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**A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel
Group Study to Evaluate the Efficacy and Safety of Sirukumab in the
Treatment of Patients with Giant Cell Arteritis**

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Statistical Analysis Plan

Version 1.0

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List of Abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below Limit of Quantification
CI	Confidence Interval
CRP	C-Reactive Protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CTX	Carboxyterminal Cross-Linked Telopeptide of Bone Collagen
DBL	Database Lock
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ESR	Erythrocyte Sedimentation Rate
EQ-5D-5L	EuroQoL – 5 dimensions, 5 levels
ESR	Erythrocyte Sedimentation Rate
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-fatigue
GCA	Giant Cell Arteritis
GEE	Generalized Estimating Equations
GSK	GlaxoSmithKline
HAQ-DI	Health Assessment Questionnaire – Disability Index
ICH E9	International Council for Harmonization Efficacy guideline 9
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IL	Interleukin
IP	Investigational Product
ITT	Intent-to-Treat
MACE	Major Adverse Cardiac Events

MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NRS	Numeric Rating Scale
P1NP	Procollagen Type 1 N-propeptide
PCI	Potential Clinical Importance
PCS	Physical Component Summary
PD	Pharmacodynamics
PGIC	Patient Global Impression of Change
PH	Proportional Hazards
PK	Pharmacokinetics
PMR	Polymyalgia Rheumatica
PP	Per Protocol
PT	Preferred Term
PhGA	Physician Global Assessment of disease activity
PtGA	Patient Global Assessment of disease activity
PRO	Patient-Reported Outcomes
q2w	Every 2 weeks
q4w	Every 4 weeks
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SIQ	Steroid Impact Questionnaire
SF-36v2	36-item Short Form health survey version 2
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TEAESI	Treatment-Emergent Adverse Event of Special Interest

US	Ultrasound
VAS	Visual Analogue Scale

1. Introduction

Sirukumab is a human anti-interleukin (IL)-6 immunoglobulin G1 (IgG1) kappa monoclonal antibody with a high affinity and specificity for binding to the human IL-6 molecule that is being developed for the treatment of giant cell arteritis (GCA).

Multiple lines of evidence support a role for IL-6 in the pathophysiology of GCA. Sirukumab may have therapeutic benefit in the treatment of GCA by interruption of multiple pathogenic pathways. The purpose of this study is to evaluate the efficacy and safety of sirukumab to characterize the benefit-to-risk profile of sirukumab in the treatment of active GCA.

This Statistical Analysis Plan (SAP) is based on the protocol version 3.0 dated of 17th November 2016. This SAP contains definitions of analysis sets, derived variables and statistical methods for the analyses of efficacy and safety endpoints.

[Section 4](#) to [Section 10](#) focus on Part A of this study. Specific derivations for Part B will be presented in [Section 11](#).

1.1. Changes in the Planned Analysis due to Study Termination

This SAP reflects the analyses done given study termination, and are not aligned with planned analyses as per protocol.

Due to the sponsor's decision to terminate the study, data for the following endpoints/objectives are not available. Therefore, the following objectives will not be reported in this planned analysis:

- Pharmacokinetic objectives
- Immunogenicity objectives
- Pharmacodynamic objectives
- Pharmacogenetics objectives
- Vascular ultrasound objectives

Additionally:

- Available data for exploratory objectives / endpoints related to biomarkers will only be listed.
- No statistical analysis will be carried out for efficacy objectives / endpoints due to the limited number of subjects completing the study at week 52.
- However, [Section 2.1](#) and [Section 3.2](#) list respectively objectives and endpoints as specified in the protocol.
- Protocol endpoint "Median and cumulative prednisone dose over time" is modified to "Cumulative prednisone dose over time" as median prednisone dose will be provided as part of the summary statistics for cumulative prednisone dose.
- Protocol wording "GCA flare" is modified to "disease flare" for consistency across endpoints in this document.

Due to study termination on 10th October 2017, early withdrawal visits were completed for all subjects by 30th November 2017. All subjects are required to have a safety follow-up visit 16 weeks (+/- 1 week) after the early withdrawal visit. The study should be terminated for an individual subject after they have completed the 16-week safety follow-up visit, unless there is a need for additional post-study visits for continued evaluation of an ongoing adverse event. However, if an anti-IL6, any biologic or investigational agent is initiated, the subject will be withdrawn from the 16-week safety follow up.

To facilitate patient management, treatment codes for the blinded prednisone study drug will be broken and provided to the investigator at the Early Withdrawal Visit, when occurring after sponsor's decision to terminate the study. Treatment codes for the subcutaneous investigational product (sirukumab or placebo) will be unblinded at the end of the study, after database lock. However, unblinding for the subcutaneous investigational product can be requested for individual subjects at any time for safety management. In addition, CRP value from the Early Withdrawal Visit will be provided to the investigator to facilitate subject management.

2. Objectives

Due to the sponsor's decision to terminate the study and the data not being available, the endpoints for the following objectives will not be reported in this planned analysis:

- Pharmacokinetic objectives
- Immunogenicity objectives
- Pharmacodynamic objectives
- Pharmacogenetics objectives
- Vascular ultrasound objectives: Even though 3 subjects were randomized to the US imaging portion of the study, only one patient passed the Week 12 visit. There was no sufficient data collected to perform any analysis, so no data for this cohort of subjects will be reported.

The pharmacokinetic, immunogenicity, pharmacodynamic (IL-6) and pharmacogenetics samples will not be analyzed, therefore there will be no data related to these endpoints and these objectives that can be reported.

However, [Section 2.1](#) and [Section 2.2](#) lists objectives as specified in the protocol.

2.1. Part A: 52-Week Double-Blind Treatment Phase Objectives

2.1.1. Primary Objective

The primary objective of this study is to investigate the efficacy of sirukumab (100 mg every 2 weeks [q2w] for 12 months) as compared to placebo, each administered in addition to a 6-month prednisone treatment regimen in the 52-week double-blind treatment phase (Part A), i.e. Arm A vs. Arm D as per [Table 2](#).

2.1.2. Secondary Objectives

The secondary efficacy endpoints of this study are:

To assess cumulative prednisone doses in subjects treated with sirukumab plus prednisone as compared to placebo plus prednisone

To investigate the efficacy of:

1. Sirukumab (100 mg q2w for 12 months) administered with a 3-month prednisone treatment regimen versus placebo administered with a 6-month prednisone treatment regimen, i.e. Arm B vs. Arm D as per [Table 2](#).
2. Sirukumab (100 mg q2w for 12 months) administered with a 6-month prednisone treatment regimen as compared to placebo administered with a 12-month prednisone treatment regimen (standard of care), i.e. Arm A vs. Arm E as per [Table 2](#).
3. Sirukumab (100 mg q2w for 12 months) administered with a 3-month prednisone treatment regimen versus placebo administered with a 12-month prednisone treatment regimen, i.e. Arm B vs. Arm E as per [Table 2](#).
4. Sirukumab (50 mg every 4 weeks [q4w] for 12 months) as compared to placebo, each administered in addition to a 6-month prednisone treatment regimen, i.e. Arm C vs. Arm D as per [Table 2](#). Sirukumab (50 mg q4w for 12 months) administered with a 6-month prednisone treatment regimen as compared to placebo administered with a 12-month prednisone treatment regimen, i.e. Arm C vs. Arm E as per [Table 2](#).

To characterize sustained remission over time

To characterize disease flare over time

To assess the effect of sirukumab treatment on health-related quality of life, GCA and steroid-related symptoms and disability by patient and physician reported outcomes over time

To characterize changes in biomarkers of disease activity.

2.1.2.1. Safety Objectives

To evaluate the safety of sirukumab plus prednisone treatment compared to placebo plus prednisone treatment

To investigate corticosteroid-related toxicities.

2.1.2.2. Pharmacokinetic/Immunogenicity Objectives

To investigate the pharmacokinetics of subcutaneously administered sirukumab

To evaluate the immunogenicity of subcutaneously administered sirukumab

2.1.2.3. Pharmacodynamic Objectives

To characterize the effect of sirukumab on IL-6 levels in the blood.

2.1.2.4. Exploratory Objectives

To explore the effect of sirukumab on exploratory biomarkers of Th1 and Th17 cell function

To evaluate the effect of sirukumab on exploratory biomarkers of bone metabolism

To explore the utility of vascular ultrasound (US) imaging assessment of inflammation in temporal and axillary arteries as an indicator of disease activity in a cohort of study subjects

To explore the predictive value of US for clinical efficacy in GCA.

2.1.2.5. Pharmacogenetic Objectives

To potentially explore relationships between genetic variants and sirukumab efficacy and safety endpoints.

2.2. Part B: 104-Week Long-Term Extension Phase Objectives

The objectives for Part B, the 104 week long-term extension phase are:

To evaluate the long-term maintenance of disease remission on cessation of 12 months of sirukumab treatment

To assess the effect of sirukumab treatment on health-related quality of life, GCA and/or steroid-related symptoms and disability by patient and clinician reported outcomes over time

To assess the long-term cumulative prednisone doses

To assess the long-term safety of sirukumab

To investigate long-term corticosteroid-related toxicities

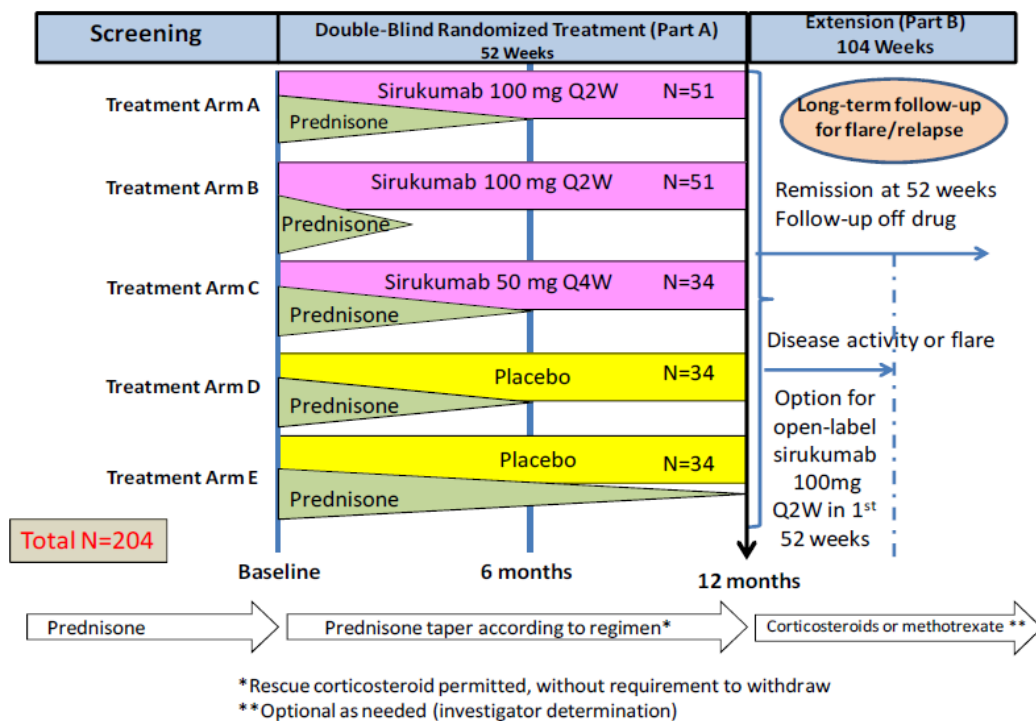
To evaluate the immunogenicity of subcutaneously administered sirukumab in subjects receiving open-label sirukumab.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of 2 doses of sirukumab in the treatment of GCA. The study design is summarized in [Figure 1](#).

Figure 1 Study Design



q2w=every 2 weeks; q4w=every 4 weeks

The study will be conducted in 2 distinct parts (Part A and Part B) and consists of the following phases:

- A screening phase of up to 6 weeks in duration.
- Part A: A 52-week double-blind treatment phase to establish the efficacy and safety of sirukumab in the treatment of GCA.
- Part B: A 104-week long-term extension phase with the option to receive open-label sirukumab (up to a 52-week duration of open-label treatment) for subjects with active disease at the end of Part A, subjects who have not been able to follow the prednisone taper during Part A, or those who newly flare during the first 52 weeks of Part B.
- An up to 16-week follow-up phase to ensure that all subjects are evaluated for safety at least 16 weeks after receiving the last dose of study drug. This will apply to subjects who are withdrawn prematurely from the study or whose open-label treatment with sirukumab in Part B will complete after Week 88. The duration of the follow-up may vary depending on the time point when the last dose of study drug is taken. Only subjects who complete their sirukumab treatment at Week 104 will require the full 16-week follow-up period.

The maximum duration of subject participation (including screening) is 178 weeks. Completion of Part A is defined as completion of the 52 weeks of double-blind treatment. Completion of Part B is defined as completion of the 104 weeks of the extension phase. Completion of the study is

defined as completion of both Parts A and B of the study and/or completion of the up to 16-week follow-up phase if applicable.

The study population will be comprised of approximately 204 subjects with a diagnosis of GCA based on the Revised GCA Diagnosis Criteria. Both new onset (diagnosis within 6 weeks of Baseline) and relapsing/refractory (established diagnosis greater than 6 weeks prior to Baseline with disease activity within 6 weeks of Baseline) GCA subjects will be eligible.

Eligible subjects will be required to have active disease within 6 weeks prior to the Randomization (Baseline) visit. Active disease is defined as the presence of unequivocal clinical signs and symptoms attributable to GCA and an erythrocyte sedimentation rate (ESR) ≥ 30 mm/hr and/or serum C-reactive protein (CRP) ≥ 1 mg/dL (10 mg/L).

For more details on the schedule of assessments, please refer to [Section 13.1](#).

3.2. Study Endpoints

Due to the sponsors decision to terminate the study and the data not being available the following endpoints will not be reported in this planned analysis:

- Pharmacokinetic endpoints
- Immunogenicity endpoints
- Pharmacodynamic endpoints
- Pharmacogenetics endpoints
- Vascular ultrasound endpoints: Even though 3 subjects were randomized to the US imaging portion of the study, only one patient passed the Week 12 visit. There was no sufficient data collected to perform any analysis, so no data for this cohort of subjects will be reported.

The pharmacokinetic, immunogenicity, pharmacodynamic (IL-6) and pharmacogenetics samples will not be analyzed, therefore there will be no data related to these endpoints and these objectives that can be reported.

Additionally:

- All available data for exploratory endpoints related to biomarkers such as IFN- γ , CTX1 and PINP will only be listed.
- No statistical analysis will be carried out for efficacy endpoints due to the limited number of subjects completing the study at Week 52.

However, [Section 3.2.1](#) and [Section 3.2.2](#) list endpoints as specified in the protocol.

3.2.1. Study Endpoints for Part A

3.2.1.1. Primary Efficacy Endpoint

The primary endpoint of this study is the proportion of subjects in sustained remission at Week 52, defined as having achieved all of the following:

1. Remission at Week 12, where remission is defined as:

- a. Clinical remission at Week 12, defined as absence of signs and symptoms of GCA and
 - b. Normalization of ESR [$<30\text{mm/hr}$] and CRP [$<1\text{mg/dL}$]
- AND**
2. Absence of disease flare following remission at Week 12 through Week 52, where disease flare defined as recurrence of symptoms attributable to active GCA, with or without elevations in ESR and/or CRP
- AND**
3. Completion of the assigned prednisone taper protocol
- AND**
4. No requirement for rescue therapy at any time through Week 52

3.2.1.2. Secondary Efficacy Endpoints

- Cumulative prednisone dose over time
 - Proportion of subjects in sustained remission at each time point of assessment from Week 12 to Week 52, where sustained remission is defined as having achieved all of the following at each visit:
 1. Remission at Week 12:
 - a. Clinical remission at Week 12, defined as absence of signs and symptoms of GCA
And
 - b. Normalization of ESR [$<30\text{mm/hr}$] and CRP [$<1\text{mg/dL}$]
- AND**
2. Absence of disease flare following remission at Week 12 through Week X, disease flare defined as recurrence of symptoms attributable to active GCA, with or without elevations in ESR and/or CRP
- AND**
3. Adherence to the assigned prednisone taper protocol through Week X,
- AND**
4. No requirement for rescue therapy at any time through Week X
- Time to first disease flare after clinical remission
 - Number of disease flares per subject over time
 - Proportion of subjects requiring hospitalizations for disease flare and number of hospitalizations for disease flare over time
 - Patient-reported outcomes (PRO) including 36-item Short Form health survey version 2 (SF-36 v2) acute, EuroQol – 5 dimensions, 5 levels (EQ-5D-5L), Functional Assessment of Chronic Illness Therapy-fatigue (FACIT-Fatigue), Pain Numeric Rating Scale (NRS), Steroid Impact Questionnaire, Health Assessment Questionnaire – Disability Index (HAQ-DI), Patient Global Impression of Change (PGIC), Patient Global Assessment of disease activity (PtGA)

- Clinician-reported outcomes: Physician Global Assessment of disease activity (PhGA)
- Change from Baseline in ESR over time
- Change from Baseline in serum CRP over time

3.2.1.3. Safety Endpoints

- Incidence of adverse events (AEs) and serious AEs (SAEs), incidence of corticosteroid-related AEs, changes in vital signs, hematology and clinical chemistry parameters

3.2.1.4. Pharmacokinetic / Immunogenicity Endpoints

- Serum concentrations of sirukumab
- Serum anti-sirukumab antibodies

3.2.1.5. Pharmacodynamic Endpoints

- Change from Baseline in free and total IL-6 over time

3.2.1.6. Exploratory Endpoints

- Change from Baseline in interferon (IFN)- γ and IL-17A
- Change from Baseline in serum markers of bone formation/resorption: carboxyterminal cross-linked telopeptide of bone collagen (CTX)1/procollagen type 1 N-propeptide (P1NP)
- Change over time in measurements of vascular inflammation in temporal and axillary arteries
- Correlation of clinical endpoints with changes in vascular inflammation.
- Correlation of changes in vascular inflammation on US with clinical activity, CRP and ESR
- Correlation of changes in vascular inflammation on US with health-related quality of life outcomes

3.2.1.7. Pharmacogenetic Endpoints

- Correlation of genetic markers with the safety and efficacy response to sirukumab. This endpoint will not be addressed in this document

3.2.2. Study Endpoints for Part B

- Proportion of subjects who remained in sustained remission without requirement for rescue therapy or treatment change at Week 24 of Part B
- Proportion of subjects in sustained remission over time
- Time to first disease flare for subjects in sustained remission at Baseline of Part B
- Number of disease flares per subject over time
- Proportion of subjects requiring hospitalizations for disease flare and number of hospitalizations for disease flare over time

- Proportion of subjects who remained in sustained remission without requirement for rescue therapy or treatment change 6 months after cessation of 12-month sirukumab treatment
- Patient-reported outcomes including SF-36v2 acute, EQ-5D (5L), FACIT-Fatigue, Pain NRS, Steroid Impact Questionnaire, HAQ-DI and PtGA
- Clinician reported outcomes including PhGA
- Cumulative prednisone dose over time
- Incidence of AE and SAEs, and changes in vital signs and hematology and clinical chemistry parameters
- Incidence of corticosteroid-related AEs
- Evaluation of serum anti-sirukumab antibodies

3.3. Treatments

Two doses of sirukumab (100 mg subcutaneous [SC] q2w and 50 mg SC q4w) were selected based on doses which have demonstrated efficacy in a Phase II study of rheumatoid arthritis subjects and are presently under investigation in Phase III studies for the treatment of moderate to severe rheumatoid arthritis. The 100 mg SC q2w dose of sirukumab has shown numerical superiority at 24 weeks in some efficacy endpoints (American College of Rheumatology criterion ACR20, change in disease activity score) over other sirukumab doses tested in the Phase II study and may be more likely to provide a clinically meaningful response in an IL-6– mediated disease such as GCA. The 50 mg q4w dose of sirukumab will also be evaluated to more fully characterize the benefit-to-risk profile of sirukumab in GCA.

Following the screening period, eligible subjects will be randomized to receive sirukumab (100 mg SC q2w or 50 mg SC q4w) or matching placebo. All subjects will receive prednisone during the 52-week double-blind treatment period according to a pre-specified taper regimen.

Table 1 Investigational Product and Other Study Treatment

Product name	Study Treatment		
	Sirukumab	Placebo	Prednisone/ prednisone placebo
Dosage form	1.0 mL prefilled syringe	1.0 mL prefilled syringe	Tablets
Unit dose strength(s) / dose level(s)	100 mg/mL or 50 mg/mL	--	Up to-60 mg/day
Route of administration	SC	SC	Oral
Dosing instructions	SC q2w (treatment arms A & B) SC q4w (treatment arm C)	SC q2w (treatment arms D & E)	20-60 mg/day open-label, then 0-18 mg/day taper (blinded)

SC=subcutaneous; q2w=every 2 weeks; q4w=every 4 weeks.

Note subjects randomized to treatment arm C will alternate between sirukumab 50 mg SC and matching placebo SC injections in order to maintain the blind.

In Part A, eligible subjects will be randomized in a ratio of 3:3:2:2:2 to one of the 5 treatment arms described in [Table 2](#). The treatment descriptors and column headings in [Table 2](#) will be used in all data displays.

Table 2 Treatment Descriptors and Column Headings for Part A

Treatment Group	Treatment Descriptor	Column Header
Arm A	Sirukumab 100 mg SC q2w for 52 weeks plus a prespecified maximum of 6-month prednisone taper regimen	Sirukumab 100mg SC q2w + 6 month prednisone
Arm B	Sirukumab 100 mg SC q2w for 52 weeks plus a prespecified maximum of 3-month prednisone taper regimen	Sirukumab 100mg SC q2w + 3 month prednisone
Arm C	Sirukumab 50 mg SC q4w for 52-weeks plus a prespecified maximum of 6-month prednisone taper regimen	Sirukumab 50mg SC q4w + 6 month prednisone
Arm D	Placebo SC q2w for 52 weeks plus a prespecified maximum of 6-month prednisone taper regimen	Placebo SC q2w + 6 month prednisone
Arm E	Placebo SC q2w for 52 weeks plus a prespecified maximum of 12-month prednisone taper regimen	Placebo SC q2w + 12 month prednisone

It is important to note that prednisone intake will be recorded from different sources:

- Prednisone taken prior to screening: recorded on the “Prior Concomitant Medications - (Screening)” eCRF page

- Prednisone taken as part of the pre-specified taper (prednisone study drug):
 - Open-label portion – recorded in “Prednisone - Open Label” eCRF page
 - Blinded portion – recorded in “Prednisone - Blinded Taper” eCRF page
- Concomitant Prednisone – recorded on the “Concomitant Medications – Corticosteroids” eCRF page.

For more details, please refer to [Section 7](#).

Two types of rescue medication can be identified:

- Those from the “Concomitant Medications – Non Corticosteroids” eCRF page when the questions regarding Rescue Medication is ticked as "Yes" and the drug identified as GCA-related
- Those from the “Concomitant Medications – Corticosteroids” eCRF page when the question regarding Rescue Medication is ticked as "Yes" and the unit is not:
 - Actuation
 - Application
 - Area under curve
 - Cubic centimeter
 - Cells
 - Cells per kilogram
 - Fingertip unit
 - Drops
 - Gum
 - Inhalation
 - Kilocalories
 - Minimum alveolar concentration
 - Mega becquerels (MBq)
 - Millicurie
 - Nebule
 - Patch
 - Powder
 - Puff
 - Ring
 - Spray
 - Suppository

All subjects will be receiving background prednisone therapy. Subjects with relapsing/refractory GCA will have active disease despite previous or concurrent steroid therapy. Prednisone treatment must be initiated at Screening for subjects not currently receiving steroid treatment. Subjects should be reminded to discontinue any other prednisone or corticosteroid treatment and take only the prednisone study treatment. The prednisone dose for all subjects at Screening will be determined by the investigator and may be adjusted in an open manner based on the subject’s disease status per investigator discretion. An increase in prednisone dose may be required for some subjects currently receiving therapy to stabilize their disease activity prior to randomization. Investigators may consider if higher doses of prednisone are warranted for subjects with visual manifestations. All subjects must be receiving prednisone (a minimum dose of 20 mg/day) at the start of Screening. Prednisone treatment must be initiated at Screening for subjects not currently

receiving steroid treatment. At Baseline (Randomization), prednisone doses must be within 20-60 mg for the starting dose when the prespecified prednisone taper is initiated. The prespecified prednisone tapering schedule is outlined in [Table 3](#).

The standardized prednisone taper regimen will be open-label with identical weekly decreases in dose according to the starting dose for all subjects, until subjects reach a dose of 20 mg/day. Thereafter, prednisone dosing will be blinded to allow the pre-specified differences in tapering. Requirements for the prednisone taper are as follows:

- Subjects will remain on the prednisone dose they are currently receiving at Baseline (Week 0) for one week.
- At Week 1, the prednisone dose will be decreased in accordance with the prespecified prednisone taper schedule ([Table 3](#)).
- The pre-specified maximum tapering schedule to be followed will depend on the subject's treatment group assignment.
- The prednisone taper will be unblinded initially (open-label) and will consist of identical weekly decreases in dose for all subjects until a dose of 20 mg/day is reached, at which point the blinded portion of the prednisone tapering regimen will commence.
- Subjects who are receiving a prednisone dose of 20 mg/day at Baseline (Week 0) should continue taking the open-label 20 mg daily dose for one week. At Week 1, these subjects will initiate the blinded taper regimen.

Subjects unable to follow the prednisone taper due to disease flare, adrenal insufficiency, or safety reasons will cease the blinded prednisone treatment and will be offered treatment with an investigator-defined, open-label corticosteroid rescue regimen in combination with double-blind injections of sirukumab or placebo for the full 52 weeks, without a requirement to withdraw from the study. This study has been designed to allow subjects who are unable to follow the prednisone taper to continue in the study and follow the assessments at each visit as specified in the protocol.

When considering use of rescue prednisone, investigators should carefully assess whether the symptoms are related to an inflammatory GCA flare which would signify failure of tapering or is more likely due to non-inflammatory symptoms which could represent adrenal insufficiency or other co-morbidities.

All subjects who complete Part A of the study will be eligible to enter Part B. The 2 populations of subjects expected to enter into Part B are:

- Subjects in remission at the primary 52-week endpoint. These subjects will discontinue the blinded study drug treatment on entry into Part B and will be followed for maintenance of response. However, in the event of a disease flare, they will have the option to receive, at the discretion of the investigator, open-label sirukumab 100 mg SC q2w for a maximum of 52 weeks during the first 52 weeks of Part B.
- Subjects not in remission, at the primary 52-week endpoint, or subjects who have not been able to taper prednisone during Part A. Upon entry into Part B, these subjects will have the option to receive, at the discretion of the investigator, open-label sirukumab 100 mg SC q2w for a maximum of 52 weeks.

For subjects who newly flare at any time during the first 52 weeks of Part B and require a treatment change, open-label sirukumab 100 mg SC q2w can be initiated within the first 52 weeks of Part B. The duration of treatment will be at the discretion of the investigator but must not exceed 52 weeks.

Treatment with open-label sirukumab 100 mg SC q2w must complete by Week 104 (the end of the extension phase). Corticosteroid use or the initiation of methotrexate therapy alone or in addition to sirukumab treatment during Part B will be at the discretion of the investigator.

Investigators should carefully consider the individual benefit-risk of continuing sirukumab in those subjects who continue to experience flares or persistent disease activity following the start of open-label treatment.

Upon study completion, decisions on treatment options for individual subjects will be at the discretion of the investigator.

Table 3 Prednisone Taper

	Up to 3 Months	Up to 6 Months	Up to 12 Months
Open-Label taper	60	60	60
	50	50	50
	40	40	40
	35	35	35
	30	30	30
	25	25	25
	20	20	20
Blinded taper	15	15	18
	10	13	17
	5	12	15
	3	10	15
	1	9	13
	0	8	10
	0	7	10
	0	6	10
	0	6	10
	0	5	9
	0	5	9
	0	4	9
	0	4	9
	0	3	8
	0	3	8
	0	2	8
	0	2	8
	0	1	7
	0	1	7
	0	0	7
	0	0	7
	0	0	6
	0	0	6
	0	0	6
	0	0	6
	0	0	5
	0	0	5
	0	0	5
	0	0	5
	0	0	4
	0	0	4
	0	0	4
	0	0	4
	0	0	3
	0	0	3

	Up to 3 Months	Up to 6 Months	Up to 12 Months
	0	0	3
	0	0	3
	0	0	2
	0	0	2
	0	0	2
	0	0	2
	0	0	1
	0	0	1
	0	0	1
	0	0	1

Note: Individual subjects will be receiving differing doses of prednisone at specified time points. Therefore, the tapering schedule indicates the required decrease in prednisone dose on a weekly basis, with the specific week varying by individual subject.

3.4. Dose Adjustment/Modifications

No dose adjustment of sirukumab will be allowed in this study.

4. General Statistical Considerations

All analyses detailed in this SAP will be conducted using Statistical Analysis System (SAS)[®] statistical analysis software version 9.3 or higher (SAS Institute, Inc., Cary, North Carolina, USA). All SAS programs used to generate analytical results will be developed and validated according to PPD SAS programming standards and validation procedures.

Summary data will be presented in tabular format by treatment. Continuous variables will be summarized by descriptive statistics including number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum.

Mean and median will be displayed to 1 more decimal place than the measured value. The SD will be displayed to 2 more decimal places than the measured value. Minimum and maximum will be displayed to the same decimal place as the measured value.

Categorical data (such as sex) will be summarized by number and percentage of subjects in each category. Percentages will be suppressed when the count is zero. A row denoted “Missing” will be included in count tabulations where necessary to account for missing values. The denominator for all percentages will be the number of subjects within the treatment (randomized or actual) group for the analysis set of interest, unless otherwise specified. Percentages which differ from 100% will be presented to 1 decimal place and 100% will be presented without a decimal.

Change from Baseline is the post-baseline value minus the baseline value. If the baseline or post-baseline value is missing, then the change from baseline is set to missing. For each scheduled post-baseline time point where change from Baseline is evaluated for continuous variables, descriptive statistics will be displayed for the values at Baseline, values at the scheduled post-baseline time point, and values for change from Baseline at the scheduled post-baseline time point for the set of subjects who have data at both Baseline and the time point being assessed. Early withdrawal visits as well as 16-week follow-up visits are considered as scheduled visits.

In case of multiple assessments for a scheduled visit, the last non missing assessment for this visit will be used for the summaries over time. All results will be listed.

Data will be displayed in all listings sorted by treatment (randomized or actual depending on the analysis set of interest) group and then subject number and visit, if applicable. In cases where more ordering is required, other variables will be included in the sort order as applicable. Subjects will be identified in the listings by the subject identification number concatenated with the investigator number. Any repeat or additional assessments performed will be included in the individual subject data listings.

For outputs displaying duration in weeks, a week will equal 7 days. For outputs displaying duration in months, a month will be defined as $(365.25/12) = 30.4375$ days, which is not equal to 4 weeks.

4.1. Sample Size

The sample size has been calculated assuming a 30% sustained remission rate on the placebo plus 6-month prednisone arms versus a 70% rate on the sirukumab plus 6-month prednisone arms at Week 52. To be able to detect that difference using a 5% significance level, the sample size of N=51 on sirukumab 100 mg SC q2w, N=34 on sirukumab 50 mg SC q4w, and N=34 on placebo when used in combination with a 6-month prednisone taper has > 91% power.

The study is also powered to detect a statistically significant difference between sirukumab 100 mg SC q2w plus 3-month prednisone (Arm B) and placebo SC q2w plus 6-month prednisone (Arm D) only if the assumptions for 6-month prednisone taper apply to the 3-month prednisone taper (i.e. 70% sustained remission rate at Week 52).

Subjects will be assigned to study treatment arms using an allocation ratio of 3:3:2:2:2. The randomization will be stratified by Baseline oral prednisone dose (<30 mg/day or ≥30 mg/day).

A sample size sensitivity analysis was performed to assess the effect on power if the sirukumab plus 6-month prednisone response rate was lower than expected at 65%, 60%, or 55%.

Table 4 Sample Size Sensitivity Analysis

Response Rate Sirukumab 100 mg + 6-Month Prednisone	Difference Active-Placebo	N Placebo +6- Month Prednisone	N Sirukumab 100mg + 6-Month Prednisone	Power
70%	40%	34	51	96%
65%	35%	34	51	89%
60%	30%	34	51	79%
55%	25%	34	51	64%

Assuming a placebo response rate of 30%, the target sample size of 34 for placebo SC q2w plus 6-month prednisone and 51 for sirukumab 100 mg SC q2w plus 6 month prednisone, a treatment difference larger than 21% will achieve statistical significance at the alpha=0.05 level.

No sample size re-estimation will be performed.

Given study termination, actual sample size will be the number of randomized subjects at study termination.

4.2. Randomization, Stratification and Blinding

Central randomization will be implemented in this study. Subjects will be randomized in a ratio of 3:3:2:2:2 and assigned to 1 of 5 treatment arms in accordance with the computer-generated randomization schedule generated prior to the start of the study, using validated software. Randomization will be performed by an Interactive Response Technology System. Once a randomization number has been assigned to a subject, it will not be re-assigned.

Randomization will be stratified by baseline oral prednisone dose (<30 mg/day or ≥ 30 mg/day). The number of relapsing/refractory subjects will be capped at approximately 50% to ensure that a sufficient number of subjects with new onset disease are recruited.

Blinding will be maintained during the 52-week double-blind treatment phase of this study by the provision of sirukumab and matching placebo for sirukumab in prefilled syringes in a matching presentation. Blinding to the prednisone dose during the taper will be maintained by providing prednisone doses below 20 mg in numbered blister packs. Depending on the subject's assignment to either the 3-, 6-, or 12-month taper, the over-encapsulated dose may or may not contain prednisone. The blister packs contain a combination of over-encapsulated 10 mg, 5 mg, and/or 1 mg prednisone tablets with cellulose filler to prevent rattling and/or placebo capsules containing only the filler. Each subject, regardless of treatment arm, will be provided the same number of capsules per day for a given week to maintain the blind.

Blinding during the q4w dosing regimen will be maintained by the provision of placebo for sirukumab such that subjects randomized to this arm will follow a q2w dosing regimen but alternate between active (starting at Baseline) and placebo treatments for the duration of the 52-week, double-blind phase.

Investigators and the sponsor/study team will remain blinded to the results of the fasting lipids, CRP and ESR laboratory tests after the start of treatment. Investigators and the study team will have access to Screening and Baseline values, and will thereafter remain blinded to these results until the end of Part A. Alerts will be provided by the central laboratory for abnormal, clinically significant findings to enable investigators to manage subject safety. Since the ESR is measured at the site, an unblinded assessor at the local laboratory will report the ESR results. The investigator will be notified of the value of the ESR result when an ESR result is >40 mm/hr in order to determine if a treatment change is warranted. Investigators are advised to consider these notifications of an elevated ESR which has reached the alert value as an additional element in the determination of whether a subject is experiencing GCA disease flare. An elevated ESR in isolation should not be the sole basis for investigator assessment of disease flare, particularly in the absence of clinical symptoms (e.g. cranial or polymyalgia rheumatic [PMR]) suggestive of disease activity.

Due to the sponsor's decision to terminate the study, to facilitate patient management, treatment codes for the blinded prednisone study drug will be broken and provided to the investigator at the Early Withdrawal Visit, when occurring after sponsor's decision to terminate the study. Treatment codes for the subcutaneous investigational product (sirukumab or placebo) will be unblinded at the end of the study, after database lock. However, unblinding for the subcutaneous investigational product can be requested for individual subjects at any time for safety management. In addition, CRP value from the Early Withdrawal Visit will be provided to the investigator to facilitate subject management.

4.3. Analysis Set

The following analysis sets will be used for Part A summaries. Part B analysis sets are defined in [Section 11.1](#).

4.3.1. All Subjects Screened

The All Subjects Screened Set will consist of all the subjects who have been screened for enrollment in the study regardless of whether they were enrolled into the study. This set will be used for summarizing reasons for screen failures.

4.3.2. Randomized

The Randomized set will consist of all subjects who meet study criteria and are randomly assigned to treatment in the study. In the event that there is a discrepancy, all subjects in the Randomized set will be analyzed according to the treatment they were randomized to receive and not according to what they actually received. The Randomized set will be used for summarizing the study, such as subject disposition.

4.3.3. Intent-to-Treat

The Intent-to-Treat (ITT) set will include all randomized subjects who received at least 1 dose of SC investigational product (IP). In the event that there is a discrepancy, all subjects in the ITT set will be analyzed according to the treatment they were randomized to receive and not according to what they actually received. The ITT set will be used for the primary efficacy analysis and all other efficacy endpoints.

4.3.4. Safety

The Safety set will include all randomized subjects who received at least 1 dose of SC IP. All subjects in the Safety set will be analyzed according to the treatment actually received and not according to the treatment they were randomized to receive, in the event there is a discrepancy. The Safety set will be used to analyze all of the safety endpoints.

4.4. Analysis Visits

Data will be presented and analyzed according to the visit recorded in the database. For other efficacy and safety data that visit are entered, no visit windows will be defined as sites should have case report form (eCRF) instructions and training to ensure reasonable data entry. If a visit happens outside the protocol-defined window (Week X \pm 3 days), one of the following will be occur:

- If it is recorded as Week X visit, no visit re-mapping will be done (except for PRO endpoints and Part B visits) and the recorded visit will be used in all analysis.
- If it is recorded as unscheduled visit, it will be treated as unscheduled visit.

In general, only those assessments which are assigned to an analysis visit will be included in the summary tables and figures and will be presented by visit. Unscheduled visits will not be included in summary tables or figures, with the following exceptions: if the table or figure includes data values for all post-baseline assessments (worst/best/maximum/minimum post-baseline assessments), or for tables which report the values during a period of time, unscheduled visits will be included. All unscheduled visits will be included in the listings.

When reporting results or events that are reported on an ongoing basis, such as cumulative prednisone dose or flare at Week X: All results/events will be taken into account that occur inclusively between the day after the Week X-1 visit and the day of the Week X visit. The actual day of the Week X visit will always be taken into account as the day of visit X, even if the actual visit occurred outside of planned visit window.

4.5. Definition of Baseline Value and Study Day

Baseline for Part A is defined as the last non-missing evaluation, including screening, re-screening and unscheduled assessments, prior to first SC IP, unless otherwise specified.

For assessments prior to the first SC IP date, the study day will be calculated as:

$$\text{Assessment date} - \text{First SC IP date}$$

For assessments on or after the first SC IP date, the study day relative to the Part A first SC IP date (i.e. the number of days from first dose date) will be calculated as:

$$\text{Assessment date} - \text{First SC IP date} + 1 \text{ day}$$

If the assessment date is completely missing or partial, the study day will be missing.

4.6. Handling of Missing Data

4.6.1. Treatment Failure Definition

For the primary endpoint derivation, a treatment failure is defined as any subject who:

1. Discontinued permanently SC IP prior to completing week 52 visit due to any reason and continued in the study (i.e. follow-up off treatment)
- or
2. Withdrew from the study for any reason earlier than 10th October 2017, the study termination date.

A subject will be considered a treatment failure from the earliest date that the subject meets any of the 2 treatment failure criteria. Only withdrawals prior to 10th October 2017 will be considered, withdrawals on or after this date will likely be result of study termination at sponsor's request and not provide an accurate summary of treatment response.

A subject that temporarily has their treatment of SC IP put on hold, will not be considered as permanent discontinuations.

4.6.2. Sustained Remission

4.6.2.1. Main Analysis

The following procedures will be used to handle missing data for derivation of sustained remission (i.e. endpoints mentioned in [Section 8.1](#) and [Section 8.2.2](#)):

1. Any subject who is classified as a treatment failure (as per definition of [Section 4.6.1](#)) will be considered as not achieving sustained remission for the primary efficacy analysis and the supportive analyses of the primary efficacy endpoint.

2. Subjects with all four of the components of the primary endpoint missing at two consecutive scheduled visits will be considered as not achieving sustained remission for these two visits.
3. Subjects with all the components missing at Week X ($X \neq 52$) visit will be considered as achieving sustained remission at Week X visit if achieving sustained remission at the neighboring visits; as not achieving sustained remission otherwise. Data recorded at unscheduled visits will be taken into account based on the unscheduled visit date and will be associated with the next scheduled visit occurring after the unscheduled visit date.
4. Subjects with at least one of the four components of the primary endpoint missing at Week 52 visit will be considered as not achieving sustained remission at Week 52 visit.
5. When only a subset of the components is missing at Week X visit, the rules will be applied to the components first and then the imputed components are used to impute the values at post-baseline values. Similar rules as for complete missing visits are applied:
 - a. Subjects with some components missing at 2 consecutive visits will be considered as not achieving sustained remission for the missing components at these 2 visits.
 - b. Subjects with some components missing at Week X ($X \neq 52$) visit will be considered as achieving sustained remission for the missing components at Week X visit if achieving sustained remission at the neighboring visits; as not achieving sustained remission otherwise
 - c. Subjects with some components missing at the Week 52 visit will be considered as not achieving sustained remission for the missing components at the Week 52 visit.

4.6.3. Cumulative Prednisone Dose over Time

4.6.3.1. Main Analysis

For the main analysis of cumulative prednisone dose over time (mentioned in [Section 8.2.1](#)), data from subjects who permanently discontinue SC IP prior to completing week 52 visit due to any reason and continue in the study will be used for the analysis. Cumulative prednisone dose will be set to missing once a subject withdraws from the study.

4.6.4. Missing Data Handling Rules

For cases where the baseline data is missing, no imputations will be performed.

GCA formal/suspected diagnosis Imputation Dates:

Time since formal diagnosis is defined as: Randomization date - formal diagnosis date + 1

Time since suspected diagnosis is defined as: Randomization date - suspected diagnosis date + 1

Partial dates for suspected/formal diagnosis recorded in the eCRF will be imputed using the following:

- If the day of suspected diagnosis is missing then day will be set to “01” month.
- If the month of suspected diagnosis is missing then month will be set to “January”.
- If either the day or month is missing for formal diagnosis then the following rules will be applied:

- If the day of formal diagnosis is missing then it will be set to “01” or to the day of suspected diagnosis, only if the year and month of suspected and formal diagnoses are equal – whichever is later.
- If the month of formal diagnosis is missing then it will be set to “January” or to the month of suspected diagnosis, only if the year of suspected and formal diagnoses are equal – whichever is later.

Concomitant Medication and Adverse Events Imputation Dates:

The following method will be used to impute missing dates for concomitant medications and adverse events (AE):

Missing start dates (where UK and UKN indicate unknown or missing day and month, respectively):

- UK-*MMM*-*YYYY*:
 - If the month and year are different from the month and year of first SC IP dose in Part A, assume 01-*MMM*-*YYYY*.
 - If the month and year are the same as the first study dose month and year and the stop/end date (after any imputation) is on or after first SC IP dose in Part A, then assume the date of first SC IP dose in Part A.
 - If the month and year are the same as first SC IP dose in Part A month and year and the stop/end date (after any imputation) is prior to first SC IP dose in Part A, then assume the stop/end date for the start date.
- DD-UKN-*YYYY*/UK-UKN-*YYYY*:
 - If the year is different from the year of first SC IP dose in Part A, assume 01-JAN-*YYYY* of the collected year.
 - If the year is the same as first SC IP dose in Part A year and the end date (after any imputation) is on or after first SC IP dose in Part A, then assume the date of first SC IP dose in Part A.
 - If the year is the same as first SC IP dose in Part A and the end date (after any imputation) is prior to first SC IP dose in Part A, then assume the end date for the start date.

Missing stop/end dates (where UK and UKN indicate unknown or missing day and month, respectively):

- UK-*MMM*-*YYYY*: Assume the last day of the month.
- DD-UKN-*YYYY*/UK-UKN-*YYYY*: Assume 31-DEC-*YYYY*.

In case of the death of the patients and the imputed end date is after the date of death, the stop/end date will be imputed as the date of death.

Completely missing dates will not be imputed.

4.7. Planned Analyses

Given study termination, only one database lock (DBL) will occur.

5. Subject Disposition

Unless otherwise specified, all tables and listings in this section will be based on the randomized set, and all summaries and data listings will use treatment labels as specified in [Section 3.3](#). Subjects will be analyzed according to the treatment they were randomized to receive.

5.1. Disposition

The number of subjects in each of the sets will be summarized. All subjects screened will be presented overall and the Randomized set, ITT set, and Safety set will be summarized overall and by treatment group using the all subjects screened set.

A summary of the subjects excluded from each analysis set and the reasons for exclusion will be presented using the Randomized set. This summary will include the number and percentage of subjects for the following categories: subjects excluded from the ITT set and reasons, and subjects excluded from the Safety set and reasons. Percentages for exclusion reasons will be based on the number of subjects excluded from the specific analysis set being summarized. Subjects could be excluded from an analysis set for more than one reason. A listing of subjects included in any analysis set as well as a listing of subjects excluded from any analysis set will be produced.

The number of subjects by country will be summarized by treatment group and overall.

A summary of subject status and reason for study withdrawal will be provided. The status section will display:

For Part A:

- Subjects who attended the Week 52 Visit with the following subcategories:
 - Did not enter Part B, defined as subjects who completed week 52 visit and did not enter Part B
 - Completed Safety Follow-up
 - Not Completed Safety Follow-up
 - Enter Part B, defined as subjects who were enrolled in Part B
- Early withdrawal or study termination:
 - Early withdrawal, is defined as subjects who permanently discontinued SC IP and prednisone study drug treatments prior to completing week 52 visit AND withdrew from the study.
 - Study termination is defined as subjects who were still in the study as of study termination date of 10 Oct 2017.

This includes the following subcategory:

- Completed Safety Follow-up, defined as the 16 week safety follow up after withdrawal or study termination
- Not Completed Safety Follow-up

For Part B:

- Completed Week 104 visit, defined as subjects who completed Part B
 - Completed Safety Follow-up
 - Not Completed Safety Follow-up
- Early withdrawal or Study Termination with the following subcategory:

- Completed Safety Follow-up, defined as subjects who attended the safety follow up period after withdrawal or study termination
- Not Completed Safety Follow-up

The reasons for study withdrawal will also be summarized within this table for each Part of the study. The reasons for study withdrawal will be presented in the order they are displayed in the eCRF.

The following information will be summarized on the Safety Set on a separate table:

- Subjects who completed SC IP treatment:
 - Prednisone study drug treatment completed
 - Permanently discontinued prednisone study drug treatment prior to completing week 52 visit
- Subjects who permanently discontinued SC IP treatment prior to completing week 52 visit (this will include subjects who discontinue SC IP due to study termination)
 - Prednisone study drug treatment discontinued prior to completing week 52 visit
 - Completed prednisone study drug treatment

Treatment status and reason for discontinuation will be provided for SC IP (sirukumab or placebo) and prednisone study drug separately. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF. Listings of discontinuation of IP SC and prednisone study drug will be generated. The listings will include last dose date, and reasons for study treatment discontinuation.

A listing of reasons for study withdrawal will be generated. A listing of subjects continuing into Part B of the study will be produced.

Listings of planned and actual treatments for subjects, and of all subjects for whom the treatment blind was broken will be generated.

Subjects will be assigned to the actual treatment groups if they received:

Subcutaneous IP for more than 50% of their injections	Prednisone study drug for more than 50% of the doses	Actual treatment
S100	3m	B
	6m	A
	12m	A
	random	A
S50	3m	C
	6m	C
	12m	C
	random	C
Placebo	3m	D
	6m	D
	12m	E
	random	E

5.2. Protocol Deviations

A protocol deviation is defined as non-compliance with the protocol/ICH-GCP which may impact subject rights, safety or well-being, or the integrity of the data:

- Significant Deviation: Non-compliance with the protocol/ICH-GCP which significantly impacts subject rights, safety or well-being, or the integrity of the data.
- Non-Significant Deviation - Non-compliance with the protocol/ICH-GCP which does not significantly impact subject rights, safety or well-being, or the integrity of the data.

All potential significant protocol deviations will be discussed and reviewed on a case-by-case basis.

Protocol deviation significance will be assessed based on the guidelines provided in GSK RAD201677 Standard Guidelines Protocol Variances.

As the study is ongoing, additional significant protocol deviations can also be spontaneously identified or defined during trending and review of protocol deviations by GlaxoSmithKline (GSK) and/or PPD teams during the regularly planned study deviation review meetings and the significant Protocol Deviations Rules document will be updated. More details of the process are provided in the Protocol Deviations Monitoring Plan (PDMP).

Prior to database lock, all protocol deviations will be revised, categorized and assessed as to significance.

Significant protocol deviations will be summarized by treatment in a table and all protocol deviations, significant and non-significant, will be presented in a listing. The subject data listing will be sorted by deviation type, treatment group, site and subject number.

6. Demographics and Baseline Characteristics

Unless otherwise specified, all tables and listings in this section will be based on the randomized set, and all summaries and data listings will use treatment labels as specified in [Section 3.3](#).

6.1. Demographics

The demographic characteristics (age, race, ethnicity, sex, as well as Baseline height, body weight and BMI) will be summarized by treatment group. Age, height and weight will be summarized using the mean, standard deviation, median, minimum and maximum. In addition, age will also be categorized and summarized by $\geq 50-64$, $\geq 65-74$, $\geq 75-84$ and ≥ 85 years. The number and percentage of subjects by age category, sex and ethnicity will be computed using the categories as provided in the eCRF. All demographic data, including female child-bearing potential will also be presented in a listing.

The proportion of subjects in each of the 3 age ranges will also be summarized (but not listed): Adult (18-64 years); $\geq 65-84$ years; ≥ 85 years.

A summary of race and racial combinations will be presented overall and by treatment group. The number and percentage of subjects by race will be reported. As a subject could have more than 1 race, the number and percentage of subjects with multiple races will also be reported. Percentages will be based on the total number of subjects in the Randomized set. All data will be listed in detail.

A specific listing displaying informed consent information will be produced.

6.2. Disease Characteristics

6.2.1. GCA Diagnosis and Disease Activity at Screening

Giant cell arteritis diagnosis at Screening will be summarized. This table includes:

- Time since formal diagnosis,
- Time since suspected diagnosis,
- Disease type (new onset or relapsing/refractory)
- Type of diagnosis
 - Temporal artery biopsy performed
 - Temporal artery ultrasound (TA US) performed
 - Angiography or cross-sectional imaging performed
- Acute-phase proteins (Screening CRP < 1mg/dL and ESR < 30mm/hr)
- Signs and symptoms present for the diagnosis
- Disease activity at screening: recorded in the eCRF page GCA Disease Activity (Screening): cranial signs or symptoms, symptoms of PMR, other signs or symptoms attributable to GCA or PMR flares, and visual signs or symptoms.

All information related to GCA diagnosis and GCA disease activity will be listed separately in detail.

Specific rules regarding imputation of missing or partial dates are provided in [Section 4.6.4](#).

6.2.2. Disease Characteristics of GCA at Baseline

The following variables will be summarized:

- Baseline prednisone dose (stratification factor)
- Acute-phase proteins (Baseline CRP < 1mg/dL and ESR < 30mm/hr)
- Remission status: clinical remission at Baseline and normalization of CRP and ESR. A subject in clinical remission is a subject that does not have any signs and symptoms, which is also determined by a lack of flare. If a subject does have a flare, they will have one or more signs and symptoms, and therefore are not considered as being in clinical remission. A subject without any flare at the Baseline visit will be considered in clinical remission.
- Baseline Patient's Global Assessment of Disease Activity VAS
- Baseline signs and symptoms: cranial signs or symptoms, symptoms of PMR, other signs or symptoms attributable to GCA or PMR flares, and visual signs or symptoms.

All data will be listed in detail.

6.3. Medical History

6.3.1. General Medical History

Relevant medical history will be summarized by number and percent of subjects by the following medical condition categories for current and past conditions separately:

- Cardiovascular Risk Factors
- Musculoskeletal and Connective Tissue Disorders
- Blood and Lymphatic System Disorders

- Eye Disorders
- Psychological Disorders
- Endocrine Disorders
- Metabolism and Nutrition Disorders
- Infection and Infestations
- Gastrointestinal Disorders
- Renal Disorders
- Urinary Tract

All medical history information will be listed in detail.

6.3.2. Disease-Specific History

Cardiovascular medical history and risk factors including are assessed at Screening. Cardiovascular risk assessment results will be listed which include: tobacco history (i.e. never smoked, current smoker, and former smoker), family history and medical/surgical procedures.

6.4. Inclusion and Exclusion Criteria

All study inclusion and exclusion criteria are presented in Sections 5.1 and 5.2 of the study protocol. All inclusion and exclusion criteria will be listed separately, using the all subjects screened set. Criteria under different protocol versions will be included in the listings.

The screening status (enrolled / failed) and reasons for screen failure will be summarized and listed using the all subjects screened set. The top 4 reasons for failing inclusion/exclusion criteria will be included in the summary. Percentages for reasons will be based on all subjects screened.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Prior and concomitant medications are recorded on 3 different concomitant medications eCRF pages:

- Prior Concomitant Medications form
- Concomitant Medications – Non-Corticosteroids
- Concomitant Medications – Corticosteroids

Prior and concomitant medications will be coded using GSK Drug coding dictionary, summarized separately on the Safety set and each summary will be split by corticosteroids and non-corticosteroids. All prior and concomitant medications will be listed for the Safety set.

In this study, prior medications are defined as those medications with a recorded start date prior to the initiation of SC IP. Prior medications are collected at Screening and are noted as to whether they are cardiovascular, GCA related, non-GCA related or corticosteroid medications.

Concomitant medications for Part A are defined as those medications which are taken on or after the initiation of SC IP in Part A, up to the Week 52 visit or the first SC IP of Part B open-label treatment, whichever is earlier for subjects participating in Part B.

Concomitant medications taken during the 16-weeks Safety follow-up visit will be summarized in Part A or Part B as relevant.

Concomitant medications where the eCRF option “Was drug administered as a rescue medication” is selected as “Yes” and that are corticosteroids when the unit is not in (Actuation, Application, Area under curve, Cubic centimeter, Cells, Cells per kilogram, Fingertip unit, Drops, Gum, Inhalation, Kilocalories, Minimum alveolar concentration, Mega becquerels (MBq), Millicurie, Nebule, Patch, Powder, Puff, Ring, Spray, suppository) or non-corticosteroid and GCA related will be considered as rescue therapies.

Three summary tables will be displayed:

- Prior medications
- Concomitant medications – rescue therapies
- Concomitant medications – non-rescue therapies

A listing of all rescue medications will be produced.

Each of the 3 summary table will be split by medication type: corticosteroids or non-corticosteroids. Within each byline, medications will be presented in the descending order of total incidence (i.e., summed across all treatment groups) by Anatomical Therapeutic Chemical (ATC) level 1 and ingredient for the Safety set.

Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients. For incidence reporting, if a subject took more than 1 concomitant medication that was coded to the same ATC level 1 or ingredient, the subject will only be counted once for the respective ATC classification or ingredient in the summary. A medication could be mapped to several ATC terms. In this case it will be displayed under all the ATC terms mapped. However, medications mapped to several ATC terms will be counted once when deriving cumulative prednisone dose.

Specific rules regarding imputation of missing or partial dates are provided in [Section 4.6.4](#).

If start date is completely missing and end date is after first dose intake or completely missing, then the medication will be classified as both prior and concomitant. If the start date is completely missing and the end date is prior to the first dose of study drug, then the medication will be classified as prior. If the end date is missing and the start date is after first dose intake, then the medication will be considered as ongoing and classified as concomitant. If the end date is missing and the start date is before first dose intake, then the medication will be considered as ongoing and classified as both prior and concomitant.

Medications with start and stop dates either side of Part A first SC IP dose date will be summarized as both prior and concomitant medications.

7.2. Study Treatments

7.2.1. Extent of Exposure

Listings of exposure to SC IP and prednisone study drug will be provided.

A summary of SC IP exposure will be provided. The following 3 parameters will be reported on the Safety set:

- Total number of injections a subject receives.
- Duration of SC IP treatment (weeks): defined as (Date of last SC IP dose – Date of first SC IP dose + 1 day) / 7. Only complete dates will be used when calculating duration of treatment. First and last injection dates will be used, regardless of any missed doses.
- Duration of SC IP exposure (weeks): defined as (Date of last SC IP dose – Date of first SC IP dose + 112 days) / 7, where 112 days corresponds to 16 weeks. Only complete dates will be used when calculating duration of exposure. First and last injection dates will be used, regardless of any missed doses.
- Cumulative SC IP dose: defined as the total dose in mg (SC IP or placebo) a subject receives.

A summary of prednisone study drug exposure will be provided. The following 2 parameters will be reported on the Safety set:

- Duration of prednisone study drug treatment (weeks): defined as (Date of last non-zero dose from the taper [i.e. the last prednisone end date from taper with a non-zero dose recorded] – Date of first dose from the taper + 1 day) / 7.
- Cumulative prednisone study drug dose (mg): defined as the total dose in mg a subject receives. For each week of the taper (both open-label and blinded), cumulative dose will be calculated as: the number of days x expected doses, the expected dose depending on the pre-specified taper schedule. Overall cumulative dose will be the sum of the cumulative doses of each week.

7.2.2. Treatment Compliance and Modifications

A subject will be considered compliant if the percentage compliance is between 80% and 120% inclusive, between first and last dose. All treatment compliance will be based on the Safety set.

7.2.2.1. Subcutaneous IP

Overall treatment compliance with SC IP will be assessed by the number of injections actually received versus the number of injections planned. The percentage compliance with SC IP will be calculated as: $100 \times (\text{number taken}/\text{number planned})$. Subjects randomized to SC IP 50 mg q4w take SC IP injections 1 week, and placebo injections 2 weeks later in order to provide blinding from those taking 100 mg q2w. For these subjects, compliance will be calculated irrespective of whether the injection was a placebo or sirukumab dose. The number of planned injections will be calculated based on the subject's last visit.

For example, if a subject's last visit = Week 20, then the planned number of injection will be 11. If this subject only reports 10 injections, the percentage compliance with SC IP will be $100 \times (10/11) = 90.9\%$.

Overall SC IP compliance and compliance categories (0; >0% and <80%; ≥80% and ≤120%; >120%) will be summarized for each treatment group. Compliant subjects (i.e. subjects with a compliance between ≥80% and ≤120%) will be summarized.

In addition, the SC IP / placebo administration will be summarized by treatment groups as following:

- Percentage of subjects who received all SC IP injections
- Percentage of subjects who missed at least 1 SC IP injection

- Percentage of subjects who missed 1/2/3/4/5/6, or more SC IP injections

All SC IP compliance data will be listed.

7.2.2.2. Prednisone Study Drug

Treatment compliance with prednisone study drug will be assessed by the number of capsules actually taken versus the number of capsules planned, for the blinded taper only. Each dispense will contain enough supply (cards containing the capsules) to cover the period of time until the next scheduled visit plus 1 additional card. The additional card is only to be used if the subject cannot return in time and ensure continuity of treatment (more details in the study procedure manual Section 2.4 Dispensing Study Medication to Subject).

Prednisone study drug – Open-label taper

No compliance will be calculated for the open-label taper.

Prednisone study drug - Blinded taper

The prednisone study drug compliance percentage will be calculated as follows:

$$100 \times (\text{total number of capsules taken} / \text{total number of capsules planned})$$

Total number of capsules taken will be calculated as: Sum of all capsule dispensed from the blinded taper – Sum of all capsules returned from the blinded taper.

The planned number of capsules will be calculated from the blinded tapering schedule:

Blinded Taper Week	Number of planned capsules to be taken per day	Blinded Taper Week	Number of planned capsules to be taken per day	Blinded Taper Week	Number of planned capsules to be taken per day
1	5	16	4	31	4
2	4	17	4	32	4
3	3	18	3	33	4
4	3	19	3	34	3
5	5	20	3	35	3
6	4	21	3	36	3
7	3	22	2	37	3
8	2	23	2	38	2
9	2	24	2	39	2
10	5	25	2	40	2
11	5	26	1	41	2
12	5	27	1	42	1
13	5	28	1	43	1
14	4	29	1	44	1
15	4	30	4	45	1

Overall prednisone study drug compliance and compliance categories (0; >0% and <80%; ≥80% and ≤120%; >120%) will be summarized for each treatment group. Compliant subjects (i.e. subjects with a compliance between ≥80% and ≤120%) will be summarized.

All prednisone study drug compliance data will be listed. Records for the open-label taper will display the number of tablets dispensed and returned and the start and stop dates for dosing. Records for the blinded taper will display the number of tablets dispensed and returned, the start and stop dates for dosing, and the overall percentage compliance calculated for the blinded taper phase.

7.3. Prednisone Intake as a Concomitant Medication

All corticosteroid dosages recorded on the Concomitant Medications - Corticosteroids page in the eCRF will be converted to a prednisone-equivalent average daily dose (mg/day) using a conversion factor for each particular medication. The list will be updated throughout the course of the study to include all corticosteroids taken by the subjects and will be finalized prior to the database lock and unblinding. The conversions of all corticosteroids will be done based on standardized medication name and using the following information from online calculator <http://www.globalrph.com/corticocalc.htm>, retrieved on 24th January 2018

Concomitant Medications with Standardized Medication Name Including the Following Term	Conversion factor for Prednisone - Equivalent Dose (mg)
Cortisone	0,2
Hydrocortisone	0,25
Prednisone	1
Prednisolone	1
Triamcinolone	1,25
Methylprednisolone	1,25
Dexamethasone	6,67
Betamethasone	8,33

Only medications with a unit reported in ‘mg’ will be converted to prednisone.

DOSE2 (prednisone-equivalent dose in mg) = DOSE (collected dose in mg) x conversion factor

DD (daily dose in mg/day) = DOSE2 (prednisone-equivalent dose in mg) x frequency factor

The records from concomitant medication datasets will be mapped to weeks corresponding to the prednisone schedule, e.g. if a subject has prednisone as rescue therapy for 10 days, the first 6 days may be mapped to Week X and the rest of the 4 days will be mapped to Week (X + 1) based on the start and end dates of the rescue medication, as well as the start and end dates of the prednisone tapering schedule at each week.

The following information on corticosteroids taken will be presented in a listing:

- Start and stop dates
- Original units, frequency and dose
- Prednisone-equivalent daily dose (in mg)
- Whether or not it was taken as a rescue medication

- Reason for medication (as collected on the Concomitant Medication-Corticosteroid eCRF page).

Two categories of concomitant prednisone intake will be identified:

- Concomitant prednisone intake as rescue therapy: all concomitant intake of corticosteroids reported for which the question “Was drug administered as a rescue medication?” is “Yes”
- Concomitant prednisone intake for non-GCA-related reasons: all concomitant intake of corticosteroids reported for which the question “Non Giant Cell Arteritis (GCA) related” is ticked

Summary statistics of cumulative prednisone intake including both taper and rescue medication will be summarized by treatment group and visit as well as overall.

Further discussions regarding the statistical analysis of cumulative prednisone intake including both taper and rescue medication is presented in [Section 8.2.1](#).

Frequencies are free text variables and need to be converted to numerical values. The following free text frequencies will be derived as follows:

Text	Frequency used for conversion
1 OF THE 3 DAYS	1/3
2 OF THE 3 DAYS	2/3
BID	2
DAIL	1
DAILY FOR 2 WEEKS	1
DQ	1
EVERY OTHER DAY	1/2
EVERY 12 HOURS	2
EVERY 2 OF 3 DAYS	2/3
EVERY 2 OF THE 3 DAY	2/3
EVERY 2 OF THE 3DAYS	2/3
EVERY 3TH DAY	1/3
EVERY TWO DAYS	1/2
EVERYDAY	1
EVRY DAY	1
MANE	1
ONCE	1
ONCE DAY	1
ONCE A DAY	1
ONCE D AY	1
ONCE EVERY DAY	1
ONCE OVER A DAY	1
ONCE THE DAY	1
ONCE/DAY	1
ONVE A DAY	1
Q3D	1/3
Q8H	3
QD	1
QOD	1/2
TID	3

8. Efficacy Analysis

All efficacy analyses will be based on the ITT set defined in [Section 4.4.3](#), unless otherwise specified. Subjects will be analyzed according to the treatment groups that they were randomized to, regardless of the treatments they actually received.

Only summary statistics will be produced given study termination.

8.1. Primary Efficacy Endpoint

The primary endpoint of this study is the proportion of subjects in sustained remission at Week 52, defined as having achieved all of the following criteria:

1. Remission at Week 12

Remission is defined as having achieved the 2 following criteria:

- a. Clinical remission is defined as absence of clinical signs and symptoms of GCA
And
- b. Normalization of ESR (<30mm/hr) and CRP (<1mg/dL).

A subject in clinical remission is a subject that does not have any signs and symptoms, which is also determined by a lack of flare for the subject. If a subject does have a flare, they will have one or more signs and symptoms, and therefore are not considered as being in clinical remission. A subject without any flare at the Week 12 visit will be considered in clinical remission.

The following rule will be used to assess remission at Week 12:

“Has the patient flared since their last visit?” should be answered “No” at Week 12 visit on the Clinical Assessment of GCA eCRF page and ESR laboratory results value at Week 12 should be < 30mm/hr and CRP laboratory results value at Week 12 should be < 1mg/dL.

AND

2. Absence of disease flare following remission at Week 12 through Week 52

Flare is determined by the investigator and defined as the recurrence of symptoms attributable to active GCA, with or without elevations in ESR and/or CRP.

The following rule will be used to assess absence of disease flare following remission at Week 12 through Week 52:

“Has the patient flared since their last visit?” should be answered “No” at each scheduled and unscheduled visit from any visit after Week 12 up to Week 52 on the Clinical Assessment of GCA eCRF page.

AND

3. Completion of the assigned prednisone taper protocol (to Week 52)

“Can the patient continue with the protocol defined taper” on the Clinical Assessment of GCA eCRF page should be answered “Yes” at all scheduled and unscheduled visits between Baseline and Week 48.

AND

4. No requirement for rescue therapy at any time through Week 52

If any concomitant corticosteroid medication when the unit is not in (Actuation, Application, Area under curve, Cubic centimeter, Cells, Cells per kilogram, Fingertip unit, Drops, Gum, Inhalation, Kilocalories, Minimum alveolar concentration, Mega becquerels (MBq), Millicurie, Nebule, Patch, Powder, Puff, Ring, Spray, Suppository) or any of concomitant non-corticosteroid medication identified as “GCA related” with the question “Was drug administered as a rescue medication?” is ticked as “Yes” and if the first SC IP Date ≤ Concomitant medication start date ≤ Week 52 visit date, then subject will fail the criterion.

If all of the 4 criteria are met, subject will be considered in sustained remission at Week 52. If 1 of the 4 criteria is not met, the subject will be considered as not in sustained remission at Week 52.

For more details on imputation of missing data for the primary endpoint, please refer to [Section 4.6.2.1](#).

Given study termination, only the subset of subjects who attended the Week 52 visit or who discontinued study treatment or withdrew from study prior to the 10th of October 2017 will be included in this analysis.

8.1.1. Primary Analysis

The proportion of subjects in sustained remission at the Week 52 visit will be summarized by treatment group. Subjects not in sustained remission will be categorized by the criterion they failed to achieve. A listing will be produced with the detail of each criteria met or not met over time. A listing of clinical assessment of GCA will be produced over time.

8.2. Secondary Efficacy Endpoints

8.2.1. Cumulative Prednisone Dose (Study Drug and Corticosteroid Rescue Therapy) over Time

Cumulative prednisone is the cumulative prednisone dose from the taper (both open-label and blinded) as well as from the corticosteroid rescue therapies, as defined in [Section 3.3](#) and [Section 7.3](#). Cumulative dose at Week X will be derived as the sum of all the doses from baseline to Week X. If a subject withdraw from study between two scheduled visits, all prednisone doses recorded between his last scheduled visit and study withdrawal will be associated to the next scheduled visit. For example, if a subject withdraw between the Week 24 visit and the Week 28 visit, all doses recorded after the day of Week 24 will be associated to Week 28. For more details on imputation of missing data for the key secondary endpoint, please refer to [Section 4.6.3.1](#).

8.2.1.1. Statistical Analysis

The cumulative prednisone dose will be summarized by treatment group and visit. Interquartile range (IQR) will also be displayed in summary statistics. The summary statistics will be generated for the total cumulative prednisone as well as for the study drug and the CS rescue therapy separately. Cumulative dose will be listed.

8.2.2. Proportion of Subjects in Sustained Remission over Time from Week 12 to Week 52

For each visit (referred to as Week X in the algorithm below) from Week 12 to Week 48, the definition of sustained remission is similar to Week 52:

1. Remission at Week 12

Remission is defined as having achieved the 2 following criteria:

- c. Clinical remission is defined as absence of clinical signs and symptoms of GCA
- And
- d. Normalization of ESR (<30mm/hr) and CRP (<1mg/dL).

A subject in clinical remission is a subject that does not have any signs and symptoms, which is also determined by a lack of flare for the subject. If a subject does have a flare, they will have one or more signs and symptoms, and therefore are not considered as being in clinical remission.

The following rule will be used to assess remission at Week 12:

“Has the patient flared since their last visit?” should be answered “No” at Week 12 visit on the Clinical Assessment of GCA eCRF page and ESR laboratory results value at Week 12 $< 30\text{mm/hr}$ and CRP laboratory results value at Week 12 $< 1\text{mg/dL}$.

AND

2. Absence of disease flare following remission at Week 12 through Week X

Flare is defined as recurrence of symptoms attributable to active GCA, with or without elevations in ESR and/or CRP.

The following rule will be used to assess absence of disease flare following remission at Week 12 through Week X:

“Has the patient flared since their last visit?” should be answered “No” at each scheduled and unscheduled visit from any visit after Week 12 up to Week X on the Clinical Assessment of GCA eCRF page.

AND

3. Completion of the assigned prednisone taper protocol (to Week X)

“Can the patient continue with the protocol defined taper” on the Clinical Assessment of GCA eCRF page should be answered “Yes” at all visits between Baseline and the visit before the Week X visit.

AND

4. No requirement for rescue therapy at any time through Week X

If any concomitant corticosteroid medication when the unit is not in (Actuation, Application, Area under curve, Cubic centimeter, Cells, Cells per kilogram, Fingertip unit, Drops, Gum, Inhalation, Kilocalories, Minimum alveolar concentration, Mega becquerels (MBq), Millicurie, Nebule, Patch, Powder, Puff, Ring, Spray, suppository) or any of concomitant non-corticosteroid medication identified as “GCA related” with the question “Was drug administered as a rescue medication?” is ticked as “Yes” and if the first SC IP date \leq Concomitant medication start date \leq Week X visit date, then the subject will fail the criterion.

Please note that once a subject fails a criterion, he/she will also fail all future criteria from subsequent visits.

For more details on imputation of missing data for sustained remission endpoint, please refer to [Section 4.8.2.1](#).

If all of the 4 items are met and the subject did not discontinue SC IP before the Week X visit date, the subject will be considered in sustained remission at Week X. If 1 of the 4 items is not met or if the subject discontinued SC IP before the Week X visit, the subject will be considered as not in sustained remission at Week X.

Given study termination, only the subset of subjects who attended the Week X visit or who discontinued study treatment or withdrew from study prior to the 10th of October 2017 will be included in this analysis.

Number of subjects who flared and subjects who did not complete the prednisone blinded taper will also be summarized over time on the ITT Set.

8.2.2.1. Statistical Analysis

The number and percent of subjects meeting each criterion and the overall criteria will be summarized by treatment group and visit. All data will be listed showing when subjects failed the criteria and which criterion they failed.

8.2.3. Time to First Disease Flare after Clinical Remission

Only subjects who achieve clinical remission will be included in this analysis. To address this endpoint, the following definitions will be used:

Clinical remission: A similar approach as for the primary endpoint will be used: Clinical remission is defined as absence of clinical signs and symptoms of GCA

A subject in clinical remission is a subject that does not have any signs and symptoms, which is also determined by a lack of flare for the subject. If a subject does have a flare, they will have one or more signs and symptoms, and therefore are not considered as being in clinical remission.

The following rule will be used to assess Clinical remission:

“Has the patient flared since their last visit?” should be answered “No” at a given visit. Clinical remission can occur at any visit between Baseline and Week 52.

Time to first disease flare after clinical remission is the time (days) from the first clinical remission date to the earliest disease flare date:

Disease flare after clinical remission: Date of first disease flare (as collected in the assessment of GCA disease activity) after clinical remission as defined above.

Time to first disease flare (days) = Date of disease flare date – Date of clinical remission + 1 day

Subjects without disease flare at the time of analysis and who have completed the Week 52 visit will be censored at the date of the Week 52 visit. Subjects without disease flare at the time of analysis withdrew from the study or die will be censored at the date of early withdrawal or death. Data observed at or prior to the baseline visit will not be included in this analysis. Handling of missing data in the clinical remission component will be as described in [Section 4.6.2.1](#).

8.2.3.1. Statistical Analysis

A Kaplan-Meier analysis will be summarized. The number of subject achieving clinical remission, as well as the number of subjects with a disease flare and the number of subjects censored with their censoring reasons will be summarized. 25th percentile, median and 75th percentile time to first flare will be summarized in days for each treatment group.

A listing of details of flares will be produced (date of first clinical remission, date of first flare after clinical remission, time from clinical remission to flare).

8.2.4. Number of Disease Flares per Subject over Time

The cumulative number of disease flares is the total number of flares from first SC IP to the Week 52 visit, as collected in the “Clinical Assessment of GCA” eCRF page. Field “Has the patient flared since their last visit?” will be used to count the number of flares. Scheduled and unscheduled visits will be used.

8.2.4.1. Statistical Analysis

Number of flares and subjects with at least one flare from Baseline to the Week 52 visit will be summarized by treatment group over time. Cumulative number of flare at the Week X visit is the cumulative number of flare between Baseline and the Week X visit

8.2.5. Proportion of Subjects Requiring Hospitalizations for Disease Flare and Number of Hospitalizations for Disease Flare over Time

The hospitalizations for disease flare will be identified through the adjudication of AESI, and will include events from the following category: “Severe Flare including Hospitalizations”.

8.2.5.1. Statistical Analysis

Number of hospitalizations for disease flare and subjects with at least one hospitalization for disease flare from first SC IP to the Week 52 visit, will be summarized by treatment group over time

8.3. Other Efficacy Endpoints

No handling rule for missing data will be done in [Section 8.3](#), apart from the specific rules detailed within each sub-section.

8.3.1. Patient and Physician-Reported Outcomes

The following summaries on Patient and physician-reported outcomes will be performed on the ITT set except for the HAQ-DI which is only filled out for subjects with symptoms of PMR. Therefore, summaries of the HAQ-DI will be performed on the subset of ITT subjects who are indicated to have symptoms of PMR at screening.

If the date of result does not match the scheduled visit date, a visit mapping will be applied. A result will be mapped to Visit Week X if it occurs +/- 14 days to visit X.

8.3.1.1. Patient’s and Physician’s Global Assessment (PGA) of Disease Activity

The PtGA and PhGA of disease activity will be recorded on a 10 cm visual analogue scale (VAS) and will be conducted at each visit.

The PtGA asks “Considering all of the ways your condition has affected you, how do you feel today?” and uses a 10 cm VAS with anchors 0 (“very well”) to 10 (“very poor”).

The PhGA asks “What is your assessment of the patient's current disease activity?” and uses a 10 cm VAS ranging from 0 (“none”) to 10 (“extremely active”).

For both endpoints, a negative change from baseline reflects an improvement, and a positive change from baseline reflects a worsening.

The scores and change from Baseline will be summarized by treatment and visit.

All PtGA and PhGA data will be listed separately.

8.3.1.2. Patient Global Impression of Change (PGIC)

Patient-reported response to treatment will be assessed using the Patient Global Impression of Change (PGIC) measure, a single item completed by subjects to provide a clinically meaningful

summary of an individual's response to treatment. The assessment provides an estimate of the magnitude of treatment response at different time points during the study. Responses include: Much Better, Better, Slightly Better, No Change, Slightly Worse, Worse, and Much Worse.

The categorical data of subject rating of change will be summarized by treatment group, visit and response category.

All PGIC data will be listed.

8.3.1.3. Pain Numeric Rating Scale

The assessment of pain severity will be made using a single pain severity item on which subjects will be asked to rate the severity of their average pain now on an 11-point numeric rating scale ranging from 0, "no pain" to 10, "the worst pain imaginable".

The pain NRS and change from Baseline will be summarized by treatment group and visit. A negative change from baseline in pain NRS reflects an improvement in pain, and a positive change from baseline reflects a worsening in pain.

All pain NRS data will be listed.

8.3.1.4. Health Assessment Questionnaire – Disability Index (HAQ-DI)

The HAQ-DI indicates the extent of the subject's functional ability during the past week, and will be assessed for the subgroup of subjects with symptoms of PMR. Only subjects with the "Symptoms of PMR" answered to "Yes" at screening (GCA Diagnosis form) will be included in the analysis of the HAQ-DI.

The HAQ-DI consists of 20 questions in 8 categories of functioning – dressing and grooming, arising, eating, walking, hygiene, reach, grip, and usual activities.

Each functional area contains at least two questions. For each question, there is a 4-level difficulty scale that is scored from 0 to 3, representing "no difficulty" (0), "some difficulty" (1), "much difficulty" (2), and "unable to do" (3).

In addition to assessing functional ability during the past week, the questionnaire asks if any aids or devices are needed for any of the activities. When aids or devices are indicated by a subject and if the unmodified score is 0 or 1, then the score will be raised to 2.

The aids and devices are assigned to the specific HAQ sections as follows:

- Dressing and Grooming: Devices used for dressing (button hook, zipper pull, shoe horn, etc.)
- Arising: Special or built-up chair
- Eating: Built-up or special utensils
- Walking: Cane, walker, crutches, wheelchair
- Hygiene: Bathtub bar, long-handled appliances in bathroom, raised toilet seat
- Reach: Long-handled appliances for reach
- Grip: Jar opener for jars previously opened
- When "Other" is ticked, all functions recorded on the same eCRF page will be raised to 2

There are no specific aids and devices assigned to usual activities.

The score for each of the 8 category scores is taken as the maximum score given to the related questions. If no questions within a given functional area were answered, no score will be provided for that category (even if answers on aids or equipment are available).

EXAMPLE:

If a subject answers as follows for the Dressing and Grooming category:

Q. Are you able to dress yourself, including tying shoelaces and doing buttons?

Answer: without any difficulty → Score = 0

Q. Are you able to shampoo your hair?

Answer: with some difficulty → Score = 1.

The score for the Dressing and Grooming category would be 1. However, if devices used for dressing (button hook, zipper pull, shoe horn, etc.) are indicated then the score for the Dressing and Grooming category would be raised to 2.

The average of these non-missing functional area scores defines the continuous HAQ-DI score ranging from 0 to 3, with higher scores indicating worse disability. If there are less than 6 functional area scores available, no imputation will be done and the HAQ-DI will be set to missing for the according assessment.

Absolute and change from baseline in HAQ-DI score will be summarized by treatment group and visit. A negative CBF reflects an improvement in functional disability

All HAQ-DI data will be listed: Raw scores; aids and devices used; help from another person; and derived scores.

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

The FACIT-Fatigue is a 13-item questionnaire formatted for self-administration that assesses subject reported fatigue and its impact upon daily activities and function over the past seven days. Specifically, subjects are asked to answer each question using a 5-point Likert-type scale (4 = Not at all; 3 = A little bit; 2 = Somewhat; 1 = Quite a bit; and 0 = Very Much). Each of the 13 items of the FACIT-Fatigue Scale ranges from 0-4, with a range of possible total score from 0-52, with 0 being the worst possible score and 52 the best (i.e. less fatigue). Scores below 30 indicate severe fatigue. To obtain the 0-52 score each negatively-worded item response is recoded so that 0 is a bad response and 4 is good response. All responses are added with equal weight to obtain the total score. The total score is calculated as the sum of all the individual items after recoding some of the items. Recoded items are displayed in **Table 5** with a “-” sign.

Table 5 FACIT-Fatigue Question Reversal

Item Number	Reverse Item?	
1	4	-
2	4	-
3	4	-
4	4	-
5	4	-
6	4	-
7	0	+
8	0	+
9	4	-
10	4	-
11	4	-
12	4	-
13	4	-

If more than 50% of the items are answered (i.e. if at least 7 questions are answered), the scores will be pro-rated: [Sum of item scores] x [N of items in the questionnaire: 13] / [N of items answered]. If less than 50% of the items are answered, no imputations will be done and the score will be considered as missing.

EXAMPLE

If a subject responds to 10 questions and the total score for these 10 questions is 22 then Total score will be:

$$\text{TOTAL_Score} = (22 \times 13) / 10 = 28.6$$

Absolute and change from baseline in FACIT-Fatigue following endpoints will be summarized by treatment group and visit. A negative CFB reflects an improvement in fatigue

All FACIT-Fatigue data will be listed.

8.3.1.6. Steroid Impact Questionnaire

The benefits, side effects and impact of steroids on GCA symptoms and subjects will be assessed using a GCA disease-specific subject-reported questionnaire, the Steroid Impact Questionnaire (SIQ). The SIQ contains 32 and 21 items at baseline and post-baseline visits, respectively. The SIQ assesses items in the following categories:

- Steroid Dose/Duration
- General Impact
- Benefits
- Work/Productivity
- Side Effects
- Emotions
- Overall Satisfaction

All the SIQ data will be listed.

8.3.1.7. 36-Item Short Form Version 2 Acute (SF-36v2 Acute)

The SF-36v2 acute health survey questionnaire was developed as part of the Rand Health Insurance Experiment and consists of the following 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 8 scales are scored from 0 to 100 with higher scores indicating better health. Another algorithm yields 2 summary scores, the Physical Component Summary (PCS) score and Mental Component Summary (MCS) score. These summary scores are also scaled with higher scores indicating better health.

Normalized scores based on the 2009 United States general population will be generated by QM Certified Scoring (Software) version 4.5 (QualityMetric, Inc, Lincoln, RI, USA). This software will be used to generate the scores used in the outputs. The full description of the derivations and the missing questions handling rules are described in the manual. All the default approaches will be used to derive these values. In particular, summary scores (PCS and MCS) will be set to missing if the subject is missing any one of the 8 individual domains.

The following endpoints will be summarized by treatment group and visit:

- Absolute and change from baseline in the 2 summary scores (a positive change from baseline reflects an improvement).

All SF-36v2 acute data will be listed.

8.3.1.8. EuroQoL-5Dimensions, 5 Levels

EQ-5D essentially consists of 2 elements: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

The EQ-5D descriptive system comprises the following 5 dimensions:

- Mobility
- Self-Care
- Usual Activities
- Pain/Discomfort
- Anxiety/Depression

Each of these 5 dimensions has 5 levels: 1: no problems; 2: slight problems; 3: moderate problems; 4: severe problems; 5: Unable to do.

The digits for each of the 5 dimensions can be combined in a 5-digit number describing the subject's health state: e.g. state 11111 indicates no problem on any of the 5 dimensions, while state 12345 indicates no problems with Mobility, slight problems with Self-Care, moderate problems with doing Usual Activities, severe Pain or Discomfort and extreme Anxiety or Depression. A total of 3125 possible health states is defined, therefore the health states will not be summarized. Instead, the health states will be converted into a single summary index (EQ-5D Index) by applying a formula that attaches weights to each of the levels in each dimension. The weights based from the UK population will be used for the conversion, regardless of the origin country of the subject.

In order to create the EQ-5D Index (Utility Index), the conversion provided from the "EQ-5D-5L Crosswalk Index Value Calculator" Excel file will be used. This file is downloadable from: http://www.euroqol.org/fileadmin/user_upload/Documenten/Excel/Crosswalk_5L/EQ-5D-5L_Crosswalk_Index_Value_Calculator.v2.xls. [Van Hout B, Janssen MF, et al.]. The "UK" column of the "EQ-5D-5L Value Sets" sheet will be used for the conversion.

The EQ VAS records the subject's self-rated health on a 20-cm vertical VAS where the endpoints are labelled 'best imaginable health state' (score of 100) and 'worst imaginable health state' (score of 0). The EQ VAS can be used as a quantitative measure of health outcome as judged by the individual subjects.

The following endpoints will be summarized by treatment group and visit:

- Absolute and change from baseline in EQ-5D index (Utility Index)
- Absolute and change from baseline in EQ-5D VAS

For both changes from baseline, a negative change indicates an improvement, and a positive change indicates a worsening.

All EQ-5D-5L data (raw and derived) will be listed. Conversion between each of the 5-digit numbers and associated weight will be listed.

9. Safety Analyses

All safety analyses will be performed on the Safety set. Subjects will be analyzed according to the treatment actually received, regardless of the treatment group they were randomized to. Percentages for safety summaries based on the number of subjects with a given event or attribute will be based on Safety set. All safety data will be included in listings.

9.1. Adverse Events

The definition of an AE is detailed in Section 12.4.1 in Appendix 4 of the protocol.

Treatment-emergent AEs:

A treatment-emergent AE for Part A is defined as an AE with a start date during the exposed period.

The exposed period is defined as the period from the 1st dose of SC IP to:

- Early withdrawal: last dose of SC IP + 16 weeks

- Completers (subjects who attended the week 52 visit):
 - Week 52 visit if entering into part B
 - Last dose of SC IP + 16 weeks if not entering into part B

Unless otherwise specified, AE outputs will be based on TEAEs.

All AEs will be coded by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 19.0 or higher).

An overview summary of TEAEs, including counts and percentages of subjects will be generated by actual treatment group, with any of the following categories:

- Any TEAE, TEAEs related to study treatment (SC IP and/or prednisone study drug), TEAEs leading to permanent discontinuation of study treatment, TEAEs leading to dose interruption/delay, TEAEs leading to dose reduction, TEAEs leading to dose increase, TEAEs leading to dose not changed.
- Any serious TEAEs, serious TEAEs related to study treatment (SC IP and/or prednisone study drug), fatal serious TEAEs, and fatal serious TEAEs related to study treatment.
- Any TEAE of special interest (TEAESI) (see [section 9.1.8](#) for further details), TEAESIs related to study treatments (SC IP and/or prednisone study drug), TEAESIs leading to permanent discontinuation of study treatment, TEAESIs leading to dose reduction, TEAESIs leading to dose increase, TEAESIs leading to dose not changed, TEAESIs leading to dose interruption/delay.

A listing presenting the relationship between SOC, PT, and AE reported will be provided.

9.1.1. Incidence of Adverse Events

Summaries of the total number of TEAEs and the number and percentage of subjects with at least 1 TEAE will be provided by actual treatment group and ordered by SOC and PT. This summary will be repeated for pre-study treatment (i.e. AEs starting before the exposed period as defined in [Section 9.1](#)) and post-study treatment AEs (i.e. AEs starting after the exposed period as defined in [Section 9.1](#)).

Treatment-emergent AEs will be presented in descending order from the SOC with the highest total incidence (that is, summed across all treatment groups) to the SOC with the lowest total incidence. If the total incidence for any 2 or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in alphabetical order. At each level of subject summarization, a subject is counted once if the subject reported 1 or more events.

Common AEs are defined as those reported by more than 5% of the subjects in any of the treatment arm. Summaries of common AEs and common non-serious AEs will be provided (no rounding for the percentage will be used in terms of 5% threshold, e.g. event with 4.9% incidence rate should not be included in this table). The summary will be displayed in descending order of incidence in total column by PT only.

The proportions of subjects with common AEs and relative risks will be summarized for the six comparisons. This will be done using the RELRISK option of the table statement of the SAS PROC FREQ procedure.

Incidences per 100 subject-year will be calculated for the 3 groups of AEs described below, for each SOC and PT. The table will include the number of subjects and AEs, the total subject-years of exposure, the incidence per 100 subject-years of exposure as well as the 95%CI (exact Poisson confidence intervals). For each subject, the duration of exposure is defined as follows:

- For subjects who have an event: from 1st dose of SC IP until the occurrence of the first event.
- For subjects who do not have an event: duration of exposed period.

The exposure-adjusted incidence rates will be calculated for 3 groups of AEs:

- All AESIs (for each category, SOC and PT)
- All fatal serious AEs (for each SOC and PT)
- All SAEs (for each SOC and PT)

All AEs will be listed and TEAEs, pre-study treatment and post-study treatment AEs will be flagged. Additionally, a listing of subject identification numbers for each individual AE preferred terms will be produced.

9.1.2. Relationship of Adverse Events to Study Treatments

A separate summary will be provided for study treatment-related TEAEs. A study treatment-related TEAE is defined as a TEAE for which the investigator classifies the relationship to study treatment (subcutaneous IP or prednisone study drug) as “Yes”. One summary table will be produced. The table will be split in five parts: TEAEs Related to SC IP (regardless of relationship to Prednisone), TEAEs related to both SC IP and prednisone study drug, TEAEs related to SC IP only, TEAEs related to prednisone study drug (regardless of relationship to SC IP), TEAEs related to prednisone study drug only. A worst-case scenario approach will be taken to handle missing relatedness data (i.e. TEAEs with missing relationship will be considered as TEAEs related to study drug). The summary table will be displayed in descending order of incidence in the total column by SOC and PT. A separate table will also display the summary by severity (as for all AEs).

9.1.3. Severity of Adverse Events

A summary of TEAEs by severity (SOC and PT) will be presented in a table. The severity that will be presented represents the most extreme severity captured on the eCRF page. The possible severities are “Mild,” “Moderate,” and “Severe.” In the TEAE severity table, if a subject reported multiple occurrences of the same TEAE, only the most severe will be presented. Treatment-emergent AEs that are missing severity will be presented in tables as “Unknown” and will be presented in the data listing with a missing severity.

9.1.4. Serious Adverse Events

The definition of a SAE is detailed in Section 12.4.2 in Appendix 4 of the protocol.

All serious TEAEs will be tabulated based on the number and percentage of subjects who experienced the event. Separate summaries will also be provided for:

- Study treatment-related serious TEAEs,
- Fatal serious TEAEs,

- Treatment-related fatal serious TEAEs.

The summary tables will be displayed in descending order of incidence in total column by SOC and PT, or PT only depending on the output.

All SAEs are included in the listing of all adverse events. Separate supportive listings with subject-level details will be generated for all SAEs (including details of why AE was considered as serious based on reasons given on the SAE page).

9.1.5. Adverse Events Leading to Permanent Discontinuation of Study Treatments

Treatment-Emergent AEs leading to discontinuation of study treatment (subcutaneous IP or prednisone study drug) will be summarized. One summary table will be produced. The table will be split in two parts: one part for TEAEs leading to permanent discontinuation of SC IP and one for TEAEs leading to permanent discontinuation of prednisone study drug. All subjects who have an AE where the outcome is marked as “Study Treatment(s) withdrawn” is “Yes” will be summarized in a table by SOC and PT. All data will be listed.

9.1.6. Adverse Events Leading to Dose Interruption / Delay of Study Treatments

Treatment-Emergent AEs leading to dose interruption / delay of SC IP will be summarized. One summary table will be produced. The table will summarize TEAEs leading to dose interruption / delay in SC IP. All subjects who have an AE where the action taken with SC IP is marked as “Dose interrupted / delayed” will be summarized in a table by SOC and PT. All data will be listed. TEAEs leading to dose interruption / delay in SC IP and/or dose interruption / delay in prednisone study drug will be listed.

9.1.7. Death

Fatal SAEs will be listed. Listings of death certificate details and cause of death will be generated to provide subject-specific details on subjects who died prior to study completion.

9.1.8. Adverse Events of Special Interest

The identification, classification and adjudication of adverse events of special interest (AESI) will occur in a blinded fashion quarterly by the GSK medical monitor. The final adjudication will take place prior to database releases and will be performed for reporting purposes.

Where available, AEs will have SMQ flags assigned to help the adjudication process at GSK. These flags will help but not over-rule individual event adjudication performed by GSK. All AE terms will be adjudicated at the subject level by GSK, in order to identify any events that are AESI as defined by the protocol as well as to assign each AESI category which will support later tabulation.

The groups of adverse events of special interest are defined below:

- Gastrointestinal perforation
- Diverticulitis
- Tuberculosis activation
- Serious/opportunistic infections

- Hypersensitivity
- Cytopenias
- Serious cardiovascular events
 - Major Adverse Cardiac Events (MACE) adjudicated by the CEC
 - MACE
- Malignancies
- Injection site reactions
- Severe flares including hospitalizations
 - Total/partial blindness
 - Limb claudication
 - Scalp or tongue necrosis
- Lipid increases
- Liver function test abnormalities
- Corticosteroid-related AE

An overall summary of AESIs will be presented summarizing numbers and percentages of subjects with events within each of the above categories as well as by SOC and PT.

Further details will be provided in summaries of each AESI separately. The summary of event characteristics will also be provided, including number of subjects with at least one event, number of events, the event characteristics (i.e. seriousness, relationship to study drug, severity and if the event was fatal or not), the number of occurrences, the outcome, the maximum intensity and the action taken. The worst case approach will be applied at subject level for the event outcome and the action taken, (i.e. a subject will only be counted once as the worst case from all of the events that that subject had). In addition, onset and duration of the first occurrences for each type of events will be summarized.

Time to onset of first AESI will be displayed and calculated as:

$$\text{Date of onset of first AESI} - \text{Date of first SC IP date} + 1 \text{ day}$$

Duration of first AESI will be displayed and calculated as:

$$\text{End date of first AESI} - \text{Start date of first AESI} + 1 \text{ day}$$

The proportions of subjects with AESIs and relative risks for the six comparisons will be summarized in a table. This will be done using the RELRISK option of the table statement of the SAS PROC FREQ procedure.

A supportive listing of all AESI will be presented.

9.1.9. Cardiovascular Events

For any AEs and SAEs that are classified as one of the following Cardiovascular Events, additional information will be collected on the eCRF:

- Arrhythmias
- Congestive heart failure
- Cerebrovascular events/stroke and transient ischemic attack
- Deep venous thrombosis/pulmonary embolism
- Myocardial infarction/unstable angina
- Peripheral arterial thromboembolism
- Pulmonary hypertension
- Coronary revascularization
- Peripheral revascularization
- Valvulopathy

All data collected on the eCRF pages will be listed. A listing presenting subjects with a least one cardiovascular event during the study will also be displayed.

9.2. Clinical Laboratory Evaluations

Clinical laboratory safety test (hematology, serum chemistry, fasting lipids and other tests) will be collected as specified in [Appendix 13.1](#) and will be analyzed by a central laboratory.

All summaries will be based on the standard international units.

Laboratory data will be listed and abnormal values will be flagged in the data listings. A listing of laboratory data outside of normal ranges will be presented by actual treatment group. A listing of laboratory test reference ranges will also be provided. Test reference ranges used will be the references range provided with the lab results.

Summary tables presenting observed values and changes from Baseline will be presented for clinical laboratory tests with numeric values by actual treatment group for subjects in the Safety set, separately for each laboratory category.

The assessment of laboratory toxicities will examine all Common Terminology Criteria for Adverse Events (CTCAE V4.03) gradable laboratory tests. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCICTCAE) will be used to grade laboratory gradable abnormalities. Maximum CTCAE post-Baseline grade will be summarized over time for each CTCAE gradable laboratory parameter. Summary of CTCAE grade shifts from Baseline will also be produced over Time and for the worst post-baseline value. CTCAE grades will be displayed in laboratory listings.

Abnormal (i.e. outside of laboratory test reference ranges) chemistry and hematology values will be summarized by actual treatment. Shift from baseline tables of normal ranges by actual treatment will also be provided for the chemistry and hematology parameters, over time and for the worst-post baseline value.

A summary table for abnormal laboratory tests Alanine Aminotransferase (ALT), Aspartate aminotransferase (AST), Absolute Neutrophil Counts and Platelet Counts will be generated over time and the following abnormal categories will be used:

Table 6 Abnormal Categories for AST, ALT, Neutrophils and Platelet Counts

Test Name	Categories		
AST	≥3 x ULN	≥5 x ULN	
ALT	≥3 x ULN	≥5 x ULN	≥8 x ULN
Neutrophils	<0.5 x 10 ⁹ /L	0.5 to ≤1.0 x 10 ⁹ /L	>1.0 x 10 ⁹ /L
Platelet Counts	<50 x 10 ⁹ /L	50 to ≤ 100 x 10 ⁹ /L	>100 x 10 ⁹ /L

ULN: upper limit of normal

Plots of laboratory parameters over time will be provided. A scatter plot of maximum vs. Baseline ALT will be produced. A scatter plot of maximum ALT vs maximum Total Bilirubin will be produced.

Individual plot over time of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and total bilirubin will be created, only for subjects with a total bilirubin > 2 ULN and alanine aminotransferase > 3 ULN at the same visit.

9.2.1. Hematology and Fasting Lipids

Hematology assessments presented in [Table 7](#) are taken at predefined visits as specified in [Appendix 13.1](#) (i.e. at Screening, Week 0, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48 and Week 52) including unscheduled visits used to assess flares and early withdrawal visits. Fasting lipids as presented in [Table 7](#) will be summarized as part of the hematology assessment. Fasting lipids are collected at Week 0, Week 12, Week 24, Week 36, and Week 52.

Table 7 Hematology and Fasting Lipids Parameters

Hematology		
Hemoglobin	Hematocrit	Red blood cell (RBC) count
White blood cell (WBC) count with differential	Neutrophils, absolute	Neutrophils, segs (%)
Neutrophils, bands (%)	Basophils (%)	Eosinophils (%)
Eosinophils, absolute	Lymphocytes (%)	Monocytes (%)
Platelet count	Hemoglobin A1c	
Fasting lipids		
Total cholesterol	Low density lipoprotein (LDL)	High density lipoprotein (HDL)
Triglycerides	Total cholesterol to HDL ratio	

9.2.2. Serum Chemistry

Serum chemistry assessments presented in CPK and LDH will be listed as part of Chemistry parameters but will not be summarized.

Table 8 are taken at predefined visits as specified in [Appendix 13.1](#) (i.e. at Screening, Week 0, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48 and Week 52), including unscheduled visits used to assess flares and early withdrawal visits. CPK and LDH will be listed as part of Chemistry parameters but will not be summarized.

Table 8 Serum chemistry Parameters

Serum Chemistry		
Sodium	Potassium	Chloride
Bicarbonate	Blood urea nitrogen (BUN)	Creatinine
Glucose	Aspartate aminotransferase	Alanine aminotransferase
Alkaline phosphatase	Calcium	Phosphate
Albumin	Total protein	Bilirubin, direct, indirect and total

9.2.3. Other Laboratory Variables

To characterize changes in biomarkers of disease activity, absolute value and change from Baseline in ESR and CRP will be summarized over time.

Serology for virus infection (serology for human immunodeficiency virus (HIV), hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C antibody) will be performed at Screening. All results (except serology for HIV) will be listed.

All QuantiFERON-TB Gold test results will be listed.

Serum pregnancy test will be performed at Screening, for premenopausal women only. Urine test will be conducted following the Screening visit, as specified in [Appendix 13.1](#) (i.e. at Screening, Week 0, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48 and Week 52). Pregnancy tests will be listed.

All available biomarkers will be listed (CTX-1, P1NP and IFN- γ are expected for a subset of subjects/visits).

Table 9 Other Laboratory Parameters

Other tests	
Serum and urine pregnancy test for premenopausal women only	
Serology for human immunodeficiency virus, hepatitis B surface antigen, hepatitis B core antibody and hepatitis C antibody	
C-reactive protein (CRP)	Erythrocyte sedimentation rate (ESR)
QuantiFERON-TB Gold	

9.3. Vital Sign Measurements

Vital signs assessments are taken as specified in [Appendix 13.1](#) (i.e. at Screening, Week 0, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48 and Week 52).

Summary table and change from baseline table will be presented for vital sign data, including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beats/min), temperature ($^{\circ}$ C) and weight (kg), over time by actual treatment group. All vital sign data by subject will be presented in a listing. A summary of worst case emergent (i.e. post-baseline) vital sign results by normal range category will be created and displayed by actual treatment group.

Normal ranges for vital sign are displayed in the table below:

Vital Sign Parameter (Absolute)	Units	Normal Range Limit	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	Bpm	< 40	> 110
Temperature	°C		≥ 38.3

9.4. Signs and Symptoms of GCA

At Baseline and each subsequent week, a clinical assessment of GCA is performed.

A summary table will be provided over time for each scheduled visit, with the number of subjects with each of the signs and symptoms, when no flare and when flare.

Clinical assessment of GCA will be listed in detail.

9.5. Electrocardiogram

Triplicate 12-lead electrocardiograms (ECGs) will be obtained at the Screening visit using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and correct QT intervals. Besides screening, ECG is only required when any suspected cardiac abnormality arise.

Listings of ECG interpretations and ECG values will be provided and worst screening interpretation will be summarized and listed.

9.6. Other Safety Data

9.6.1. Liver Events

A summary of Liver Monitoring/Stopping Event Reporting will be produced. This summary will display:

- Number of subjects with liver monitoring and/or stopping event
- Number of subjects with liver stopping event:
 - Number of subject with start of liver stopping event will be split based on the exposed period.
 - Number of subjects with liver stopping events resolved / not resolved
- Number of subjects with liver monitoring event that never reached stopping criteria:
 - Number of subject with start of liver stopping event will be split by based on the exposed period.
 - Number of subjects with liver stopping events resolved / not resolved
 - Number of subjects with Restart/Re-challenge of events

All liver events information will be presented in separate listings:

- Listing of subjects experiencing liver monitoring/stopping event during the study
- Liver PK
- Liver Biopsy

- Liver Monitoring/Stopping Event Reporting
- Liver Imaging
- Liver Events
- Medical Conditions at Onset of Liver Event
- Other Liver Disease Conditions
- Other Medical Conditions

For each listing all data collected in the eCRF will be listed in detail.

An additional summary of subjects meeting emergent hepatobiliary laboratory abnormality criteria (as defined in protocol section 5.4.3.) will be displayed.

9.6.2. Injection Site Reaction

An injection site reaction is any unfavorable or unintended sign that occurs at the study drug injection site. All subjects must be carefully observed for symptoms of an injection site reaction. Prior to and including through Week 4, subjects will be observed for at least 30 minutes after the SC injection of study drug for symptoms of an injection site reaction.

After Week 4, subjects do not need to be observed for 30 minutes for the post-administration injection-site evaluation if they are self-administering at home. However, subjects should promptly notify the site if they experience a reaction at the site of injection. If an injection site reaction is observed, the subject should be treated at the investigator's discretion.

An injection site reaction will also be reported as an AE in the study.

All data related to injection site reaction will be listed in detail.

9.6.3. Columbia-Suicide Severity Rating Scale

Suicidality assessments are completed at every visit (i.e. at Week 0, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48 and Week 52). Assessments are done using the C-SSRS. If a "yes" response is given to any suicidal behavior (not including self-injurious behavior) or a "yes" response to suicidal ideation questions 3, 4 or 5 on the C-SSRS, the investigator will be prompted to discuss the alert with the subject. A standard PSRAE (Possible suicidality-related AE) data collection form is available that is intended to collect detailed information on the circumstances of reported AEs which, in the investigator's opinion, are possibly suicidality-related. A summary table of C-SSRS post-baseline results will be provided. All C-SSRS and Possible Suicidality Related Questionnaire information will be listed in detail.

10. IDMC Reviews

An Independent Data Monitoring Committee (IDMC) will monitor data from this study. The overall responsibility of the IDMC is to protect the ethical and safety interests of subjects recruited into 201677 while protecting as far as possible the scientific validity of the data.

The IDMC will make recommendations concerning conduct of the study, including changes to the informed consent. The IDMC will meet at predefined times to identify potential treatment harm and all-cause mortality/morbidity.

After the initial organizational meeting, the first data review meeting will be held once 12 subjects have completed 12 weeks of treatment. Thereafter, the frequency of scheduled meetings depends on subject enrollment, information accumulated and safety event rates but will occur no less than quarterly.

Full details are provided in the IDMC charter document (dated 20JAN2016).

Due to study termination, the IDMC agreed to have the last formal meeting on Oct 25, 2017. Monthly cumulative SAE listing are sent to the IDMC until study end (LSLV). If the committee has any inquiries regarding safety, they can raise it with PPD and GSK even though no additional formal IDMC meeting is scheduled.

11. Part B

Only demographic and baseline characteristic as well as Safety will be displayed for Part B. All demographic and baseline characteristic as well as Safety summaries produced for Part A will be produced for Part B. Part B outputs will be displayed using the same general layout of Part A outputs, using the same Part A group as the treatment groups.

Each output will be split using a by-line which will contain information on Part B:

- “Never Received OL Sirukumab during Part B” will include all subjects who did not take a dose of Received OL Sirukumab during Part B.
- “Received at Least 1 Dose of OL Sirukumab during Part B” will include all subjects who took at least one dose of OL Sirukumab during Part B.

The Baseline for Part B will be the last measurement done up to and including the Week 52 visit date of Part A.

11.1. Analysis Set

11.1.1. Intent-to-Treat – Part B

The Intent-to-Treat – Part B (ITT – Part B) set will include all randomized subjects who received at least 1 dose of SC investigational product (IP) in Part A and entered Part B. In the event that there is a discrepancy, all subjects in the ITT – Part B set will be analyzed according to the treatment they were randomized to receive in Part A and not according to what they actually received in Part A. The ITT – Part B set will be used for the summaries of demographic, background, disposition and efficacy outputs in Part B.

11.1.2. Safety – Part B

The Safety – Part B set will include all randomized subjects who received at least 1 dose of SC IP in Part A and entered Part B. All subjects in the Safety – Part B set will be analyzed according to the treatment actually received in Part A and not according to the treatment they were randomized to receive in Part A, in the event there is a discrepancy. The Safety – Part B set will be used to analyze all of the safety endpoints in Part B.

11.2. Extent of Exposure

The following 3 parameters will be reported on the Safety set:

- Total number of injections a subject receives during Part B.

- Duration of SC IP treatment (weeks): defined as (Date of last SC IP dose in Part B – Date of first SC IP dose in Part B + 1 day) / 7. Only complete dates will be used when calculating duration of treatment. First and last injection dates will be used, regardless of any missed doses.
- Duration of SC IP exposure (weeks): defined as (Date of last SC IP dose in Part B – Date of first SC IP dose in Part B + 112 days) / 7. Only complete dates will be used when calculating duration of exposure. First and last injection dates will be used, regardless of any missed doses.
- Cumulative SC IP dose: defined as the total dose in mg a subject receives during Part B.

No compliance will be calculated for Part B.

11.3. Concomitant Medications

Concomitant medications for Part B are defined as those medications which are taken on or after the Part A Week 52 visit date or the first SC IP of Part B open-label treatment, whichever is earlier.

11.4. Efficacy Analysis

11.4.1. Endpoints Specific to Part B

The following endpoints are specific to Part B and will be displayed only on the subset of subjects in sustained remission at the Week 52 visit of Part A and enrolled in Part B:

- Proportion of subjects in sustained remission over time (including week 24):
Subjects who remained in sustained remission without requirement for rescue therapy or treatment change at each scheduled visit of Part B will be defined as subjects having achieved all of the following criteria:
Subjects in sustained remission at the Week 52 visit of Part A, as defined in [Section 8.1](#).

AND

Absence of disease flare:

Flare is determined by the investigator and defined as the recurrence of symptoms attributable to active GCA, with or without elevations in ESR and/or CRP.

The following rule will be used to assess absence of disease flare:

“Has the patient flared since their last visit?” should be answered “No” at each scheduled and unscheduled visit from any Part B visit up to Week X visit of Part B on the Clinical Assessment of GCA eCRF page.

AND

No requirement for rescue therapy at any time through Week X of Part B

If any concomitant corticosteroid medication when the unit is not in (Actuation, Application, Area under curve, Cubic centimeter, Cells, Cells per kilogram, Fingertip unit, Drops, Gum, Inhalation, Kilocalories, Minimum alveolar concentration, Mega becquerels (MBq), Millicurie, Nebule, Patch, Powder, Puff, Ring, Spray, Suppository) or any of concomitant non-corticosteroid medication identified as “GCA related” with the question “Was drug administered as a rescue medication?” ticked as “Yes” and if the first SC IP date \leq Concomitant medication start date \leq Week X visit date, then the subject will fail the criterion.

AND

No requirement for treatment change at any time through Week X of Part B

If any OL Sirukumab dose is taken prior or on the Week X visit of Part B, subject will fail the criterion.

If all of the 4 criteria are met, subject will achieve the endpoint at the Week 24 visit of Part B. If 1 of the 4 criteria is not met, the subject will be considered as not meeting the endpoint. For more details on imputation of missing data for the primary endpoint, please refer to [Section 4.6.2.1](#).

Given study termination, only the subset of subjects who attended the Week X visit of Part B or who discontinued study treatment or withdrew from study prior to the 10th of October 2017 will be included in this analysis.

The proportion of subjects achieving the endpoint over time will be presented by Part A treatment group. Subjects achieving the endpoint will be categorized by the criterion they failed to achieve. A listing will be produced with the detail of each criteria met or not met over time.

- Time to first disease flare for subjects in sustained remission at Baseline of Part B:

Only subjects who achieve sustained remission at the Week 52 visit of Part A will be included in this analysis.

Time to first disease flare after clinical remission is the time (days) from the Week 52 visit date to the earliest disease flare date:

Subjects without disease flare at the time of the analysis will be censored at the date of their last visit.

A Kaplan-Meier analysis will be summarized. The number of subject achieving clinical remission, as well as the number of subjects with a disease flare and the number of subjects censored with their censoring reasons will be summarized. 25th percentile, median and 75th percentile time to first flare will be summarized in days for each treatment group.

11.4.2. Endpoints from Part A Reported during Part B

The following efficacy endpoints will be summarized and listed for Part B as for Part A using the by-line as specified in [Section 11](#), unless otherwise specified. The visit displayed in the outputs will be the re-mapped visit as specified in [Section 11.5](#).

- Cumulative prednisone dose over time:
Derivation will be the same as for Part A, as described in [Section 8.2.1](#). Only corticosteroid rescue therapies, as defined in [Section 3.3](#) and [Section 7.3](#) will be taken into account in the derivation of cumulative prednisone dose over time. All medication taken the day after the Week 52 visit of Part A will be considered in the analysis.
An additional summary will be displayed taking into account prednisone dose taken during both Part A and Part B.
- Number of disease flares per subject over time:

Derivation will be the same as for Part A, as described in [Section 8.2.4](#). All events occurring the day after the Week 52 visit of Part A will be considered in the analysis. The summary table will not use the Part B by-line.

An additional summary will be displayed taking into account all flares occurring during both Part A and Part B.

- Proportion of subjects requiring hospitalizations for disease flare and number of hospitalizations for disease flare over time:
Derivation will be the same as for Part A, as described in [Section 8.2.5](#). All events occurring the day after the Week 52 visit of Part A will be considered in the analysis. The summary table will not use the Part B by-line
- Patient-reported outcomes including SF-36v2 acute, EQ-5D (5L), FACIT-Fatigue, Pain NRS, Steroid Impact Questionnaire, HAQ-DI, PtGA and PhGA are exploratory endpoints in Part B and will only be listed

11.5. Adverse Events

Since some subjects may not take any study drug during Part B, all AEs (not only TEAEs) will be summarized for Part B. An AE for Part B is defined as an AE starting from the Part A Week 52 visit date or the first SC IP of the Part B open-label treatment, whichever is earlier, to the end of study.

All adverse events summary table will be duplicated:

- The first table will use the byline: “Never Received OL Sirukumab during Part B” vs. “Received at Least 1 Dose of OL Sirukumab during Part B”
- The second table will use the following byline:
 - “Exposed” adverse events: Defined as all AEs occurring within 16 weeks after Sirukumab (SC IP or OL Sirukumab intake during Part B)
 - “Non-exposed” adverse events: Defined as all AEs not occurring within 16 weeks after Sirukumab (SC IP or OL Sirukumab intake during Part B)

It is important to note that all adverse events occurring during Part B within 16 weeks after the last intake of SC IP will be considered as “Exposed”, even if a subject never took OL Sirukumab during Part B.

No adverse events leading to discontinuation of study that is related to prednisone study drug will be displayed since prednisone study drug is only taken during Part A. TEAE related to prednisone will be displayed for Part B (instead of related to prednisone study drug for Part A).

11.6. Visit-based outputs

All outputs displaying Part B visit will use a mapped visit in relation to the Baseline of Part B.

For example, if a subject starts OL Sirukumab at the Week 24 Visit of Part B, the visit 2 weeks after initiation of OL Sirukumab will be mapped Week 26 Visit of Part B.

All listings displaying data by visit will show both the original visit collected and the mapped visit. For example, a subject that flares and has a Week 12 PLUS 2 visit would have the following original and mapped visits:

- Original: Week 12 PLUS 2 Weeks Visit
- Mapped: Week 14 Visit

Note that the visit mapping will only affect subjects receiving OL Sirukumab at any time after (but not immediately upon) entry into Part B.

12. References

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13. Appendices

13.1. Schedule of Study Procedures

Table 10 Time and Events Table for Part A of the Study (52-Week Double-Blind Treatment Phase)

	Screening (~Wk -6+ 3d)	Baseline (Wk 0)	wk 2±3d	wk 4±3d	wk 8±3d	wk 12±3d	wk 16±3d	wk 20±3d	wk 24±3d	wk 28±3d	wk 32±3d	wk 36±3d	wk 40±3d	wk 44±3d	wk 48±3d	wk 52±3d	Flare	Early Withdrawal	Follow Up
Written Informed Consent ¹	x																		
Subject Demography	x																		
Medical and disease history	x																		
Inclusion/Exclusion Criteria	x	x																	
Randomization		x																	
Autoinjector training ²		x	x	x															
Dispense Investigational Product		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x ³			
Assess Invest. Product compliance			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant Medications			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Prior Medications	x																		
Efficacy Assessments																			
GCA disease activity	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
PGA (patient, physician) ⁴	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Health Outcomes																			
PGIC ⁴						x			x							x	x	x	
Pain NRS ⁴		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
HAQ-DI ⁴		x				x			x			x				x	x	x	
FACIT-Fatigue ⁴		x				x			x			x				x	x	x	
Steroid Impact ⁴		x				x			x			x				x	x	x	
SF-36v2 (acute) ⁴		x				x			x			x				x	x	x	
EQ-5D (5L) ⁴		x				x			x			x				x	x	x	

	Screening (~Wk -6+ 3d)	Baseline (Wk 0)	wk 2±3d	wk 4±3d	wk 8±3d	wk 12±3d	wk 16±3d	wk 20±3d	wk 24±3d	wk 28±3d	wk 32±3d	wk 36±3d	wk 40±3d	wk 44±3d	wk 48±3d	wk 52±3d	Flare	Early Withdrawal	Follow Up
Safety Assessments																			
Physical Examination ⁵	x	x														x	x	x	x
Vital Signs ⁶	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
12-lead ECG ⁷	x																		
Chest radiograph	x																		
TB evaluation ⁸	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x
QuantiFERON-TB Gold Test ⁹	x																		
Height and weight	x					x			x							x	x	x	
Adverse Events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
C-SSRS ⁴		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory Assessments																			
Hematology	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum chemistry	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CRP	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ESR	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Lipid panel (fasting)		x				x			x			x				x	x	x	
Hemoglobin A1c	x	x				x			x			x				x	x	x	
Pregnancy Test ¹⁰	S	U		U	U	U	U	U	U	U	U	U	U	U	U	U			U
HIV, HBsAg, HBeAg, Hepatitis C ¹¹	x																		
PK ¹²		x	x	x	x	x	x	x	x	x				x		x	x	x	x
Immunogenicity ¹²		x							x					x		x	x	x	x
Exploratory Lab Assessments																			
IL-6 measurements	x	x				x										x			
Blood Biomarkers & exploratory markers		x		x		x			x							x	x	x	
Blood and Urine Markers, Transcriptomics (optional) ¹³	x	x				x			x							x	x	x	
Pharmacogenetics sample ¹⁴		x																	
Exploratory US Imaging																			
Ultrasound imaging ¹⁵	x ¹⁶	x				x										x	x		

1. Including consent for pharmacogenetics.
2. Assuming placebo will also be administered using autoinjector. Additional training may be provided when required.
3. Only for those subjects who initiate open-label sirukumab treatment at the start of Part B.

4. PROs to be completed by subjects before other clinically evaluated assessments or blood draws and before the administration of study drug. At visits where subject is fasting for blood draws, the option exists to perform blood draws prior to completing PROs as necessary to end the fast. HAQ-DI administered only to subset of subjects with PMR. PGA assessed using PtGA (subjects) and PhGA (physicians, after subject completion of questionnaires and after conducting subject assessments).
5. Complete physical exam at Screening and brief physical exam at other time points.
6. Measure in a semi-supine position after 5 minutes rest; includes blood pressure, temperature and heart rate.
7. And when any suspected cardiac abnormality. Average of triplicate recordings.
8. Suggested questions. A QuantiFERON-TB Gold Test should be performed at any time during the study if tuberculosis is suspected.
9. Chest radiograph taken up to 3 months prior to Week 0 may be used to qualify at screening.
10. Pregnancy test: urine = U, serum = S. Premenopausal women only.
11. If hepatitis C antibody positive, a hepatitis C RNA PCR assay should be reflexively performed on a fresh sample to confirm the result.
12. On study drug administration days, PK serum samples must be collected prior to study drug administration. Blood collected from 1 venipuncture will be divided into multiple aliquots of serum for PK serum (sirukumab concentration and antibodies to sirukumab) and backup samples.
13. To be collected only for those subjects consenting to provide samples for the biobank for future exploration of GCA disease biology.
14. Sample should be collected at the Baseline visit but may be collected at any visit post-Baseline if not collected at the Baseline visit.
15. Selected sites participating in the exploratory US imaging portion only; restricted to subjects with new onset disease
16. Optimally (but not required), to be performed prior to or within 3 days of the start of prednisone.
The time window for the Safety Follow-up visit is +/- 7 days

Table 11 Time and Events Table for Part B of the Study (104-Week Extension): Subjects NOT Receiving Open-Label Sirukumab During Part B

	Wk 0/(Wk 52 of Part A)	wk 4±5d	wk 8±5d	wk 12±5d	wk 16±5d	wk 24±5d	wk 36±5d	wk 52±5d	wk 76±5d	wk 104±5d	Flare	Early Withdrawal
Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x
Assess Invest. Product compliance ¹	x											
Efficacy Assessments												
GCA disease activity	x	x	x	x	x	x	x	x	x	x	x	x
PGA (patient, physician) ²	x	x	x	x	x	x	x	x	x	x	x	x
Health Outcomes												
Pain NRS ²	x	x	x	x		x		x	x	x	x	x
HAQ-DI ²	x			x		x		x	x	x	x	x
FACIT-Fatigue ²	x			x		x		x	x	x	x	x
Steroid Impact ²	x			x		x		x	x	x	x	x
SF-36v2 (acute) ²	x			x		x		x	x	x	x	x
EQ-5D (5L) ²	x			x		x		x	x	x	x	x
Safety Assessments												
Physical Examination ³	x							x		x	x	x
Vital Signs ⁴	x	x	x	x	x	x	x	x	x	x	x	x
TB evaluation ⁵	x	x	x	x	x							x ⁶
Height and weight	x									x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x
C-SSRS ²	x	x	x	x	x						x	x
Laboratory Assessments												
Hematology	x	x	x	x	x						x ⁶	x ⁶
Serum chemistry	x	x	x	x	x						x ⁶	x ⁶
CRP	x	x	x	x	x	x	x	x	x	x	x	x

	Wk 0/(Wk 52 of Part A)	wk 4±5d	wk 8±5d	wk 12±5d	wk 16±5d	wk 24±5d	wk 36±5d	wk 52±5d	wk 76±5d	wk 104±5d	Flare	Early Withdrawal
ESR	x	x	x	x	x	x	x	x	x	x	x	x
Lipid panel (fasting)	x			x	x						x ⁶	x ⁶
Hemoglobin A1c	x			x	x						x ⁶	x ⁶
Pregnancy Test ⁷	U	U	U	U	U							U ⁶
Exploratory Lab Assessments												
IL-6 measurements	x											
Blood Biomarkers & exploratory markers	x											
Blood and Urine Markers, Transcriptomics (optional)	x											
Exploratory US Imaging												
Ultrasound imaging ⁸											x	

1. Assessment from Week 52 visit of Part A
2. PROs to be completed by subjects before other clinically evaluated assessments or blood draws and before the administration of study drug. At visits where subject is fasting for blood draws, the option exists to perform blood draws prior to completing PROs as necessary to end the fast. HAQ-DI administered only to sub-set of subjects with PMR. PGA assessed using PtGA (subjects) and PhGA (physicians, after subject completion of questionnaires and after conducting subject assessments).
3. Brief physical exam.
4. Measure in a semi-supine position after 5 minutes rest; includes blood pressure, temperature and heart rate.
5. Suggested questions. A QuantiFERON-TB Gold Test should be performed at any time during the study if tuberculosis is suspected.
6. To be performed only if Early Withdrawal visit or flare occurs on or before Week 16 visit.
7. Pregnancy test: urine = U, serum = S. Premenopausal women only.

8. For subjects participating in the exploratory US imaging cohort. Ultrasound scans to be performed only in the event of disease flare or relapse in Part B. Part B scans will conclude when the last subject in the US imaging cohort completes Part A.

Table 12 Time and Events Table for Part B (104-Week Extension) of the Study: Subjects Receiving Open-Label Sirukumab Immediately Upon Entry Into Part B

	Wk 0/(Wk 52 of Part A)	Wk2±5d	wk 4±5d	wk 8±5d	wk 12±5d	wk 16±5d	wk 24±5d	wk 36±5d	wk 48±5d ¹	wk 52±5d	wk 76±5d	wk 104±5d	Flare	Early Withdrawal	Follow Up
Dispense Investigational Product	x	x	x	x	x	x	x	x	x						
Assess Invest. Product compliance	x	x	x	x	x	x	x	x		x			x	x	
Concomitant Medications	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Efficacy Assessments															
GCA disease activity	x	x	x	x	x	x	x	x		x	x	x	x	x	
PGA (patient, physician) ²	x	x	x	x	x	x	x	x		x	x	x	x	x	
Health Outcomes															
Pain NRS ²	x	x	x	x	x		x			x	x	x	x	x	
HAQ-DI ²	x				x		x			x	x	x	x	x	
FACIT-Fatigue ²	x				x		x			x	x	x	x	x	
Steroid Impact ²	x				x		x			x	x	x	x	x	
SF-36v2 (acute) ²	x				x		x			x	x	x	x	x	
EQ-5D (5L) ²	x				x		x			x	x	x	x	x	
Safety Assessments															
Physical Examination ³	x									x		x	x	x	x
Vital Signs ⁴	x	x	x	x	x	x	x	x		x	x	x	x	x	x
TB evaluation ⁵	x	x	x	x	x	x	x	x		x	x	x		x	
Height and weight	x											x	x	x	
Adverse Events	x	x	x	x	x	x	x	x		x	x	x	x	x	x
C-SSRS ²	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Laboratory Assessments															
Hematology	x	x	x	x	x	x	x	x		x	x	x	x	x	

	Wk 0/(Wk 52 of Part A)	Wk2±5d	Wk 4±5d	Wk 8±5d	Wk 12±5d	Wk 16±5d	Wk 24±5d	Wk 36±5d	Wk 48±5d ¹	Wk 52±5d	Wk 76±5d	Wk 104±5d	Flare	Early Withdrawal	Follow Up
Serum chemistry	x	x	x	x	x	x	x	x		x	x	x	x	x	
CRP	x	x	x	x	x	x	x	x		x	x	x	x	x	
ESR	x	x	x	x	x	x	x	x		x	x	x	x	x	
Lipid panel (fasting)	x				x	x	x	x		x	x	x	x	x	
Hemoglobin A1c	x				x	x	x	x		x	x	x	x	x	
Pregnancy Test ⁶	U		U	U	U	U	U	U	U	U	U	U		U	U
PK ⁷	x				x					x		x	x	x	x
Immunogenicity ⁷	x				x					x		x	x	x	x
Exploratory Lab Assessments															
IL-6 measurements	x														
Blood Biomarkers & exploratory markers	x														
Blood and Urine Markers, Transcriptomics (optional)	x														
Exploratory US Imaging															
Ultrasound imaging ⁸													x		

1. Visit only to dispense IP; no assessments are required.
2. PROs to be completed by subjects before other clinically evaluated assessments or blood draws and before the administration of study drug. At visits where subject is fasting for blood draws, the option exists to perform blood draws prior to completing PROs as necessary to end the fast. HAQ-DI administered only to subset of subjects with PMR. PGA assessed using PtGA (subjects) and PhGA (physicians, after subject completion of questionnaires and after conducting subject assessments).
3. Brief physical exam.
4. Measure in a semi-supine position after 5 minutes rest; includes blood pressure, temperature and heart rate.
5. Suggested questions. A QuantiFERON-TB Gold Test (or if not approved at the site, a tuberculin skin test) should be performed at any time during the study if TB is suspected.

6. Pregnancy test: urine = U, serum = S. Premenopausal women only. A urine pregnancy test should be performed every 4 weeks while taking open-label sirukumab and for 16 weeks after discontinuation of sirukumab treatment. Subjects should perform a urine pregnancy test at home when there is no study visit corresponding to the 4-weekly interval. Pregnancy test kits will be provided by the central laboratory for subject use at home.

7. On study drug administration days, PK serum samples must be collected prior to study drug administration. Blood collected from 1 venipuncture will be divided into multiple aliquots of serum for PK serum (sirukumab concentration and antibodies to sirukumab) and backup samples.

8. For subjects participating in the exploratory US imaging cohort. Ultrasound scans to be performed only in the event of disease flare or relapse in Part B. Part B scans will conclude when the last subject in the US imaging cohort completes Part A.

The time window for the Safety Follow-up visit is +/- 7 days

Table 13 Time and Events Table for Part B (104-Week Extension) of the Study: Subjects Receiving Open-Label Sirukumab at Any Time AFTER (but NOT Immediately Upon) Entry into Part B

	Start of open-label sirukumab ¹	PLUS 2 Wks±5d	PLUS 4 Wks±5d	PLUS 8 Wks±5d	PLUS 12 Wks±5d	PLUS 16 Wks±5d	PLUS 24 Wks±5d	PLUS 36 Wks±5d	PLUS 48 Wks±5d ²	PLUS 52 Wks±5d	PLUS 76 Wks±5d	PLUS 104 Wks±5d ³	Flare	Early Withdrawal	Follow Up
Dispense Investigational Product		X	X	X	X	X	X	X	X						
Assess Invest. Product compliance		X	X	X	X	X	X	X		X	X	X	X	X	
Concomitant Medications		X	X	X	X	X	X	X		X	X	X	X	X	X
Efficacy Assessments															
GCA disease activity	X	X	X	X	X	X	X	X		X	X	X	X	X	
PGA (patient, physician) ⁴		X	X	X	X	X	X	X		X	X	X	X	X	
Health Outcomes															
Pain NRS ⁴		X	X	X	X		X			X	X	X	X	X	
HAQ-DI ⁴					X		X			X	X	X	X	X	
FACIT-Fatigue ⁴					X		X			X	X	X	X	X	
Steroid Impact ⁴					X		X			X	X	X	X	X	
SF-36v2 (acute) ⁴					X		X			X	X	X	X	X	
EQ-5D (5L) ⁴					X		X			X	X	X	X	X	
Safety Assessments															
Physical Examination ⁵										X		X	X	X	X
Vital Signs ⁶		X	X	X	X	X	X	X		X	X	X	X	X	X
TB evaluation ⁷		X	X	X	X	X	X	X		X	X	X		X	
Height and weight												X	X	X	
Adverse Events		X	X	X	X	X	X	X		X	X	X	X	X	X
C-SSRS ⁴	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Laboratory Assessments															
Hematology		X	X	X	X	X	X	X		X	X	X	X	X	
Serum chemistry		X	X	X	X	X	X	X		X	X	X	X	X	

	Start of open-label sirukumab ¹	PLUS 2 Wks±5d	PLUS 4 Wks±5d	PLUS 8 Wks±5d	PLUS 12 Wks±5d	PLUS 16 Wks±5d	PLUS 24 Wks±5d	PLUS 36 Wks±5d	PLUS 48 Wks±5d ²	PLUS 52 Wks±5d	PLUS 76 Wks±5d	PLUS 104 Wks±5d ³	Flare	Early Withdrawal	Follow Up
CRP		x	x	x	x	x	x	x		x	x	x	x	x	
ESR		x	x	x	x	x	x	x		x	x	x	x	x	
Lipid panel (fasting)					x	x	x	x		x	x	x	x	x	
Hemoglobin A1c					x	x	x	x		x	x	x	x	x	
Pregnancy Test ⁸			U	U	U	U	U	U	U	U	U	U		U	U
PK ⁹					x					x		x	x	x	x
Immunogenicity ⁹					x					x		x	x	x	x
Exploratory US Imaging															
Ultrasound imaging ¹⁰													x		

1. Upon the initiation of open-label sirukumab, perform the assessments from “Time and Events Table for Part B of the Study (104-week Extension): Subjects NOT Receiving Open-label Sirukumab During Part B” at the visit the subject was scheduled to undergo when study drug is started.
2. Visit only to dispense IP; no assessments are required.
3. Although this visit is labelled as 104 weeks since the start of open-label sirukumab, it does not take into account the exact start time, since this will be different for each subject depending upon when in the first 52 weeks of Part B open-label sirukumab was started. The important point to note, is that this last visit should be scheduled when each of these subjects will complete 104 weeks in Part B.
4. PROs to be completed by subjects before other clinically evaluated assessments or blood draws and before the administration of study drug. At visits where subject is fasting for blood draws, the option exists to perform blood draws prior to completing PROs as necessary to end the fast. HAQ-DI administered only to sub-set of subjects with PMR. PGA assessed using PtGA (subjects) and PhGA (physicians, after subject completion of questionnaires and after conducting subject assessments).
5. Brief physical exam.
6. Measure in a semi-supine position after 5 minutes rest; includes blood pressure, temperature and heart rate.

7. Suggested questions. A QuantiFERON-TB Gold Test should be performed at any time during the study if tuberculosis is suspected.
8. Pregnancy test: urine = U, serum = S. Premenopausal women only. A urine pregnancy test should be performed every 4 weeks while taking open-label sirukumab and for 16 weeks after discontinuation of sirukumab treatment. Subjects should perform a urine pregnancy test at home when there is no study visit corresponding to the 4-weekly interval. Pregnancy test kits will be provided by the central laboratory for subject use at home.
9. On study drug administration days, PK serum samples must be collected prior to study drug administration. Blood collected from 1 venipuncture will be divided into multiple aliquots of serum for PK serum (sirukumab concentration and antibodies to sirukumab) and backup samples.
10. For subjects participating in the exploratory US imaging cohort. Ultrasound scans to be performed only in the event of disease flare or relapse in Part B.
Part B scans will conclude when the last subject in the US imaging cohort completes Part A.
The time window for the Safety Follow-up visit is +/- 7 days



PPD Biostatistics and Programming

Statistical Analysis Plan (SAP) Client Approval Form

Client:	GlaxoSmithKline
Protocol Number:	201677
Document Description:	Final Statistical Analysis Plan: GSK201677_SAP_V1.0
SAP Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Sirukumab in the Treatment of Patients with Giant Cell Arteritis
SAP Version Number:	Version 1.0
Effective Date:	04JUNE2018

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05 JUN 2018

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05 JUN 2018

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