this measurement.

8.2.2. Vital Signs

Temperature, pulse/heart rate, respiratory rate and blood pressure will be assessed at each visit.

At study intervention SC administration visits, vital signs should be obtained before the SC injection, and if the participant reports any symptoms after study intervention administration.

Blood pressure and pulse/heart rate measurements will be tested in both arms using a completely automated device. Manual techniques will be used only if an automated device is not available. Bilateral measurement of blood pressure and pulse is required for the first measurement only per visit. Subsequent measurements can be performed on a single arm (unilateral).

If feasible, 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).

8.2.3. Electrocardiograms

A 12-lead electrocardiogram (ECG) will be performed at screening.

During the collection of the ECG, 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.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for blood chemistry, hematology, coagulation, serology, and other safety laboratory assessments will be collected as noted in Section 1.3. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents.

The following tests panels will be performed by the central laboratory (see Section 10.2) unless otherwise specified or approved by the medical monitor or designee:

- Hematology assessments
- Blood chemistry assessments
- Coagulation assessment (screening only)
- Serology assessment (screening only)
- QuantiFERON-TB test or TB skin test (screening only; performed locally).

A medical monitor or designee and the clinical site will be notified if pre-specified abnormal laboratory values defined in the Laboratory Manual are identified in any participant during the conduct of the study.

8.2.5. Pregnancy Testing

Urine pregnancy testing will be done for women of childbearing potential only (performed locally), see definition in Section 10.7. Additional urine pregnancy tests may be performed, if applicable, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

8.2.6. Columbia-Suicide Severity Rating Scale

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 PsO treated with an IL-17R antagonist (brodalumab), the C-SSRS will be used as a screening tool to prospectively evaluate suicidal ideation and behavior among study participants (Rodriguez 2019).

The C-SSRS measures 5 possible levels of suicidal ideation and 4 possible suicidal behaviors, as well as non-suicidal self-injurious behavior. The C-SSRS is an investigator-administered questionnaire (Mundt 2013; Posner 2011). Two versions of the C-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.

The investigator or trained study-site personnel will interview the participant and complete the C-SSRS. The C-SSRS will be provided in the local languages in accordance with local guidelines.

At the screening visit, the C-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 C-SSRS should be completed after all PROs and before any other tests, procedures, or other consultations. Participants will be interviewed by the investigator or trained study site personnel in a private, quiet place.

At the conclusion of each assessment, the trained personnel administering the C-SSRS will determine the level of suicidal ideation or behavior, if any. They will then determine the next course of action if any level of suicidal ideation or behavior is reported. The participant should not be released from the site until the C-SSRS has been reviewed by the investigator and the participant's risk has been assessed and follow-up determined, as appropriate.

At screening (within the last 6 months) and Week 0, participants with a C-SSRS rating of Ideation level 4 or 5 (ie, Suicidal Ideation with Intention to Act, Suicidal Ideation with Specific Plan and Intent), or suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt), must be determined to not be at risk by the investigator based on an evaluation by a mental health professional (eg, psychiatrist, psychologist, or appropriately trained social worker or nurse) in order to be randomized.

Participants with C-SSRS ratings of Ideation level 1-3 (ie, Wish to be Dead, Non-Specific Active Suicidal Thoughts, Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act) or non-suicidal self-injurious behavior must be determined not to be at risk by the investigator in order to be randomized in the study. Any questions regarding eligibility of such participants should be discussed with the medical monitor or designee.

For each C-SSRS assessment after Week 0, the following actions should be taken, if applicable:

- No suicidal ideation or behaviors (including self-injurious behavior without suicidal intent): No further action is needed
- Suicidal ideation levels 1-3 or non-suicidal self-injurious behavior: Participant risk is assessed by the investigator
- Suicidal ideation levels 4 or 5 or any suicidal behavior: Participant risk assessed and referral to a mental health professional.

Interruption or the discontinuation of study treatment 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) C-SSRS assessment and who is deemed to be at risk by the investigator based upon evaluation by a mental health professional. If a participant can be adequately treated with psychotherapy and/or pharmacotherapy then the participant, at the discretion of the investigator, may be continued with treatment if agreed to by

the medical monitor or designee. 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 C-SSRS findings, which in the opinion of the investigator are new or considered to be a worsening and clinically significant, should be reported on the AE eCRF (see Section 10.4).

8.2.7. Concomitant Medication Review

Concomitant medications will be reviewed at each visit.

8.2.8. Injection-Site Reactions

An injection-site reaction is any AE at a SC study intervention injection-site. Participants should be monitored for the occurrence of injection-site reactions for at least 30 minutes following SC injections. Injection sites will be evaluated for reactions and any injection-site reaction will be recorded as an AE. Participants in the LTE period will not be actively monitored for injection-site reactions but will be asked to report injection-site reactions to the investigator.

8.2.9. 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). Potential cases of anaphylaxis should be assessed according to Sampson's Criteria (Sampson 2006).

Hypersensitivity reactions including anaphylaxis should preferably be managed conform the standard operating procedures (SOPs) of the site. If the site does not have SOPs, the following guidance should be used (Muraro 2014).

In the case of a severe allergic reaction (eg, anaphylaxis), SC aqueous epinephrine, corticosteroids, respiratory assistance, and other proper resuscitative measures are essential and must be available when study intervention is being administered. Participants who experience serious adverse reactions related to an injection should be discontinued from further study intervention administrations.

8.2.10. Infections

Investigators are required to evaluate participants for any signs or symptoms of infection at scheduled visits. 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, discontinuation of study intervention must be strongly considered (see Section 7.1). Any serious infection should be discussed with the medical monitor or designee, and study intervention should be withheld until the clinical assessment is complete.

8.2.11. Tuberculosis Evaluations

8.2.11.1. Initial TB Evaluation

Participants must undergo testing for TB 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 patients. If no local country guidelines for immunocompromised patients 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 medical monitor or designee and recorded in the participant's source documents and initialed by the investigator.

8.2.11.2. 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 patients. If no local country guidelines for immunocompromised patients 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 (Sections 1.3 and 1.4).

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 SOPs 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 SOPs.

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 combination product, malfunctions or deficiencies of a device constituent will be reported as PQC.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as PQCs, refer to Section 10.4.

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 non-serious, 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.

Any possible Hy's law case (AST or ALT ≥3×ULN together with total bilirubin ≥2×ULN or INR >1.5) is considered an important medical event and must be reported to the sponsor in an expedited manner using the Serious Adverse Event Form and Safety Report form of the eCRF, even before all other possible causes of liver injury have been excluded (INR criterion is not applicable to participants receiving anticoagulants).

Serious adverse events, including those spontaneously reported to the investigator by the final safety visit, must be reported using the SAE form and Safety Report Form of the eCRF. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Information regarding SAEs will be transmitted to the sponsor using the SAE Form and Safety Report Form of the eCRF, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a SAE should be transmitted electronically or (in case of technical issues) 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 adverse event, serious adverse event, 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 Section 10.4.

8.3.4. Regulatory Reporting Requirements for Serious Adverse 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 Independent Ethics Committee/Institutional Review Board (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.

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 a serious adverse event reporting form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required (see Sections 10.7 and 10.4).

8.3.6. Disease-Related Events and Disease-Related Outcomes not Qualifying as Adverse Events or Serious Adverse Events

The cause of death of a participant in a study within 12 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.

8.3.7. Adverse Events of Special Interest

Any newly identified malignancy, case of active TB, or venous thromboembolism 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 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

8.4.1. Evaluations

Venous blood samples will be collected for measurement of serum concentrations of guselkumab and antibodies to guselkumab (Section 8.7) at the timepoints shown in the SoA (Sections 1.3 and 1.4).

Venous blood samples will be collected, and each serum sample will be divided into 3 aliquots (1 each for PK, anti-guselkumab antibodies, and a back-up).

Samples collected for analyses of guselkumab serum concentration and antibodies to guselkumab may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, for further characterization of immunogenicity or for the evaluation of relevant biomarkers. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained. 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 guselkumab concentrations using a validated, specific, and sensitive immunoassay method by the sponsor 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

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

8.5. Pharmacogenomics

Participation in pharmacogenomic research is optional. A pharmacogenomic (DNA) blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, where local regulations permit.

Genetic (DNA) variation may be an important contributory factor to interindividual variability in drug response and associated clinical outcomes. Genetic 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 also be analyzed for identification of genetic factors that may be associated with clinical response. This research may consist of the analysis of 1 or more candidate genes, assessment of single nucleotide polymorphisms, or analysis of the entire genome (as appropriate) in relation to guselkumab intervention and/or GCA. Whole blood samples of approximately 6 mL will be collected for genetic analyses as specified in the SoA (Sections 1.3 and 1.4).

8.6. Biomarkers

Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to guselkumab treatment, GCs and GCA, where local regulations permit. Assessments will include the evaluation of relevant biomarkers in serum, whole blood, and PBMCs collected as specified in the SoA (Sections 1.3 and 1.4), where local regulations permit.

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

1. To understand the molecular effects of guselkumab
2. To understand GCA pathogenesis
3. To understand why individual participants may respond differently to guselkumab
4. To understand the impact of treatment with guselkumab on vascular or systemic inflammation
5. To develop diagnostic tests to identify GCA populations that may be responsive or non-responsive to treatment with guselkumab

Serum-based Biomarkers

Blood samples for serum-based biomarker analyses will be collected from all participants. Serum will be analyzed for levels of specific proteins, and other inflammation-related molecules and/or disease-associated serologies relevant to GCA and GCA pathogenesis and treatment and response to guselkumab.

Whole Blood-based Biomarkers

Whole blood will be collected by venipuncture from participants for ribonucleic acid (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 treatment and/or GCA, and to evaluate markers that can predict clinical response. Transcriptome studies will be conducted using microarray, and/or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of multiple RNA species resulting in a transcriptome profile for each blood sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to GCA and/or the action of guselkumab.

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, single cell transcriptomics, or functional assessment of cells in response to guselkumab treatment.

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.

8.7. Immunogenicity Assessments

8.7.1. Evaluations

Serum samples for detection of antibodies to guselkumab will be collected and evaluated according to the SoA (Sections 1.3 and 1.4). Additionally, serum samples should also be collected at the final visit from participants who were withdrawn from the study.

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

8.7.2. Analytical Procedures

The detection and characterization of antibodies to guselkumab will be performed using a validated assay method by or under the supervision of the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s).

8.8. Medical Resource Utilization and Health Economics

This section is not applicable for this protocol.

8.9. Exploratory FDG-PET/CT Imaging

^{18}F-FDG (FDG) PET imaging is a non-invasive functional imaging modality that provides tomographic images and can be used to obtain quantitative parameters concerning the metabolic activity of target tissues of inflammatory diseases (Ito 2020). Computerized tomography scanning (CT) uses a combined X-ray transmission source and detector system rotating around the participant to generate tomographic images. CT allows not only attenuation correction but also the visualization of morphological and anatomical structures with a high spatial resolution. Anatomical and morphological information derived from CT can be used to improve the localization, extent and characterization of large vessel inflammation detected by FDG-PET.

The combined FDG-PET/CT imaging modality has been used as a non-invasive way to assess inflammatory disease activity in the arterial wall in large vessel vasculitis including GCA by visualizing enhanced glycolytic activity of inflammatory cells (Grayson 2018). This imaging methodology has been further standardized by an international joint working group via a consensus paper on FDG-PET/CT imaging in LLV (Sampson 2006).

In this study, FDG-PET/CT scans of the body will be performed in all participants according to the SoA (Sections 1.3 and 1.4). FDG-PET/CT is to be performed during screening prior to Week 0, and at Week 52 (or timepoint of flare if earlier). FDG-PET/CT scan is being obtained as part of exploratory endpoint and week 52 FDG-PET/CT should not be used in determining disease status of participants for the associated week 52 visit. If a participant has a flare prior to Week 52, an attempt will be made to perform the FDG-PET/CT imaging at that flare timepoint, preferably

within 1 week from identification of GCA flare by the principal investigator. In the LTE period, another FDG-PET/CT scan is to be performed at Week 104 (LTE Week 52) or timepoint of flare if earlier, preferably within 1 week from identification of GCA flare by the principal investigator. FDG-PET/CT scan is being obtained as part of exploratory endpoint and week 104 (LTE Week 52) FDG-PET/CT should not be used in determining disease status of participants for the associated week 104 (LTE Week 52) visit. A participant may decline the LTE PET/CT as noted in footnote e of the LTE SoA. If the participant has a GCA flare within 1 month of the Week 52 main study FDG-PET/CT scan (or other timeframe in accordance with local country regulations), the FDG-PET/CT scan will not be performed.

Participant preparation for an FDG-PET/CT scan includes instructions to consume a carbohydrate-sparse meal on the day prior, and to be in fasting condition prior to imaging (details are provided in a separate FDG-PET/CT Imaging Manual).

Study independent central imaging assessment will be used to analyze all FDG-PET/CT scans included in this study. The central imaging assessment of imaging will be blinded to the clinical data. FDG-PET/CT scan interpretation will determine whether findings are consistent with active or inactive vasculitis based upon assessment of vascular FDG uptake.

8.10. Digital Health – Actigraphy Measurements

Digital health has emerged as one of the important advancements that may help to objectively capture patient well-being. Wearable devices equipped with powerful sensors and self-reporting mobile apps are becoming handy in keeping continuous track of patient symptoms and providing useful insights on disease progression, clinical response, or complications.

The use of remote sensing technology for data collection will enable to compare the actigraphy measures obtained in placebo versus guselkumab treated participants to better understand the underlying differences from the treatment effects. Digital sensing technologies will provide valuable data that supplements clinical data streams such as clinical endpoints, PROs, objective measures from clinical laboratory and biomarker assessments to better characterize the disease status and well-being of patients with GCA when treated with guselkumab. To enable this work stream, we will use an actigraph device from actigraph corporation.

Actigraphy data, including physical activity, mobility, and sleep parameters, will be captured as specified in the SoA (Sections 1.3 and 1.4). A wrist-worn actigraph device validated against polysomnography to assess sleep-related variables will be used.

Each participant will be dispensed a single actigraph device (wristwatch) at screening with instructions for use. Participants will be asked to continuously wear the device preferably on the non-dominant wrist from screening until Week 52, and bring the actigraph device to each clinic visit, during which the data from the device will be downloaded as needed. Sites and participants will not have access to data generated from the use of the device during the study. All devices will be collected at the Week 52 visit and inventoried.

Participants may decline actigraphy measurements in case the participant is at risk for withdrawal of consent or if this assessment is a reason for participants not wanting to join the 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 Statistical Analysis Plan (SAP).

9.1. Statistical Hypothesis

The primary hypothesis is that guselkumab treatment with a 26-week GC taper is superior to placebo with a 26-week GC taper in participants with new-onset or relapsing GCA as assessed by the proportion of participants achieving GC-free remission at Week 28.

9.2. Sample Size Determination

Approximately 51 participants are planned to be enrolled into the study. The assumptions for the sample size and power calculation were based on the data from the Actemra Phase 3 GCA study. In the Actemra Phase 3 study, the proportions of participants in GC-free remission at Week 28 were estimated to be approximately 38% and 74% for placebo (+26-week GC taper) and Actemra qw (+26-week GC-taper), respectively, for a treatment difference of 36% (Stone 2017).

Based on the data above, the GC-free remission rates at Week 28 are assumed to be 40% for placebo and 80% for guselkumab treatment arm. Based on these assumptions, with approximately 51 participants planned to be randomized in a 2:1 ratio to either the guselkumab group (N 34) or the placebo group (N 17). These sample sizes provide the study with 82% power to detect a difference in the primary endpoint between the 2 treatment groups.

Table 2 shows the power to detect a difference in proportions of participants in GC-free remission between the guselkumab and placebo intervention groups at Week 28 under various assumptions.

More participants may be enrolled to compensate for higher than anticipated attrition.

Table 2: Power to Detect Difference in Proportions of Participants Achieving Glucocorticoid-free Remission between the Guselkumab and Placebo Intervention Groups at Week 28

Placebo (n = 17)	Guselkumab (n = 34)	Power (%)
35%	70%	68
	75%	81
	80%	90
40%	75%	69
	80%	**82**
	85%	91

Notes:
- The power calculation is based on two-sample Z test with continuity correction (pooled variance) under the normal distribution approximation.
- Power calculation is based on a 2-sided significance level of 0.10.
- Total sample size is 51.

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who signed the informed consent form (ICF).
Full Analyses Set	All participants who were randomized in the study and received at least one administration of study intervention.
Safety Analysis Set	All participants who received at least one dose of study intervention.
Immunogenicity Analysis Set	All participants who received at least 1 administration of guselkumab and have at least one sample obtained after their first dose of guselkumab
PK Analysis Set	All participants who received at least 1 administration of guselkumab and have at least one valid blood sample drawn for PK analysis.
PD Analysis Set	All participants who received at least 1 administration of study intervention and have at least one post-dose sample collection.

9.4. Statistical Analyses

The SAP will be finalized prior to the DBL at Week 28. 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

Data primarily will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, SD, median, interquartile range, minimum and maximum, as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate. Median time will be reported for time to event variables. In addition, graphical data displays (eg, line plots) and participant listings may also be used to summarize/present the data.

For continuous endpoints, Mixed-Effect Model Repeated Measure model and Analysis of Covariance will be used for analysis. For binary endpoints, Cochran-Mantel-Haenszel test stratified by new-onset and relapsing GCA, and the baseline prednisone dose (≤30 mg/day or >30 mg/day) will be used to analyze data. For time to first event data, Kaplan-Meier curves and Cox proportional hazards regression will be used to analyze the data. In addition, treatment differences and their associated 90% confidence intervals will be presented.

In general, all statistical tests will be performed at a 2-sided significance level of α 0.10. No multiplicity adjustment will be made for the secondary endpoints being tested and nominal p values will be reported.

9.4.2. Primary Endpoint

Definition of Primary Endpoint

The primary endpoint is the proportion of participants achieving GC-free remission at Week 28 (ie, meeting remission definition and not on GC for GCA at Week 28).

Estimand: The estimand, based on the primary objective above, is defined by the following 5 components based on the composite strategy which assesses the treatment effects not only based on the variable measurements, but also based on intercurrent events:

- **Population:** adult participants 50 years or older with active new-onset or relapsing GCA
- **Variable:** GC-free remission at Week 28
- **Treatment:**

  Guselkumab in addition to 26-weeks GC-taper

  Placebo in addition to 26-weeks GC-taper
- **Intercurrent Events:** discontinuation of study intervention due to lack of efficacy or an AE of worsening of GCA, or initiation of a protocol-prohibited medication or therapy during the study that could improve GCA, or initiation of GC rescue therapy
- **Population level summary:** difference in proportion of GC-free remission at Week 28 between the guselkumab group and the placebo group

Primary Endpoint Analysis

Analyses of the primary efficacy endpoint (GC-free remission at Week 28) will include data from all randomized participants who received at least one administration of study intervention based on their assigned intervention group, regardless of the actual intervention received and have baseline data (Full Analyses Set population).

In this primary analysis, the number and proportion of participants who achieve GC-free remission at Week 28 will be summarized for each treatment group. Participants who experienced intercurrent events prior to Week 28 will be considered as not achieving the endpoint. In addition, participants with missing data at Week 28 will also be considered as not achieving the endpoint. To address the primary objective, Cochran-Mantel-Haenszel chi-square statistic stratified by new-onset and relapsing GCA, and the baseline prednisone dose (≤30 mg/day or >30 mg/day) at a 2-sided significance level of 0.10 will be used. Difference in response rates between the 2 treatment groups and the corresponding 90% CI will be presented.

Subgroup analysis (based on demographics, baseline characteristics, new-onset vs relapsing, GC dose at baseline [≤ 30 mg/day or >30 mg/day]) will be performed for the primary endpoint.

9.4.3. Secondary Endpoints

Secondary Endpoints:

- The proportion of participants achieving GC-free remission from Week 28 by visit through Week 52
- The proportion of participants achieving GC-free remission and normalization of ESR at Week 28 and by visit through Week 52
- The proportion of participants achieving GC-free remission and normalization of CRP at Week 28 and by visit through Week 52

- The proportion of participants achieving GC-free remission and normalization of both ESR and CRP at Week 28 and by visit through Week 52
- The cumulative GC dose through Week 28 and through Week 52
- The time to first GCA disease flare or discontinuation of study intervention due to AE of worsening of GCA through Week 28 and through Week 52
- The number of GCA disease flares or discontinuation of study intervention due to AE of worsening of GCA through Week 28 and through Week 52

Secondary Endpoint Analyses

The Full Analyses Set population will be used for analysis and participants will be counted in the intervention group assigned, regardless of the study intervention received.

The details of the analysis of the secondary endpoints will be included in the SAP.

9.4.4. Tertiary/Exploratory Endpoints

Other Efficacy Endpoints

- Proportion of participants in sustained remission through Week 52.

Sustained remission through Week 52 is defined as: No signs and symptoms of GCA through Week 52, and completion of the protocol defined GC taper, and not having required GC rescue therapy at any time by Week 52.

- Change from baseline in CRP through Week 52
- Change from baseline in ESR through Week 52

Clinical Outcome Assessments

- Change from baseline in PGA by visit through Week 52
- Change from baseline in Pain Assessment by visit through Week 52
- Change from baseline in SF-36 individual domains by visit through Week 52
- Change from baseline in FACIT-fatigue score by visit through Week 52
- Change from baseline in PhGA by visit through Week 52.

Further details of tertiary/exploratory endpoints analyses and analyses for efficacy during the LTE will be provided in the SAP.

9.4.5. Safety Analyses

All safety analyses will be analyzed using the Safety Analysis Set population (refer to Section 9.3 for definition).

Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities. Any AE occurring at or after the initial

administration of study intervention through the end of the study is considered to be treatment emergent. All reported TEAEs 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. In addition, comparisons between intervention groups will be provided if appropriate.

The following analyses of AEs will be used to assess the safety of participants in the main study:

- Number and proportion of participants with TEAEs by treatment intervention through Week 60
- Number and proportion of participants with TEAEs by system organ class and preferred term with a frequency threshold of 5% or more by treatment intervention through Week 60
- Number and proportion of participants with treatment-emergent SAEs by treatment intervention through Week 60
- Number and proportion of participants with reasonably related TEAEs as assessed by investigator by treatment intervention through Week 60
- Number and proportion of participants with infections, serious infections, and infections requiring oral or parenteral antimicrobial treatment through Week 60
- Number and proportion of participants with TEAEs leading to discontinuation of study intervention by treatment intervention through Week 60
- Number and proportion of participants with TEAEs temporally associated with an IV infusion by treatment intervention through Week 8
- Number and proportion of participants with injection-site reactions by treatment intervention.

Summaries, listings, datasets, or participant narratives may be provided through Week 28 and Week 60 by treatment intervention, for the above AEs, deaths, and severe AEs.

Similar safety analyses from Week 52 (LTE Week 0) through Week 112 (LTE Week 60) will be performed for participants in the LTE period.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test over time and by treatment intervention. National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grades (specified in the SAP) 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.

The following summaries of clinical laboratory tests will be used to assess participant safety:

- Laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry)
- Summary of maximum NCI-CTCAE toxicity grade for postbaseline laboratory values (hematology and chemistry)

- Listings of participants with any abnormal postbaseline laboratory values of NCI-CTCAE Grade ≥2 will also be provided

Columbia-Suicide Severity Rating Scale

Suicide-related thoughts and behaviors based on the C-SSRS will be summarized descriptively by treatment group.

Vital Signs

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized.

Weight

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

9.4.6. Other Analyses

Pharmacokinetic Analyses

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

Serum guselkumab concentrations will be summarized over time for all participants who receive at least 1 dose of guselkumab. Descriptive statistics will be calculated at each sampling timepoint. All serum concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. Pharmacokinetic data may also be displayed graphically.

If feasible, population PK analysis of serum concentration-time data may be performed using nonlinear mixed-effects modeling. Details will be provided in a separate technical report.

Immunogenicity Analyses

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

A listing of participants who are positive for antibodies to guselkumab will be provided. The maximum titers of antibodies to guselkumab will be summarized for participants who are positive for antibodies to guselkumab.

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

Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

Biomarkers/Pharmacodynamic Analyses

The biomarker analyses will characterize the effects of guselkumab to identify PD markers and biomarkers relevant to treatment, and to determine if these markers can predict response to guselkumab. Changes in serum analytes, RNA levels in whole blood and in single cells from PBMC, and leukocyte subset counts and frequencies in PBMC over time will be summarized by intervention group, in separate technical reports. Associations between baseline levels and changes from baseline in select markers and clinical response on primary and major secondary endpoints in Sections 9.4.2 and 9.4.3 will be explored and summarized in separate technical reports.

Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information. 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.

Pharmacokinetic/Pharmacodynamic Analyses

The relationship between serum concentrations of guselkumab and the efficacy measures and/or relevant PD endpoints may be explored graphically when appropriate.

Pharmacogenomic Analyses

Genetic (DNA) analyses will be conducted only in participants who sign the consent form to participate in the pharmacogenomic substudy. DNA samples will be used for research related to guselkumab, GCs, or GCA. They may also be used to develop tests/assays related to guselkumab, GCs and GCA. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome (as appropriate) in relation to guselkumab, GCs or GCA clinical endpoints. These analyses are considered exploratory and will be summarized in a separate technical report.

Exploratory FDG-PET/CT Imaging Analyses

FDG-PET/CT scans will be qualitatively assessed for FDG uptake in 9 arterial territories (carotid arteries, subclavian arteries, brachiocephalic artery, ascending aorta, aortic arch, descending thoracic aorta, and the abdominal aorta). The degree of arterial uptake will be visually assessed relative to liver uptake as: 0 no uptake; 1 less than liver; 2 same as liver; 3 greater than liver. To assess the qualitative inflammatory burden by arterial FDG uptake across multiple arterial regions, a summary score (hereafter termed PET Vascular Activity Score [PETVAS]) will be created by adding the qualitative scores in specific arterial territories (Grayson 2018).

Large-Vessel Imaging (FDG-PET/CT) changes from baseline in PETVAS at Week 52 (or flare) and Week 104 (LTE Week 52) (or flare), if applicable will be summarized per participant and by treatment intervention. Correlation of PETVAS score with clinical features and laboratory tests, and additional semi-quantitative assessments and analyses may also be explored. These analyses are considered exploratory and will be summarized in a separate technical report.

Digital Health - Actigraphy Analyses

The raw data sampled by Actiwatch sensors will be transformed into the following derived digital health endpoints, assessing the changes from baseline in on physical activity, mobility, and sleep components by visit through Week 52, including but not limited to the following:

- Activity
  - Total activity counts
  - Average activity (counts/minute)
  - Maximum activity (counts/minute)
  - Time above sedentary
  - Mean daily activity
  - Activity threshold analysis
  - Daily peak activity
- Sleep
  - Total sleep time
  - Onset latency
  - Sleep efficiency
  - Wake time after sleep onset
  - Percent (%) wake
  - Number of wake bouts (number of awakenings)
  - Average wake bout
  - Fragmentation index
- Mobility
  - Immobile time within the given interval
  - Percentage immobile time within the given interval
  - Number of immobile bouts
  - Average duration of immobile bouts
  - Mobile time within the given interval
  - Percentage mobile time within the given interval
  - Number of mobile bouts
  - Average duration of mobile bouts
  - Number of immobile bouts of ≥1-minute duration, within the given interval
  - Percentage of immobile bouts that are ≥1-minute duration
  - Fragmentation index

Additional actigraphy digital health endpoints may be derived using emerging algorithms. Associations between baseline measurements and changes from baseline in selected measurements and clinical response on primary and secondary endpoints in Sections 9.4.2 and 9.4.3 may be explored. All Actigraphy data related analyses are considered exploratory and will be summarized in a separate technical report.

9.5. Interim Analyses

No interim analyses are planned for this study.

9.6. Data Monitoring Committee

An independent DMC will be established as noted in Committees Structure in Section 10.3. The DMC will monitor safety data on an ongoing basis until all participants complete the study or terminate the study. The main focus of the DMC will be on reviewing interim unblinded safety data, but the DMC may also review efficacy data needed to ensure the full benefit: risk profile for guselkumab.

The DMC will consist of at least one external and one internal clinical physician with relevant therapeutic expertise (rheumatology) and one internal statistician, not related to the study team. The content of the safety summaries, the DMC's role and responsibilities, the general procedures (including communications), and their recommendations on the study conduct are defined and documented in the DMC charter, which will be finalized prior to the first DMC review.

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCG	Bacille Calmette-Guérin
CRF	case report form(s) (paper or electronic as appropriate for this study)
CRP	C-reactive protein
CT	computed tomography
DBL	database lock
DCS	data collection systems
DILI	drug induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
C-SSRS	Columbia-Suicide Severity Rating Scale
eDC	electronic data capture
ESR	erythrocyte sedimentation rate
FACIT	Functional Assessment of Chronic Illness Therapy
FDG	fluorodeoxyglucose
GC	glucocorticoid
GCA	Giant cell arteritis
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
HS	Hidradenitis suppurativa
IB	investigator's brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobin
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
LN	Lupus Nephritis
LTE	long-term extension
MTX	methotrexate
NOAEL	no-observed-adverse-effect level
NSAID	non-steroidal anti-inflammatory drug
p	Point(s)
PBMC	peripheral blood mononuclear cell
PETVAS	PET Vascular Activity Score
PD	pharmacodynamic(s)
PET	positron emission tomography
PFS	prefilled syringe
PFS-U	UltraSafe Plus™ Passive Needle Guard
PGA	Patient's Global Assessment of Disease Activity
PhGA	Physician's Global Assessment of Disease Activity
PK	pharmacokinetic(s)
PMR	polymyalgia rheumatica

PQC	Product Quality Complaint
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
PsA	psoriatic arthritis
PsO	psoriasis
PT	prothrombin time
PTT	Partial thromboplastin time
q4w	every 4 weeks
q8w	every 8 weeks
RA	rheumatoid arthritis
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical analysis plan
SC	subcutaneous
SD	standard deviation
SF-36	short-form 36
sIPPM	Site Investigational Product Procedures Manual
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
UC	ulcerative colitis
US	United States
ULN	upper limit of normal
VAS	Visual Analog Scale

Definitions of Terms

PRO	Reports directly from the patient without interpretation by clinician or anybody else.

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the SoA 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 (RBC) count
Hemoglobin
Hematocrit</td><td><u>RBC Indices:</u>
MCV
MCH
% Reticulocytes</td><td><u>White Blood Cell count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="3">Note: A white blood cell 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
AST/Serum glutamic-oxaloacetic
ALT/Serum glutamic-oxaloacetic
Gamma-glutamyltransferase</td><td>Total bilirubin, reflex test indirect bilirubin if abnormal
Alkaline phosphatase
Creatine phosphokinase (CPK)
Lactic acid dehydrogenase (LDH)
Uric acid
Calcium
Phosphate
Albumin
Total protein
Cholesterol
Triglycerides
Magnesium</td></tr>
<tr><td colspan="3">Note: Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 10.9, Appendix 9: Liver Safety.

Potential Hy’s Law case (ALT or AST ≥3×ULN together with Tbili ≥2×ULN or INR >1.5) reporting requirements are defined in Section 8.3.</td></tr>
<tr><td>Other Tests</td><td colspan="3">• Urine Pregnancy Testing for women of childbearing potential only (performed locally)
• Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and Hepatitis B, surface antibody [anti-HBs], Hepatitis B core antibody [anti-HBc], hepatitis C virus antibody, and HBV DNA, screening only)
• Coagulation (prothrombin time [PT], partial thromboplastin time [PTT], INR), at screening only
• CRP and ESR (Westergren method). ESR will be performed locally</td></tr>
</table>

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

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current international council for harmonization (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country- or territory-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) involves 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 CRF 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/territory, 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 pharmacogenomics and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional pharmacogenomic 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/Territory Selection

This study will only be conducted in those countries/territories 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 4.2.2., Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.2.

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.

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, PD/biomarker, PK, and immunogenicity 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.

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. 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 is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed. The physician may also recontact the participant for the purpose of obtaining consent to collect information about his or her survival status.

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 of 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 and 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.

Where local regulations require, a separate ICF may be used for the required DNA component of the study.

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 treatment, GCs, to understand GCA, to understand differential intervention responders, and to develop tests/assays related to guselkumab treatment, GCs and GCA. The research may begin at any time during the study or the post-study storage period.

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

COMMITTEES STRUCTURE

Data Monitoring Committee

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

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding guselkumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker, imaging, digital health research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of guselkumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory biomarker, imaging, digital health 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 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 International Committee of Medical Journal Editors 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.

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 CRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor may review the CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

CASE REPORT FORM COMPLETION

Data from each study participant will be captured in an eCRF or ancillary data collection systems (DCS) such as the IWRS, PRO tablets, laboratory database, and imaging database. Electronic CRFs prepared by the sponsor are provided to the site for each participant. If the site is required to enter data directly into an ancillary DCS, the applicable system will be prepared by the ancillary data provider and provided to the site for each participant.

Case report forms are prepared and provided by the sponsor for each participant in electronic CRF. All data relating to the study must be recorded in the CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, or the ancillary DCS, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used as source documentation to capture data and facilitate completion of the eCRF or entry of data into the applicable ancillary data system. Data entry in the applicable DCS must be completed as soon as possible after a participant visit and the data should be available for review at the next scheduled monitoring visit. The investigator must verify that all data entries in the eCRF are accurate and correct.

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 electronic data capture (eDC) tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

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 patient-reported outcomes (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 PRO 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 added into the electronic device and will be considered source data:

- Clinical Outcome Assessments/PROs
- Physician global assessment of disease activity

- GCA signs and symptoms assessment may be considered source, if collected through electronic device.

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

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

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by 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. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system, but information collected through eSource may not be limited to that found in the CRF.

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. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). At these visits, the monitor may compare data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

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.

RECORD RETENTION

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

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 intervention.

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

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Council for Harmonisation [ICH]).

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

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 8.3.1).

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

Serious Adverse Event

A 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, serious adverse events include adverse device effects that resulted in any of the consequences characteristic of a serious adverse event. 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 adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For guselkumab, the expectedness of an adverse event will be determined by whether or not it is listed in the IB.

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 AE.

Related

There is 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.

Not Related

There is no reasonable causal relationship between study intervention administration and the AE.

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).

SPECIAL REPORTING SITUATIONS

Safety events of interest on a sponsor study intervention 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 a SAE should be recorded on the SAE page of the eCRF.

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

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 participation in the study, must be followed until any of the following occurs:

- The event resolves

- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study 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 a SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any adverse event 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 12 weeks of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered a SAE.

Disease progression should not be recorded as an adverse event or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the SAE definition (refer to Adverse Event Definitions and Classifications in this section).

Expected progression of disease should not be considered an adverse event (or SAE). However, if determined by the investigator to be more likely related to the study intervention than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study intervention is enhancing disease progression, should be reported per the usual reporting requirements.

Information regarding serious adverse events will be transmitted to the sponsor using a serious adverse event reporting form, which must be completed and signed 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 a serious adverse event should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

PRODUCT QUALITY COMPLAINT HANDLING

Definition

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

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: Revised American College of Rheumatology Criteria for Diagnosis of GCA

2016 Revised American College of Rheumatology criteria for diagnosis of Giant Cell (Temporal) Arteritis[a,] (Salehi-Abari 2016).

Entry Criteria

- Age at onset ≥50 years old
- Absence of exclusion criteria[b]

Domain I Criteria

- New onset localized headache[c] 1p
- Sudden onset of visual disturbances[c] 1p
- Polymyalgia Rheumatica (PMR) 2p
- Jaw Claudication[c] 1p
- Abnormal temporal artery[d] up to 2p

Domain II

- Unexplained fever and/or anaemia 1p
- ESR ≥50 mm/hour[e] 1p
- Compatible pathology[f] up to 2p

[a] In the presence of 3 points (p) or more out of 11 with at least one point belonging to domain I along with all entry criteria, the diagnosis of Giant cell arteritis can be established;
[b] Exclusion criteria are including: ENT and eye inflammation, kidney, skin and peripheral nervous system involvement, lung infiltration, lymphadenopathies, stiff neck and digital gangrene or ulceration;
[c] No other etiologies can better explain any one of the criteria;
[d] Enlarged and/or pulseless temporal artery: 1.p./tender temporal artery: 1.p;
[e] It must be ignored in the presence of PMR;
[f] Vascular and/or perivascular fibrinoid necrosis along with leucocyte infiltration: 1.p. /and granuloma: 1.p.

10.6. Appendix 6: Hepatitis B Virus (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 study
- 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 study
- Participants who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this study
- Participants who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this study, 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 hepatitis B virus deoxyribonucleic acid (HBV DNA test). 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

Eligibility based on hepatitis B virus test results

	Hepatitis B test result		
Action	**Hepatitis B surface antigen (HBsAg)**	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**
Include			
		+	
		+	+
Exclude	+	*or* +	*or* +
Require testing for presence HBV DNA*			+

* If HBV DNA is detectable, exclude from the clinical study. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, exclude from the clinical study.

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

10.7. Appendix 7: 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 Sections 8.3.5, Pregnancy and 10.4, 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 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 follicle stimulating hormone 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**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, 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)
• Azoospermic partner *(vasectomized or due to medical cause)* *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] oral intravaginal transdermal injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] oral injectable
• 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) 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.

10.8. Appendix 8: Protocol Defined 26-Week Glucocorticoid Taper

Table 3: Protocol Defined 26-Week Glucocorticoid Taper[#]

Week	Initial prednisone[+] dose at Randomization [(*)]			
	60-50 mg	49-40 mg	39-30 mg	29-20 mg
	Daily dose (mg/day)	Daily dose (mg/day)	Daily dose (mg/day)	Daily dose (mg/day)
0[**]	60-50	49-40	39-30	29-20
1	50	40	30	20
2	40	35	25	20
3	35	30	20	17.5
4	30	25	20	17.5
5	25	20	17.5	17.5
6	20	17.5	17.5	15
7	17.5	15	15	15
8	15	15	15	15
9	12.5	12.5	12.5	12.5
10	12.5	12.5	12.5	12.5
11	10	10	10	10
12	10	10	10	10
13	9	9	9	9
14	8	8	8	8
15	7	7	7	7
16	6	6	6	6
17	6	6	6	6
18	5	5	5	5
19	5	5	5	5
20	4	4	4	4
21	4	4	4	4
22	3	3	3	3
23	3	3	3	3
24	2	2	2	2
25	1	1	1	1
26	0	0	0	0
27	0	0	0	0
28	Primary Endpoint Assessment Week 28			

* Individual participants will be receiving different doses of prednisone (or equivalent) at specified time points, depending on their initial GC dose at randomization. Therefore, the tapering schedule indicates the required decrease in prednisone dose on a weekly basis, with the specific week varying by individual participant.

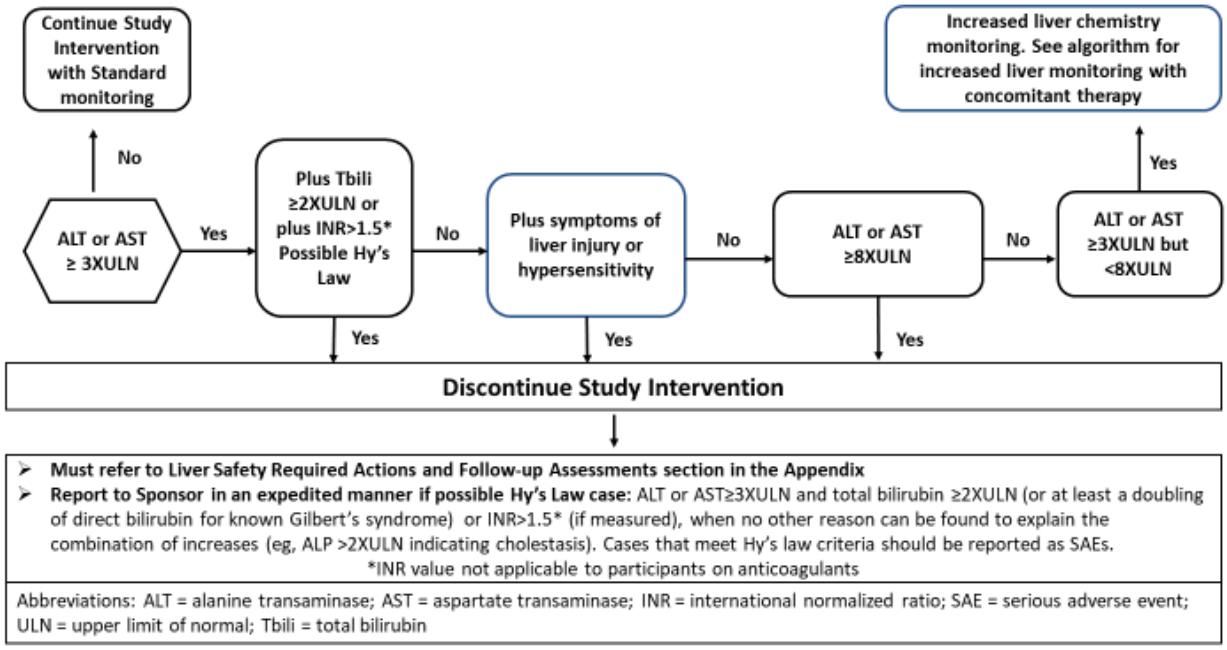
** The first week (Week 0) after randomization the participant will take their initial GC dose, and per Week 1 start with their taper in accordance with this table and their initial starting dose.

+ If the participant continues on GC other than prednisone or prednisolone, the Investigator should contact the Sponsor to ensure that the taper is appropriately adjusted for the GC equivalency compared with prednisone, using the Appendix 10 conversion table to convert the Prednisone Taper doses to the equivalent alternate glucocorticoid.

In countries where not all required tablet strengths are available to comply with the lower doses of the protocol-defined taper, where authorized (ie, HA and Ethics Committee approval in place), small variations in daily steroid dose of up to 0.5 mg/day are allowed to make the taper feasible. Sites that are impacted by this should reach out to the sponsor clinical team for further guidance before any participants start their taper. If tablets need to be cut in half or in quarters this should preferably be performed by site staff.

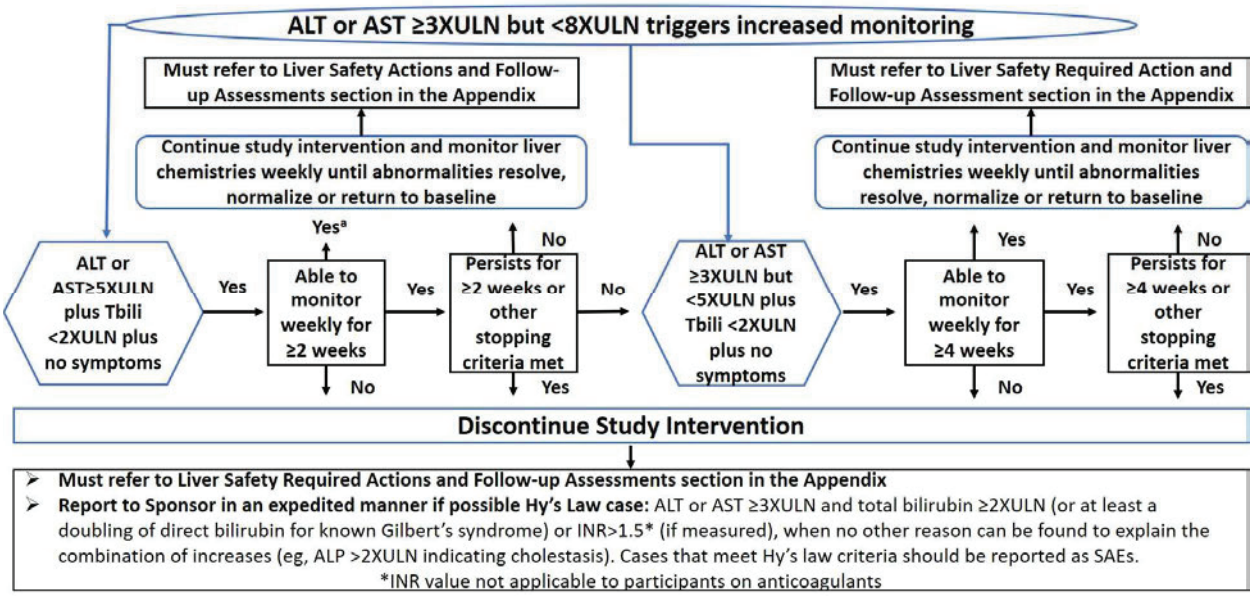
10.9. Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments

Guideline Algorithm for Monitoring, Assessment & Evaluation of Abnormal Liver Tests in Participants with no Underlying Liver Disease



Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase, INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin

Liver Chemistry Increased Monitoring Algorithm with Continued Study Intervention for Participants with ALT or AST ≥3× ULN but <8× ULN



Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase, Tbili = total bilirubin; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin

[a]In participants whose liver function tests (ALT or AST) are ≥5× ULN, medication should be interrupted until a decrease in liver function test is noted.

In those cases of liver function tests (ALT or AST) ≥5× ULN where a potential etiology other than guselkumab is identified, the study intervention may be interrupted for an extended period (>2 weeks) until a thorough assessment is performed by the investigator and Sponsor prior to the restart of study intervention. If liver function tests remain ≥5× ULN for 2 weeks and are considered related to study intervention, investigational treatment will be discontinued.

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** international normalized ratio (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 [CRF as per CRF 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, aspartate transaminase [AST], alkaline phosphatase, total and direct bilirubin and INR) and perform liver event follow-up assessments within **24 hours**	• Viral hepatitis serology[4] • Obtain blood sample for pharmacokinetic (PK) analysis 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 [CRF as per CRF completion guidelines] • Record use of concomitant medications (including acetaminophen, herbal remedies, recreational drugs, and other over-the-counter medications) • Record alcohol use on the [Relevant Substance use tobacco CRF as per CRF 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) or INR >1.5 (if measured)</u>** obtain the

• 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** • **Do not restart/rechallenge** participant with study intervention.	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 • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease; complete [CRF as per CRF completion guidelines] • Liver biopsy may be discussed with local specialist if available, for instance: In patients when serology raises the possibility of autoimmune hepatitis (AIH) In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention In patients with acute or chronic atypical presentation: hepatic vascular disorder, chronic hepatitis fibrosis, micro vesicular statosis • If liver biopsy conducted complete (CRF as per CRF 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. 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 CRF. 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.

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention	
Criterion	**Actions**
ALT or AST≥3xULN and <5xULN **and** total bilirubin <2xULN or INR<1.5**, 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 7.1. • If, after 4 weeks of monitoring, ALT or AST<3xULN and total bilirubin <2xULN, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to baseline.

10.10. Appendix 10: Glucocorticoid Conversion Table

GC	Replacement/Equivalence
Cortisone acetate	25 mg
Hydrocortisone	20 mg
Deflazacort	7.5 mg
Prednisone	5 mg
Prednisolone	5 mg
Triamcinolone	4 mg
Methylprednisolone	4 mg
Dexamethasone	0.75 mg
Betamethasone	0.75 mg

10.11. Appendix 11: 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, isolation/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 judgement 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 intervention may be interrupted. 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 COVID-19 pandemic, 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 using the examples contained in this appendix, after consultation between the participant and investigator, and with the agreement of the sponsor (see below).

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 responsible medical officer 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 clinical study report.

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 drug storage and administration (including training where pertinent)

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 case report form (CRF).

  other relevant study data elements impacted by the pandemic should also be documented / labeled as "COVID-19-related" in CRFs 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).

- NOTES on COVID-related exclusion:

  1. If a patient is excluded due to recent COVID-19-related features, the reason for screen failure should be documented in the case report form under the exclusion criterion of having a condition for which participation would not be in the participant's interest or could confound study assessments.

  2. 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 (eg, those aged over 65 years), follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

10.12. Appendix 12: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents. A summary of previous amendments is provided below.

Amendment 4 (17 September 2021)

Overall Rationale for the Amendment: This clinical study has been experiencing slow enrollment of participants and 2 participants had withdrawn consent during screening. Based on feedback from the study sites, the actigraphy watch appeared to be a hurdle for participants to participate in the trial. As actigraphy is an exploratory endpoint, the study team is introducing the possibility for participants to decline this assessment to increase enrollment rates. Additional assessments were also adjusted to increase enrollment rates.

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA); 7.2. Participant Discontinuation/Withdrawal From the Study; 8.10. Digital Health – Actigraphy Measurements	Footnote 'm': Added that participants have the opportunity to decline use of the actigraphy watch. Statement revised to allow for a participant withdrawing consent the opportunity to decline actigraphy assessment/ measurements.	Based on feedback from participants and site, actigraphy assessments have been made optional to minimize burden on participants.
1.3. Schedule of Activities (SoA)	Timepoints for weight assessment was changed. Timepoints for efficacy assessments were changed: • All assessments under early termination visits were deleted • Assessments for Physician's Global Assessment for Disease Activity (PhGA), Patient's Global Assessment of Disease Activity (PGA), Pain Assessment, FACIT-Fatigue, and SF-36 were deleted for Week 12, 20, 36 and 44. • Assessment for ESR/CRP were deleted for early termination visit. Timepoints for pharmacokinetics and immunogenicity changed: • Assessments at Week 20, 24, 40 and 60 were deleted Timepoints for biomarker assessments were changed: • Assessments for serum biomarkers and whole blood (PAXgene) were deleted for Week 8, 12, 20, 40, and early termination visit and PBMC sample collection was deleted for Week 12 and Flare visit.	Assessments were reduced to decrease potential burden to participants.

Section Number and Name	Description of Change	Brief Rationale
1.4. Schedule of Activities (SoA) – Long Term Extension	• Timepoints for weight assessment was changed • C-SSRS assessment was deleted under timepoints: Week 100 (LTE Week 48), Week 112 (LTE Week 60), and early termination visit in LTE period; added under Week 104 (LTE Week 52). • All efficacy assessments under early termination visits were deleted • Assessments for Clinical Assessor's GCA Disease Assessment S&S, Physician's Global Assessment of Disease Activity (PhGA), Patient's Global Assessment of Disease Activity (PGA), Pain Assessment, FACIT-Fatigue, and SF-36 were deleted for Week 112 (LTE Week 60). • Assessment for ESR/CRP was deleted on Week 112 (LTE Week 60) and early termination visit in the LTE period. • Serum biomarkers and whole blood (PAXgene) were deleted.	Adjustments made in 12 week safety follow up visit and early termination visit to to reduce participant burden. Serum biomarkers and whole blood removed to reduce participant burden.
4.1. Overall design	• Clarification of visit in Safety Follow-up period in main study. Adding timing of the Flare visit. • Clarification of visit in Safety Follow-up period in LTE period of the study. Adding the follow-up visits after participants experience a Flare (timing of Flare visit and early termination visit). For participants in the placebo arm, they ~~***can***~~ ***may*** still continue in the study until Week 112.	Clarification of visits to be scheduled after flare or study discontinuation during LTE period according to SoA.
1.1. Synopsis; 1.4. Schedule of Activities (SoA) – Long Term Extension; 4.1. Overall Design; 6.1. Study Interventions Administered; 8.9 Exploratory FDG-PET/CT imaging	Under Intervention Groups and Duration, GC rescue medication was deleted. Footnote 'c': GC rescue medication was deleted. Footnote 'e' updated to include the following regarding a GCA flare, "*or other timeframe in accordance with local country regulations"*	Removal of redundant text. Harmonize footnote with wording in body of protocol. Reduce assessments.

Section Number and Name	Description of Change	Brief Rationale
	Footnote 'e' amended to add the ability of participants to decline PET-CT that is obtained in the LTE.	
2.3.1. Risks for Study Participation	Table was updated for infections and transaminase increases identified as adverse reactions of guselkumab as well as hypersensitivity.	Added language as a rationale for the existing exclusion and discontinuation criteria and safety assessments in the study.
3. Objective and Endpoints	Exploratory objective (LTE): The endpoints for the participant and clinician-reported assessments was revised to remove Week 112 (LTE Week 60) or ET visit.	Focus follow up safety and early termination visit on safety assessments.
1.1. Synopsis; 3. Objective and Endpoints	Moved Secondary Objective 'To evaluate the changes in immune-markers to guselkumab compared to placebo, in combination with a 26-week GC taper regimen, in adult participants with new-onset or relapsing GCA' to Exploratory objectives.	Objective is degraded to Exploratory, Immune-markers ESR and CRP are non-specific markers of inflammation and changes in these markers alone (without signs and symptoms of GCA) may have other causes.
3. Objective and Endpoints; 9.4.3. Secondary Endpoints	Modified endpoint to include 'or discontinuation of study intervention due to AE of worsening of GCA' to the objectives 'time to first GCA disease Flare' and 'number of GCA disease flares'	Objectives broadened to include participants that have worsening of GCA without classification as having a Flare, for example for participants that have not reached the status "in remission"
5.1. Inclusion Criteria	Criteria 4 amended to add that both temporal artery biopsy revealing features of GCA and evidence of cranial GCA can be obtained either at time of diagnosis or at any time point during disease history	Protocol clarification
5.2. Exclusion Criteria; 6.8.1. Permitted Therapy	Criteria 23 amended to include **new** text: 'stable dose for minimally **4** weeks'. The duration of stable methotrexate dosage (if used) was revised from 6 to 4 weeks. Maximum dose was increased to 25mg oral or SC methotrexate and ~~15 mg SC~~ was deleted	To align with standard of care in GCA.
7.1. Discontinuation of Study Intervention	Treatment discontinuation criteria text relocated to clarify that study intervention discontinuation is required if GCA flare occurs during LTE period.	Protocol clarification. Discontinuation of study intervention should not be 'considered' and therefore should be mentioned in the first section. The description of the follow-up visits was incorrect and is already described elsewhere in the protocol.
8. Study Assessments and Procedures	Total blood volume to be collected from each participant was reduced from 450 mL to 300 mL.	Total volume is lower due to reduced assessments implemented in this amendment

Section Number and Name	Description of Change	Brief Rationale
8.1.1. GCA Disease signs and symptoms	Removed text "new-onset" and changed 'findings' to 'signs'	Minor clarification
8.2.2. Vital signs	Reduce number of assessments required with SC administration in absence of symptoms	Reduce patient burden and align with other protocols.
3. Objective and Endpoints; 9.4.3. Secondary Endpoints	Moved 'Supportive Secondary Endpoints' to 'Exploratory endpoints'	Protocol clarification
10.7. Appendix 7: Contraceptive and Barrier Guidance	Bilateral tubal occlusion was deleted from Examples of Contraceptives.	Clarification of categorization of bilateral tubal occlusion.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 3 (09 July 2021)

Overall Rationale for the Amendment: To add a long-term extension (LTE) period to the study for evaluating the long-term effectiveness of guselkumab, and to offer participants who are still in remission at Week 52, the opportunity to continue to be treated with the study intervention until they become non-responsive.

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis	Deleted 'a generalized linear model with logit link for binary repeated measurement data and/or' for binary endpoint analysis.	To clarify that logistic regression will be used as sensitivity analysis for the primary endpoint only, and that the primary endpoint and major secondary endpoint will use Cochran-Mantel-Haenszel test. To align with changes made to Section. 9.4.1. General Considerations during Amendment 2.
1.2. Schema	The schematic overview of study was updated to indicate start of follow-up period from Week 48 onwards.	To correctly align with the protocol.
1.2. Schema	The study design for the LTE period was added.	To accommodate information for the LTE period of the study.
1.3. Schedule of Activities (SoA)	Footnote's' for Week 52 visit was added.	
1.4. Schedule of Activities (SoA) – Long-Term Extension	The schedule of activities for the LTE period was added.	
1.1. Synopsis; 3. Objective And [Endpoints And/Or Estimands]	The exploratory objective and endpoints for the LTE period were added.	
2.3.1. Risks for Study Participation; 8.9. Exploratory FDG-PET/CT Imaging	• The details on additional fluorodeoxyglucose-positron emission tomography/computed tomography scan in the LTE period were added. • Added a note that FDG-dose may be modified in consultation with the sponsors in countries where local regulations require this.	
4.1. Overall Design	• The duration of the LTE period was added.	

Section Number and Name	Description of Change	Brief Rationale
	• The count of DBL for the study was changed from 2 to 3 and information on DBL for the LTE period was defined. • The study design for the LTE period was added.	
4.4. End of Study Definition	The definition of study completion was modified.	
5.1. Inclusion Criteria (#19)	Inclusion criteria for the LTE period was added.	
1.1. Synopsis; 6.1. Study Intervention(s) Administered	The period for SC injection in participants of the LTE period was added.	
1.1. Synopsis; 1.2. Schema; 6.6. Continued Access to Study Intervention After the End of the Study	The option to enter the LTE period was mentioned.	
7.1. Discontinuation of Study Intervention	The conditions for discontinuation of study intervention in the LTE period were added.	
9.4.4. Tertiary/Exploratory Endpoint(s)	The following text was ***modified*** as '*Further details of tertiary/exploratory endpoints analyses **and analyses for efficacy during the LTE** will be provided in the SAP*'.	
1.3. Schedule of Activities (SoA) (Footnote l)	Footnote was updated to define that the C-SSRS is physician administerd.	To provide clarity to the protocol.
1.2. Schema; 2.3.1. Risks for Study Participation; 4.1 Overall Design; 4.4. End of Study Definition; 6.6. Continued Access to Study Intervention After the End of the Study; 9.4.5. Safety Analyses	The terms 'main' or 'main study' were added.	To distinguish the study information for Main study and the LTE period.
1.1. Synopsis; 6.1. Study Intervention(s) Administered	Sentence revised to include "*or the participants discontinues treatment due to unblinding after the Week 60 DBL for the Main study*"	
4.1. Overall Design; 4.4. End of Study Definition; 7.1. Discontinuation of Study Intervention	The term 'double-blind treatment period' or 'double-blind phase' was changed to 'main study treatment period' or 'main study phase'.	To avoid the suggestion that participants will be unblinded after completing treatment in the main study.
4.4. End of Study Definition;	The pronouns 'he or she' was replaced with 'the participant'.	To adhere with the current standards for gender inclusivity.

Section Number and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria (#16 and #17); 5.2. Exclusion Criteria (Note); 5.3. Lifestyle Considerations; 7.3. Lost to Follow-up		
5.2. Exclusion Criteria (#2)	The term 'PMR' was removed.	To avoid confusion, as PMR is also a symptom of GCA and listed in the revised ACR diagnostic criteria.
6.3. Measures to Minimize Bias: Randomization and Blinding	Subheading Blinding: Sentence was revised to clarify **main** study with a database finalization at **Week 60**.	To distinguish the study information for main study and the LTE period.
6.8.1. Permitted Therapy (Anti-Hypertensive Therapy, Non-steroidal Anti-inflammatory Drugs)	Week 52 was changed to '4 weeks after the last dose of study intervention' for anti-hypertensive therapy and non-steroidal anti-inflammatory drugs.	To make the timelines applicable for both the main study as the LTE.
6.8.1. Permitted Therapy (Non-live vaccines, including COVID-19 vaccines)	Information on non-live vaccines including COVID-19 vaccines was added.	To provide guidance on the use of COVID-19 vaccine.
8.2.8. Injection-Site Reactions	Information around reporting of injection-site reactions for LTE participants was added.	To allow for short dosing visits on days where minimal assessments are performed in the LTE period.
8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; 10.2. Appendix 2: Clinical Laboratory Tests	Instructions for investigators on reporting cases of biochemical Hy's law was included in the protocol body.	To provide clarity to the protocol.
9.4.5. Safety Analyses	The safety analyses was defined for participants in the LTE period.	To encompass the LTE period.
9.4.6. Other Analyses	The analyses of large-vessel imaging changes from baseline in PETVAS was summaries per participant and by treatment intervention was updated to include Week 104 participants.	
9.6. Data Monitoring Committee	The monitoring of safety data by DMC was extended until study completion (or termination).	
10.3 Appendix 3: Regulatory, Ethical, and Study Oversight Considerations (Regulatory and Ethical Considerations)	Added text on protocol clarification communications.	To account for potential use of a 'Protocol Clarification Communication.

Section Number and Name	Description of Change	Brief Rationale
10.9. Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments	• Appendix replaced with latest version with updated definition for Hy's Law • Section title was updated to remove ~~[and Study Intervention Rechallenge Guidelines]~~ • Stopping criteria and follow-up assessments added	• Update to align with current standards • Removal of not applicable language between brackets • Adding pages that were missing.
10.10. Appendix 10: Glucocorticoid Conversion Table	The value of betamethasone was changed from 0.6 to 0.75	Protocol clarification to promote consistency between sites
10.11. Appendix 11: Guidance on Study Conduct during the COVID-19 Pandemic	• Section was updated • Information on direct-to-patient shipments is removed • Information on exclusion criteria is removed.	• To align with the latest template • Direct-to-patients shipments is not applicable for the study • To avoid duplication, because COVID-19 exclusion criteria have been incorporated in protocol Section 5.2 with Protocol Amendment 2.
Throughout the protocol	Minor grammatical and formatting changes were made.	Minor errors were noted.

Amendment 2 (18 December 2020)

Overall Rationale for the Amendment: The primary driver for this amendment is to add clarifying language to Section 10.8, Appendix 8, Protocol Defined 26-Week Glucocorticoid Taper to allow for more flexibility to execute the protocol-defined 26-week steroid taper. This flexibility is needed to accommodate the use of tablet strengths other than 1 mg prednisone equivalent to achieve required doses if these tablets are not locally available. Other changes are made in response to feedback acquired from the Health Authorities (HA), Ethics Committees, and Investigators.

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis; 3. Objective and [Endpoints and/or Estimands]; 10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations (Source Documents)	Replaced 'Health-Related Quality of Life' by 'Clinical Outcome Assessments'.	To better describe the questionnaires performed in the study. To clarify that only the SF-36 falls under the definition of Health-Related Quality of Life and the other questionnaires are better described as 'Clinical Outcome Assessments.
9.4.4. Tertiary/Exploratory Endpoint(s)	Replaced 'Health-Related Quality of Life and Fatigue' by 'Clinical Outcome Assessments'.	
1.1. Synopsis (Statistical Methods); 9.3. Analysis Sets	Definition for Pharmacokinetic Analysis Set was updated.	To align with the standard definition in statistical analysis plan and for consistency within the protocol.
1.1. Synopsis; 9.4.1. General Considerations	Deleted 'nominal' and clarified that statistical tests will be performed at a 2-sided significance level. Added the terms 'secondary' to clarify that multiplicity adjustment will not be done for	Protocol clarification and update to align with statistical analysis plan.

Section Number and Name	Description of Change	Brief Rationale
	secondary endpoints and nominal p values will be reported.	
1.3. Schedule of Activities (SoA)	Updated footnote j to include direction for baseline use of fluorodeoxyglucose - positron emission tomography/computed tomography scan.	To provide clarification to align with inclusion criterion 4 and to avoid excess radiation exposure of participants.
1.3. Schedule of Activities (SoA)	Added footnote r: Recommended additional optional telephone contact with participant to verify correct tapering of steroid intake.	To increase compliance to protocol-defined taper.
2.1.1. Unmet Need in Giant Cell Arteritis	Split sentence and added the word 'often' in first sentence to 5th paragraph.	To accommodate an HA request for clarification.
2.2. Background	Update the number of participants exposed to guselkumab in the clinical development program.	To accommodate updates from the latest edition (edition 11) of Investigator's Brochure.
4.2. Scientific Rationale for Study Design	Indicated that the biomarker sample collection was restricted by local regulations.	To accommodate potential country specific restrictions for biomarker sample collection (such as samples for pharmacogenomic research).
5.1. Inclusion Criteria	Modified inclusion criterion 6 to accommodate update to criterion 4 from amendment 1.	Updated to provide clarification.
5.2. Exclusion Criteria	Modified exclusion criterion 22 to include "Within 3 months of first study intervention or at least 5 half-lives (whichever is greater)" for hydroxychloroquine, cyclosporine A, azathioprine, tacrolimus, sirolimus, sulfasalazine, leflunomide with cholestyramine washout or mycophenolate mofetil/mycophenolic acid.	To accommodate an HA request, safety measure, and protocol clarification, because wash-out period of 6 weeks may not always be sufficient.
6.8.2. Prohibited therapies	Added 'use of' and 'for GCA' to oral glucocorticoids (GCs).	Updated to provide clarification (limited use for other indications was not prohibited).
6.8.2. Prohibited therapies	Added 'until end of study" to intramuscular, intra-articular, intrabursal, epidural, intra-lesional, or IV GCs subsection.	Updated to provide clarification.
6.8.3. Rescue Medication	Languages changed from "the participant should continue" to "the participant may continue" plus added additional explanation on the follow-up procedures.	Updated to allow the investigator to decide whether a participant that has a flare should continue on study agent given there are alternative treatments other than GC such as tocilizumab. Additionally, updated to accommodate an HA request.
	Deleted the paragraph on the posttreatment phase.	To avoid duplication and because the paragraph should not be part of the Section 6.8.3. Rescue Medication.
7.1. Discontinuation of Study Intervention	Clarification of discontinuation criterion regarding TB: replacement of "is deemed ineligible" by "becomes ineligible".	To correct the language.
7.1. Discontinuation of Study Intervention; 10.2. Appendix 2: Clinical Laboratory Tests;	• Removed the liver function tests results that will lead to discontinuation but instead and refer only to the Section 10.9 which now contains both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) evaluations.	• To not duplicate criteria for treatment discontinuation that are presented and updated in Section 10.9 to avoid misinterpretation.

Section Number and Name	Description of Change	Brief Rationale
10.9. Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments [and Study Intervention Rechallenge Guidelines]	• Included the evaluation of AST in the note section of clinical chemistry. • The Algorithm was updated. Added footnote to Section 10.9 to clarify that in this trial the study intervention should be interrupted in case of ALT or AST ≥5× ULN and <8× ULN until a decrease in liver function test is noted or new results require to permanently discontinue treatment.	• To ensure consistency between Section 10.2 and 10.9 and align with liver function test related discontinuation criteria previously specified in Section 7.1. that were selected for this study. • Footnote was added to Section 10.9 to accommodate an HA request.
8.2.10. Hypersensitivity Reactions	Added the assessment criteria for potential cases of anaphylaxis guidance.	To accommodate an HA request.
8.2.10. Hypersensitivity Reactions	Added the guidance around the management of hypersensitivity reactions.	To accommodate an Ethics Committee request.
9.4.1. General Considerations	Deleted 'a generalized linear model with logit link for binary repeated measurement data and/or' for binary endpoint analysis.	To clarify that logistic regression will be used as sensitivity analysis for the primary endpoint only, and that the primary endpoint and major secondary endpoint will use Cochran-Mantel-Haenszel test.
9.4.5. Safety analysis	Definition of treatment emergent adverse event adjusted: "day of last dose plus 12 weeks" replaced by "end of the study".	To be aligned with the programmed definition of treatment emergent adverse events.
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 (Attribution Definitions)	Corrected definition of Not Related Adverse Events.	Updated to correct error in language.
10.8. Appendix 8: Protocol Defined 26-Week Glucocorticoid Taper	Additional language was added to provide flexibility to the taper regimen.	To accommodate tapering with tablets strength >1 mg if these are not available locally. Small variations in tapering regimen are not considered clinically relevant as long as steroid taper is gradual and reaches 0 in Week 26.
11. References	Added new literature references #23 and 35 (guidance document on the management of hypersensitivity reactions and anaphylaxis).	To support information added in Section 8.2.10.
Throughout the protocol	The word 'subject' was replaced by 'participant'.	To conform with the company standard naming convention.
	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 1 (09 July 2020)

Overall Rationale for the Amendment: The imaging requirements for confirmation of diagnosis (Inclusion Criterion #4) were expanded to increase the eligibility of sites to participate in this study. Next to temporal artery biopsy and doppler-ultrasound, imaging techniques using Magnetic Resonance (Magnetic Resonance Imaging and Magnetic Resonance Angiography) are allowed to confirm giant cell arteritis (GCA) diagnosis. In addition, the protocol has been updated with respect to the conditions and analyses of the fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT)-imaging, according to the imaging protocol and analyses plan that has become available after finalization of the initial protocol.

Section number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	PROs added to Week 44	PROs were inadvertently omitted at this timepoint.
1.3 Schedule of Activities	Additional serum sample for biomarkers added to visit Week 40 and extra sample for Whole blood (PAXgene) added to visit Week 8 and Week 40.	These timepoints have been identified as high interest for understanding of the disease and of mechanism of action of the compound.
2.3.1 Risks for Study Participation	Adjusted the estimated radiation dose and removed statement that CT scan will be limited to the torso.	More details on the exact PET/CT procedure have become available requiring an update of the protocol text.
5.1 Inclusion Criteria	Expanded acceptable imaging modality for inclusion criterion #4.	Allow additional imaging modalities that are readily available at sites as long as focus remains on cranial manifestations of GCA.
5.2 Exclusion Criteria	Reworded Exclusion criterion #21	To describe more clearly under which conditions certain previous therapies are not allowed. Changed based on feedback from sites.
8.9 Exploratory FDG-PET/CT Imaging	Removed the word ‘upper’	More details on the exact procedure have become available requiring an update of the protocol text.
8.9 Exploratory FDG-PET/CT Imaging	Changed wording on fasting condition	Clarification
9.4.6 Other Analyses	Adjusted procedure for exploratory FDG-PET/CT Imaging Analyses	More details on the exact procedure have become available requiring an update of the protocol text.
1.1 Synopsis 1.3 Schedule of Activities 8.4.1 Evaluations	Added text to clarify that pharmacokinetic (PK) sample should be drawn from a different line than the IV administration line	To prevent potential aberrant data due to sampling from the same line as the IV administration.
Appendix 10.2	Removed ‘HCV RNA (if applicable)’ template text	Not applicable in this study.
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: _____

(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	25-May-2022 17:02:29 (GMT)	Document Approval