TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

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

Compound Number: GSK2973327

Development Phase: III

Effective Date: 17-NOV-2016

Protocol Amendment Number: 3

Author (s):

PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N227575_00	2015-MAY-11	Original
2015N227575_01	2015-OCT-15	Amendment No. 1
The original protocol has been amended to clarify the secondary objectives and endpoints of characterization of sustained remission in Parts A and B, collection of patient and physician reported outcomes, including correction of the version of the EQ-5D version that will be administered and pain assessment using a numeric rating scale. Further clarifications have been included in updates to the potential signs and symptoms of GCA, prednisone use during screening and taper initiation, subject eligibility for receiving open-label sirukumab in Part B and investigator consideration of the individual subject benefit-risk of continuing sirukumab in Part B. This amendment includes additional information on risk mitigation for GI perforations and serious allergic/hypersensitivity events, including adjudication and classification of such events using Sampson criteria. The inclusion criteria for GCA diagnostic criteria for temporal artery biopsy and imaging and symptoms of active GCA have been updated. The exclusion criteria have been updated to include restrictions relating to prolonged use or requirement for continued use of systemic corticosteroids and amendment of the time frames for previous use of anti-TNFα therapies, which are detailed in the prohibited medications section. Additional clarifications on circumstances for re-testing of QuantiFERON-TB Gold test results, ECG assessment and provision of open-label prednisone to study sites have been included. Other changes include removal of restrictions on the use of NSAIDs, clarification of circumstances requiring discontinuation of study treatment but not study withdrawal, and circumstances in which subjects may withdraw from the study. The Time and Events table has been updated and corrections included. Other additions include guidance to investigators related to treatment of glucocorticoid-induced osteoporosis. Study withdrawal is no longer required for events meeting QTc withdrawal criteria, liver chemistry stopping criteria and pregnancy. Females using hormonal contraception are required to use a secondary method of contraception. Changes to statistical considerations include amendment of the sample size sensitivity analysis and specification of subjects who discontinue treatment in efficacy and safety analyses. Other changes include clarification of protocol-specified exploratory biomarkers and optional exploratory biomarkers, updated information on the study number for the exploratory imaging sub-study, randomization system and correction of typographical errors.		
2015N227575_02	2016-MAR-31	Amendment No. 2
The previous amendment, Protocol Amendment No. 1, has been revised to include the assessment of the utility of ultrasound imaging as an indicator of disease activity in an exploratory cohort of subjects. Other modifications include updates to the inclusion criteria for diagnosis of GCA to allow for diagnosis by ultrasound imaging in sites qualified to participate in the ultrasound imaging portion of the study, to further clarify features consistent with GCA or PMR flares, and to clarify requirements for the		

prednisone dose at Screening. The inclusion criteria have also been amended to include the acceptability of a single view of chest radiographs if consistent with local guidelines. Updated information on the pre-filled syringes has been included. Other modifications include the clarification that the daily prednisone dose should be taken in a single daily administration in the morning. Country-specific requirements have been included for Germany, the Netherlands, and Australia and New Zealand. These include a requirement to discontinue study drug administration in the event of a serious infection (Germany), a requirement for subjects to discontinue the study at the conclusion of Part A after completing the 16-week follow up phase (the Netherlands) and a requirement to notify investigators when the value of the ESR result is > 40 mm/hr or has increased > 10 mm/hr from baseline or previous result (Australia and New Zealand).		
2015N227575_03	2016-NOV-17	Amendment No. 3
The previous amendment, Protocol Amendment No. 2, has been revised to include the implementation of the Columbia-Suicide Severity Rating Scale to prospectively monitor suicidal ideation and behavior. Other modifications include revision of the endpoints for the exploratory imaging cohort, further clarifications regarding the initiation of the prednisone taper and prednisone sourcing information, and inclusion of malignancies as a potential risk of clinical significance. In addition, a requirement for male contraception and restrictions on sperm donation, amendment of QTc exclusion and stopping criteria, revision of criteria to allow prior anti-IL-6 use if not associated with intolerance or inadequate response, and addition of an exclusion criterion related to suicidality are included. Pregnancy testing is now required at 4-weekly intervals while subjects are receiving study drug during Parts A and B and during the 16-week follow up period after drug discontinuation. Additional clarification of reflex testing for hepatitis and tuberculosis testing have been included. Updated information regarding database locks and unblinding and treatment comparisons has also been included.		

SPONSOR SIGNATORY

PPD

17 Nov 2016

Kurt Brown, MD
Sirukumab, Project Physician Leader
Immuno-inflammation Therapy Area

Date

PPD

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 201677

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 201677

Rationale

Multiple lines of evidence support a role for interleukin-6 (IL-6) in the pathophysiology of giant cell arteritis (GCA). Sirukumab is a human anti-IL-6 immunoglobulin IgG1kappa monoclonal antibody (mAb) with a high affinity and specificity for binding to the human IL-6 molecule that 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.

Objective(s)/Endpoint(s)

Part A: 52-week double-blind treatment phase

Objectives	Endpoints
Primary	
• To investigate the efficacy of sirukumab (100 mg q2w for 12 months) as compared to placebo, each administered in addition to a 6-month prednisone treatment regimen	• Proportion of subjects in sustained remission at Week 52, defined as having achieved all of the following: 1. Remission* by Week 12 **and** 2. Absence of disease flare** following remission at Week 12 through Week 52 **and** 3. Completion of the assigned prednisone taper protocol **and** 4. No requirement for rescue therapy at any time through Week 52 *Remission is defined as absence of clinical signs and symptoms of GCA and normalization of ESR [<30mm/hr] and CRP [<1mg/dL]) **Flare is defined as recurrence of symptoms attributable to active GCA, with or without elevations in ESR and/or CRP
Secondary	
• To assess cumulative prednisone doses in subjects treated with sirukumab plus prednisone as compared to placebo plus prednisone	• Median and cumulative prednisone dose over time
• To investigate the efficacy of sirukumab (100	• Proportion of subjects in

Objectives	Endpoints
mg q2w for 12 months) administered with a 3-month prednisone treatment regimen versus placebo administered with a 6-month prednisone treatment regimen • To investigate the efficacy of 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) • To investigate the efficacy of 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 • To investigate the efficacy of sirukumab (50 mg q4w for 12 months) as compared to placebo, each administered in addition to a 6-month prednisone treatment regimen • To investigate the efficacy of 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	sustained remission at Week 52
• To characterize sustained remission 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: 1. Remission at Week 12 **and** 2. Absence of disease flare following remission at Week 12 **and** 3. Adherence to the assigned prednisone taper protocol **and** 4. No requirement for rescue therapy at any time
• To characterize disease flare over time	• Time to first GCA flare after clinical remission • Number of disease flares per patient over time • Proportion of subjects requiring hospitalizations for disease flare and number of hospitalizations for disease flare over time

Objectives	Endpoints
• To evaluate the safety of sirukumab plus prednisone treatment compared to placebo plus prednisone treatment • To investigate corticosteroid-related toxicities	• Incidence of adverse events and serious adverse events, incidence of corticosteroid-related adverse events, changes in vital signs, hematology and clinical chemistry parameters
• To assess the effect of sirukumab treatment on health-related quality of life, GCA and steroid-related symptoms and disability by patient and clinician reported outcomes over time	• Patient reported outcomes including SF-36v2, EQ-5D (5L), FACIT-Fatigue, Pain Numeric Rating Scale (NRS), Steroid Impact PRO, HAQ-DI, Patient Global Impression of Change (PGIC), Patient Global Assessment of disease activity (PtGA) • Clinician reported outcomes including Physician Global Assessment of disease activity (PhGA)
• To characterize changes in biomarkers of disease activity	• Change from baseline in ESR over time • Change from baseline in serum CRP over time
Pharmacokinetic/Immunogenicity	
• To investigate the pharmacokinetics of subcutaneously administered sirukumab	• Serum concentrations of sirukumab
• To evaluate immunogenicity of subcutaneously administered sirukumab	• Serum anti-sirukumab antibodies
Pharmacodynamic	
• To characterize the effect of sirukumab on IL-6 levels in the blood	• Change from baseline in free and total IL-6 over time
Exploratory	
• To explore the effect of sirukumab on exploratory biomarkers of Th1 and Th17 cell function	• Change from baseline in IFN-γ and IL-17A
• To evaluate the effect of sirukumab on exploratory biomarkers of bone metabolism	• Change from baseline in serum markers of bone formation/resorption: CTX1/P1NP

Objectives	Endpoints
• 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 ultrasound for clinical efficacy in GCA	• 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
Pharmacogenetic	
• To potentially explore relationships between genetic variants and sirukumab efficacy and safety endpoints	• Correlation of genetic markers with the safety and efficacy response to sirukumab

GCA = giant cell arteritis; ESR – erythrocyte sedimentation rate; CRP = C-reactive protein; SF-36 v2 = 36-item short form health survey version 2; EQ-5D (3L) = EuroQoL-5 dimensions; FACIT-fatigue = functional assessment of chronic illness therapy-fatigue; PRO = patient reported outcomes; HAQ-DI = health assessment questionnaire-disability index; PGIC = Patient Global Impression of Change; P1NP = procollagen type 1 N-propeptide; CTX = carboxyterminal cross-linked telopeptide of bone collagen; IL = interleukin; US=ultrasound.

Part B: 104-week long-term extension phase

Objectives	Endpoints
• To evaluate the long-term maintenance of disease remission on cessation of 12 months of sirukumab treatment	• 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 GCA flare for subjects in sustained remission at baseline of Part B • Number of disease flares per patient over time • Proportion of subjects requiring hospitalizations for disease flare and number of hospitalizations for disease

Objectives	Endpoints
	flare over time • Proportion of subjects who remained in sustained remission without requirement for rescue therapy or treatment change 6 months post cessation of 12-month sirukumab treatment
• To assess the effect of sirukumab treatment on health-related quality of life, GCA and steroid-related symptoms and disability by patient and clinician reported outcomes over time	• Patient reported outcomes including SF-36v2, EQ-5D (5L), FACIT-Fatigue, Pain NRS, Steroid Impact PRO, HAQ-DI and PtGA • Clinician reported outcomes including PhGA
• To assess long-term cumulative prednisone doses	• Median and cumulative prednisone dose over time
• To assess the long-term safety of sirukumab	• Incidence of adverse events and serious adverse events, changes in vital signs, hematology and clinical chemistry parameters
• To investigate long-term corticosteroid-related toxicities	• Incidence of corticosteroid-related adverse events
• To evaluate immunogenicity of subcutaneously administered sirukumab in subjects receiving open-label sirukumab	• Serum anti-sirukumab antibodies

GCA = giant cell arteritis; SF-36 v2 = 36-item short form health survey version 2; EQ-5D (3L) = EuroQoL-5 dimensions; FACIT-fatigue = functional assessment of chronic illness therapy-fatigue; PRO = patient reported outcomes; HAQ-DI = health assessment questionnaire-disability index

Overall Design

This is a multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of 2 doses of sirukumab in the treatment of GCA. 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 16-week follow-up phase if applicable.

Subjects will be randomized to receive sirukumab 100 mg subcutaneous [SC] every 2 weeks [q2w] or 50 mg SC every 4 weeks [q4w] or matching placebo. All subjects will receive prednisone during the 52-week double-blind treatment period according to a pre-specified taper regimen.

An Independent Data Monitoring Committee (IDMC) and an independent Clinical Events Committee (CEC) will be utilized in this study.

Three primary database locks (DBLs) are planned for reporting of the results:

- The first DBL for the primary analysis will occur after all subjects have completed the Week 52 visit assessments in Part A or have withdrawn prematurely from the study. Treatment-level data will be unblinded to Sponsor personnel.
- The second DBL for the 6-month follow-up will occur after all subjects have completed the Week 24 visit in Part B, or have withdrawn prematurely from the study. The data from subjects undergoing the 16-week follow-up assessments at the end of Part A will also be included and will potentially comprise a separate data set/report if applicable.
- The third planned DBL will occur after all subjects have completed the last visit in Part B, or have withdrawn prematurely from the study. The Part B DBL will include the data from all visits associated with Part B of the study, including the 16-week follow-up assessments of Part B if applicable.

All subjects and study site personnel will remain blinded to the treatment group assignment until all subjects of Part B have completed the Week 24 visit assessments of Part B.

Treatment Arms and Duration

In Part A, eligible subjects will be randomized in a ratio of 3:3:2:2:2 to one of the following 5 treatment arms:

1. Treatment Arm A: Sirukumab 100 mg SC q2w for 52 weeks plus a pre-specified maximum of 6-month prednisone taper regimen

2. Treatment Arm B: Sirukumab 100 mg SC q2w for 52 weeks plus a pre-specified maximum of 3-month prednisone taper regimen
3. Treatment Arm C: Sirukumab 50 mg SC q4w for 52-weeks plus a pre-specified maximum of 6-month prednisone taper regimen
4. Treatment Arm D: Placebo SC q2w for 52 weeks plus a pre-specified maximum of 6-month prednisone taper regimen
5. Treatment Arm E: Placebo SC q2w for 52 weeks plus a pre-specified maximum of 12-month prednisone taper regimen.

The prednisone tapering schedule begins for all subjects upon randomization (Baseline, Week 0) as follows:

- Subjects will remain on the prednisone dose they are currently receiving at Baseline for one week.
- At Week 1, the prednisone dose will be decreased in accordance with the pre-specified prednisone taper schedule.
- The pre-specified maximum tapering schedule to be followed will depend on the subject's treatment group assignment.
- The prednisone taper will be unblinded (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.

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

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

For subjects who newly flare at any time during the 1st 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.

Type and Number of Subjects

Approximately 204 subjects with a diagnosis of GCA based on the Revised GCA Diagnosis Criteria will be randomized at Baseline into the 52-week double-blind, placebo controlled phase (Part A) of the study.

Subjects are required to have active GCA disease within 6 weeks of baseline where active disease is defined as the presence of unequivocal clinical signs and symptoms attributable to GCA and increased levels of inflammatory markers [ESR ≥ 30 mm/hr and/or CRP ≥ 1 mg/dL (10 mg/L)]. 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. Relapsing/refractory subjects include those who may have previously been in remission with corticosteroid treatment and have recurrence of disease activity (relapsing) or subjects who continued to have active disease without remission despite previous or ongoing corticosteroid therapy (refractory).

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.

Analysis

The proportion of subjects with sustained remission at Week 52 in the sirukumab 100 mg SC q2w plus 6 month prednisone versus placebo plus 6 month prednisone will be analyzed using a generalized estimating equations model controlling for stratification factor of baseline prednisone dose. The model will include treatment, week, treatment-by-week interaction and subject within week as a random effect. Treatment differences will be presented as odds ratios and concluded as statistically significant if $P \leq 0.05$.

Since sirukumab is as yet untested in GCA, the study may employ a futility interim analysis to enable a decision to stop the study early should there be no or little effect of sirukumab. Depending on the recruitment rate, an interim analysis may be carried out when approximately 30% of patients have completed 52 weeks. The study will only be stopped for futility (lack of efficacy) if the probability of success of the study (i.e. the conditional power based on the observed interim data) is calculated to be very low.

2. INTRODUCTION

Sirukumab is a human anti-IL-6 immunoglobulin IgG1kappa mAb 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).

2.1. Study Rationale

Multiple lines of evidence support a role for IL-6 in the pathophysiology of GCA [Emilie, 1994; Roche, 1993]. Sirukumab is a human anti-IL-6 immunoglobulin IgG1kappa mAb with a high affinity and specificity for binding to the human IL-6 molecule that 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.

2.2. Brief Background

GCA is a systemic vasculitis affecting medium-sized and large arteries usually accompanied or preceded by systemic inflammation. It is the most common primary form of vasculitis in the United States and Europe and occurs predominantly in individuals aged 50 years or over with the mean age of onset of approximately 70 years of age [Salvarani, 2004]. Women are affected about 3 times as often as men and the most common symptoms include headache, visual loss, symptoms of polymyalgia rheumatic (PMR) and jaw claudication. Diagnosis is generally confirmed by temporal artery biopsy and typically CRP and ESR rate are increased [Nesher, 2014; Waldman, 2013]. Corticosteroids are the treatment of choice starting with an initial high dose of prednisone at 40-60 mg/day for most cases followed by a tapered lowering of dose. Despite an often rapid improvement of symptoms following initial glucocorticoid treatment, most patients develop serious adverse side effects related to use of glucocorticoids. Disease relapse is common (50%-80%) during corticosteroid taper [Hachulla, 2001; Weyand, 2000]. While the general view is that steroid treatment can be reasonably stopped after 2 years, patients usually require steroid therapy for much longer [Hayreh, 2003]. Furthermore, a significant proportion (~25%) of patients do not achieve permanent remission [Proven, 2003].

It is estimated that more than 85% of GCA patients suffer from corticosteroid-related side-effects as a result of long-term treatment [Proven, 2003]. Studies with agents, including tumor necrosis factor (TNF) inhibitors, to demonstrate disease control and corticosteroid sparing properties have not been successful [Hoffman, 2007; Martinez-Taboada, 2008; Seror, 2013]. Trials with methotrexate have given conflicting results [Spies, 2010]. Furthermore, even with control of symptoms with corticosteroid therapy, persistent active vascular inflammation can be demonstrated in patients [Achkar, 1994]. Therefore, a significant unmet need for better therapies remains.

Although the trigger of the disease remains unknown, both adaptive and innate immune systems appear to be involved in the pathogenesis of GCA. Histologically, GCA is

characterised by a granulomatous infiltrate of T cells and macrophages and both Th1 and Th17 cells have been implicated [Weyand, 2013; Weyand, 2011]. IL-6, a cytokine produced by T cells, B cells, macrophages, endothelial cells and fibroblasts, is upregulated within these inflamed arteries and serum levels of IL-6 correlate with disease activity and response to corticosteroid treatment [Emilie, 1994; Roche, 1993]. IL-6 triggers the synthesis of acute phase reactants, promotes T cell activation, terminal differentiation of B cells, survival of plasma cells, differentiation of Th17 cells, and induces proinflammatory differentiation of monocyte/macrophages, while inhibiting Treg-cell differentiation and function [Rincon, 2012].

This evidence suggests that inhibition of IL-6 activity may be of therapeutic benefit in the treatment of GCA by interruption of multiple pathogenic pathways. This potential benefit is supported by experience with the open-label use of the IL-6 receptor antagonist, tocilizumab, for the treatment GCA patients, when administered with corticosteroids or as monotherapy [Besada, 2012; Beyer, 2011; Christidis, 2011; Isik, 2013; Lurati, 2012; Salvarani, 2012; Sciascia, 2011; Seitz, 2011; Unizony, 2012; Vinit, 2012]. Based on these results, a Phase III randomized, double-blind, placebo-controlled trial of tocilizumab for the treatment of GCA has been initiated [Unizony, 2013].

Similar to GCA, patients with rheumatoid arthritis (RA) often have increased levels of IL-6 in the synovial fluid and serum, together with TNFα and IL-1 [Gottenberg, 2012; Swaak, 1988]. Local concentrations of IL-6 may in turn stimulate leukocyte recruitment to the joint, promote osteoclast maturation and activation, suppress chondrocytes, and stimulate synovial proliferation, contributing to joint damage [(Flannery, 2000; Lipsky, 2006]. Systemically, elevated IL-6 in patients with RA may induce hepatic production of acute-phase proteins, increase platelet production, and likely increase hepcidin and the development of anemia of chronic inflammation [Nemeth, 2004].

Sirukumab is a fully human anti-IL-6 immunoglobulin G1-kappa with a high affinity and specificity for binding to the human IL-6 molecule. It has been shown to inhibit IL-6-mediated signal transducer and activator of transcription 3 (STAT3) phosphorylation, resulting in the inhibition of the biological effect of IL-6. A global Phase III clinical program with sirukumab for RA is on-going as a co-development partnership between GSK and Janssen-Cilag International. This program is comprised of four comparative Phase III trials in patients with RA who are DMARD- or anti-TNF-inadequate responders and a long term extension study for eligible patients. Two Phase II studies have been completed. Additional details regarding the RA clinical program are available in the Investigator Brochure.

Based upon the role of IL-6 in the pathogenesis of GCA and the supporting clinical evidence with tocilizumab, a randomized, double-blind, placebo-controlled study of subjects with active GCA is proposed. The purpose of this study will be to evaluate the efficacy and safety of sirukumab to characterize the benefit-to-risk profile of this agent in the treatment of active GCA.

3. OBJECTIVE(S) AND ENDPOINT(S)

Part A: 52-week double-blind treatment phase

Objectives	Endpoints
Primary	
• To investigate the efficacy of sirukumab (100 mg q2w for 12 months) as compared to placebo, each administered in addition to a 6-month prednisone treatment regimen	• Proportion of subjects in sustained remission at Week 52, defined as having achieved all of the following: 1. Remission* by Week 12 **and** 2. Absence of disease flare** following remission at Week 12 through Week 52 **and** 3. Completion of the assigned prednisone taper protocol **and** 4. No requirement for rescue therapy at any time through Week 52 *Remission is defined as absence of clinical signs and symptoms of GCA and normalization of ESR [<30mm/hr] and CRP [<1mg/dL]) **Flare is defined as recurrence of symptoms attributable to active GCA, with or without elevations in ESR and/or CRP
Secondary	
• To assess cumulative prednisone doses in subjects treated with sirukumab plus prednisone as compared to placebo plus prednisone	• Median and cumulative prednisone dose over time
• To investigate the efficacy of 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 • To investigate the efficacy of 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) • To investigate the efficacy of sirukumab (100 mg q2w for 12 months) administered with a 3-month	• Proportion of subjects in sustained remission at Week 52

Objectives	Endpoints
prednisone treatment regimen versus placebo administered with a 12-month prednisone treatment regimen • To investigate the efficacy of sirukumab (50 mg q4w for 12 months) as compared to placebo, each administered in addition to a 6-month prednisone treatment regimen • To investigate the efficacy of 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	
• To characterize sustained remission 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: 1. Remission at Week 12 **and** 2. Absence of disease flare following remission at Week 12 **and** 3. Adherence to the assigned prednisone taper protocol **and** 4. No requirement for rescue therapy at any time
• To characterize disease flare over time	• Time to first GCA flare after clinical remission • Number of disease flares per patient over time • Proportion of subjects requiring hospitalizations for disease flare and number of hospitalizations for disease flare over time
• To evaluate the safety of sirukumab plus prednisone treatment compared to placebo plus prednisone treatment • To investigate corticosteroid-related toxicities	• Incidence of adverse events and serious adverse events, incidence of corticosteroid-related adverse events, changes in vital signs, hematology and clinical chemistry parameters
• To assess the effect of sirukumab treatment on health-related quality of life, GCA and steroid-related symptoms and disability by patient and clinician reported outcomes over	• Patient reported outcomes including SF-36v2, EQ-5D (5L), FACIT-Fatigue, Pain Numeric Rating Scale (NRS), Steroid Impact PRO, HAQ-DI, Patient Global Impression of Change

Objectives	Endpoints
time	(PGIC), Patient Global Assessment of disease activity (PtGA) • Clinician reported outcomes including Physician Global Assessment of disease activity (PhGA)
• To characterize changes in biomarkers of disease activity	• Change from baseline in ESR over time • Change from baseline in serum CRP over time
Pharmacokinetic/Immunogenicity	
• To investigate the pharmacokinetics of subcutaneously administered sirukumab	• Serum concentrations of sirukumab
• To evaluate immunogenicity of subcutaneously administered sirukumab	• Serum anti-sirukumab antibodies
Pharmacodynamic	
• To characterize the effect of sirukumab on IL-6 levels in the blood	• Change from baseline in free and total IL-6 over time
Exploratory	
• To explore the effect of sirukumab on exploratory biomarkers of Th1 and Th17 cell function	• Change from baseline in IFN-γ and IL-17A
• To evaluate the effect of sirukumab on exploratory biomarkers of bone metabolism	• Change from baseline in serum markers of bone formation/resorption: CTX1/P1NP
• 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 ultrasound for clinical efficacy in GCA	• 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
Pharmacogenetic	
• To potentially explore relationships between genetic variants and sirukumab efficacy and safety endpoints	• Correlation of genetic markers with the safety and efficacy response to sirukumab

GCA = giant cell arteritis; ESR – erythrocyte sedimentation rate; CRP = C-reactive protein; SF-36 v2 = 36-item short form health survey version 2; EQ-5D (3L) = EuroQoL-5 dimensions; FACIT-fatigue = functional assessment of chronic illness therapy-fatigue; PRO = patient reported outcomes; HAQ-DI = health assessment questionnaire-disability index; PGIC = Patient Global Impression of Change; P1NP = procollagen type 1 N-propeptide; CTX = carboxyterminal cross-linked telopeptide of bone collagen; IL = interleukin; US=ultrasound.

Part B: 104-week long-term extension phase

Objectives	Endpoints
• To evaluate the long-term maintenance of disease remission on cessation of 12 months of sirukumab treatment	• 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 GCA flare for subjects in sustained remission at baseline of Part B • Number of disease flares per patient 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 post cessation of 12-month 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	• Patient reported outcomes including SF-36v2, EQ-5D (5L), FACIT-Fatigue, Pain NRS, Steroid Impact PRO, HAQ-DI and PtGA • Clinician reported outcomes including PhGA
• To assess long-term cumulative prednisone doses	• Median and cumulative prednisone dose over time
• To assess the long-term safety of sirukumab	• Incidence of adverse events and serious adverse events, changes in vital signs, hematology and clinical chemistry parameters
• To investigate long-term corticosteroid-related toxicities	• Incidence of corticosteroid-related adverse events
• To evaluate immunogenicity of subcutaneously administered sirukumab in subjects receiving open-label sirukumab	• Serum anti-sirukumab antibodies

GCA = giant cell arteritis; SF-36 v2 = 36-item short form health survey version 2; EQ-5D (3L) = EuroQoL-5 dimensions; FACIT-fatigue = functional assessment of chronic illness therapy-fatigue; PRO = patient reported outcomes; HAQ-DI = health assessment questionnaire-disability index

4. STUDY DESIGN

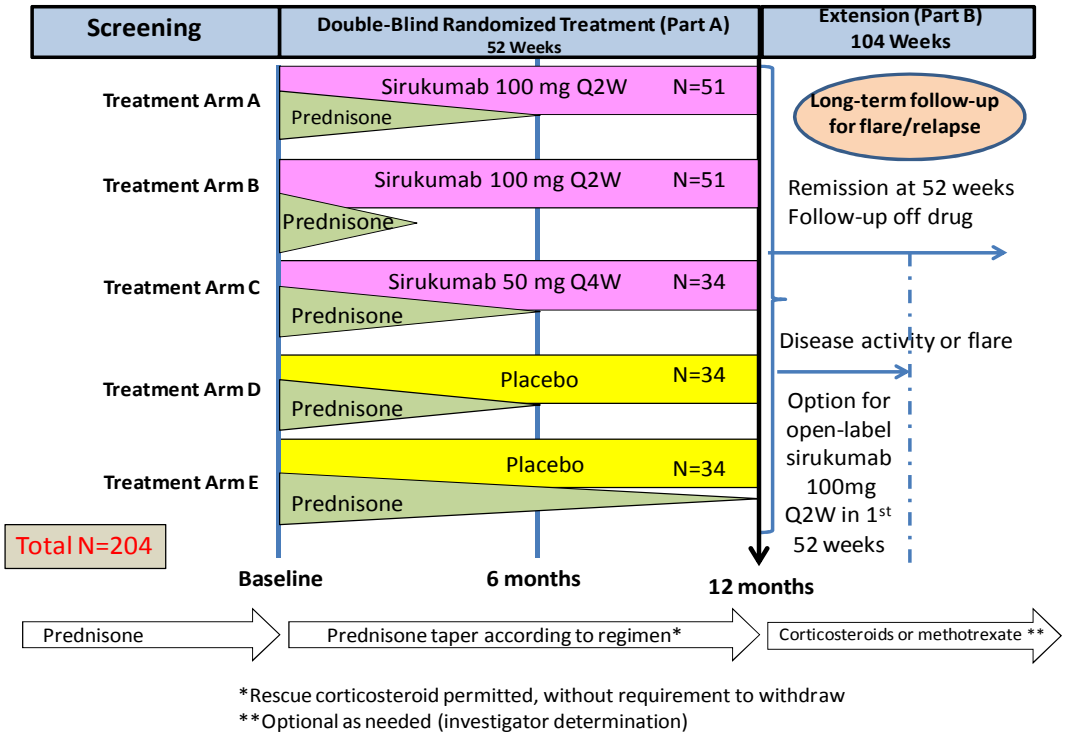
4.1. Overall Design

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. 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.

Figure 1 Study Design



This study will be conducted globally in sites selected to reflect the epidemiology of GCA.

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 ESR ≥30 mm/hr and/or serum CRP ≥1 mg/dL (10 mg/L). Signs and symptoms of GCA may include new onset headache; jaw claudication (jaw or mouth pain upon chewing); visual signs and symptoms including but not limited to amaurosis fugax, transient or episodic blurry vision, diplopia, permanent vision loss due to acute ischemic optic neuropathy (AION); temporal artery tenderness; scalp tenderness; reduced or absent pulsation in temporal artery; cord-like thickening of temporal artery; stroke; scalp necrosis; pain over face/scalp arteries; new or worsened extremity claudication; fever of unknown origin; PMR symptoms; or other symptoms that in the investigator's experience are associated with GCA.

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. 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. 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. At Baseline (Randomization), doses must be within 20-60 mg prednisone for the starting dose when the pre-specified prednisone taper is initiated. Subjects will remain on the prednisone dose they are receiving at Baseline for one week and then will decrease the dose at Week 1 as specified in the taper regimen. Subjects will follow the open-label prednisone taper regimen until they reach a 20 mg dose of prednisone, when the blinded prednisone taper regimen begins. Subjects receiving a 20 mg prednisone dose at Baseline will continue the 20 mg dose for one week and at Week 1 will initiate the blinded taper.

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. 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.

An Independent Data Monitoring Committee (IDMC) will be utilized to ensure external objective medical and/or statistical review of safety issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The composition, remit, and procedures of the committee are provided in the IDMC charter.

An independent Clinical Events Committee (CEC) will be established for this study to review case information on serious cardiovascular (CV) events (myocardial infarction, stroke, death, hospitalization for angina, hospitalization for transient ischemic attack (TIA). The operations, processes, and definitions to be employed by the committee will be defined in the CEC charter.

Three primary database locks (DBLs) are planned for reporting of the results:

- The first DBL for the primary analysis will occur after all subjects have completed the Week 52 visit assessments in Part A or have withdrawn prematurely from the study. Treatment-level data will be unblinded to Sponsor personnel.
- The second DBL for the 6-month follow-up will occur after all subjects have completed the Week 24 visit in Part B, or have withdrawn prematurely from the study. The data from subjects undergoing the 16-week follow-up assessments at the end of Part A will also be included and will potentially comprise a separate data set/report if applicable.

- The third planned DBL will occur after all subjects have completed the last visit in Part B, or have withdrawn prematurely from the study. The Part B DBL will include the data from all visits associated with Part B of the study, including the 16-week follow-up assessments of Part B if applicable.

The utility of US in monitoring disease activity in GCA will be explored in a cohort of subjects from select centers who have qualified as US imaging centers. Longitudinal changes in vascular inflammation of the temporal and axillary arteries will be assessed and changes will also be correlated with clinical markers. Additional details on the exploratory US imaging cohort are contained in Section 7.9 and Appendix 8.

4.2. Treatment Arms and Duration

4.2.1. Part A: 52-week double-blind treatment phase

Following the Screening period, eligible subjects will be randomized at Baseline into Part A in a ratio of 3:3:2:2:2 to one of five treatment arms:

1. Treatment Arm A: Sirukumab 100 mg SC q2w for 52 weeks plus a pre-specified maximum of 6-month prednisone taper regimen(n=51)
2. Treatment Arm B: Sirukumab 100 mg SC q2w for 52 weeks plus a pre-specified maximum of 3-month prednisone taper regimen (n=51)
3. Treatment Arm C: Sirukumab 50 mg SC q4w for 52-weeks plus a pre-specified maximum of 6-month prednisone taper regimen (n=34)
4. Treatment Arm D: Placebo SC q2w for 52 weeks plus a pre-specified maximum of 6-month prednisone taper regimen (n=34)
5. Treatment Arm E: Placebo SC q2w for 52 weeks plus a pre-specified maximum of 12-month prednisone taper regimen (n=34).

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. The prednisone tapering schedule (summarized in Section 6.3) will be initiated at randomization for all subjects. Subjects should remain on the prednisone dose they are currently receiving at Baseline (randomization) for one week. At Week 1, the prednisone dose should be decreased in accordance with the pre-specified prednisone taper schedule. The pre-specified maximum tapering schedule to be followed will depend on the subject's treatment group assignment. The standardized prednisone taper regimen will be unblinded (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 for the pre-specified differences in duration of the prednisone tapering. Subjects who are receiving a prednisone dose of open-label 20 mg/day at randomization should continue taking the 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 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.

4.2.2. Part B: 104-week extension phase

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

- Subjects in remission at the primary 52-week endpoint. These subjects will discontinue blinded study drug treatment on entry into Part B and will be followed for maintenance of response. However, in the event of a flare, they will have the option to receive, at the discretion of their 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 1st 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.

Treatment with open-label sirukumab 100 mg SC q2w must complete by Week 104 (the end of the extension phase). Adjustments in corticosteroid dose 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 that 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.

4.3. Type and Number of Subjects

Approximately 204 subjects with a diagnosis of GCA based on the Revised GCA Diagnosis Criteria will be randomized at Baseline into the 52-week double-blind, placebo controlled phase (Part A) of the study. Eligible subjects will include both GCA patients with new onset disease (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). Relapsing/refractory subjects include those who may have previously been in remission with corticosteroid treatment and have recurrence of disease activity (relapsing) or subjects who continued to have active disease without remission despite previous or ongoing corticosteroid therapy.

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.

4.4. Design Justification

There have been limited controlled studies conducted to evaluate therapies for GCA and no successful regulatory precedent for biologic treatment of GCA. The design of this study is similar to the ongoing Phase III study with tocilizumab in GCA subjects [Unizony, 2013].

High dose corticosteroid therapy represents the current standard of care in the treatment of GCA, providing the justification for the selection of the control arm of placebo plus prednisone taper.

Subjects may enter the study on a range of corticosteroid doses (between 20-60 mg daily dose prednisone) depending on investigator assessment of the severity of clinical symptoms and whether they are new onset or relapsing/refractory subjects (20 – 60 mg/day). A pre-specified taper will be followed for up to 3, 6 and 12 months.

Two different prednisone tapering arms (Treatment Arms A/C and B) in combination with sirukumab have been included to assess whether a more rapid taper (3 month, Treatment Arm B) has the potential to lead to high sustained remission rates in combination with sirukumab, even further reducing the adverse effects of corticosteroids. Two different placebo arms have been included to provide comparisons for maximum standardized tapers of 6 (Treatment Arm D) and 12 months (Treatment Arm E), reflective of tapering schedules used in clinical practice.

The 52-week duration of Part A was selected as a time period which would be adequate to evaluate sustained remission.

Part B of the study was designed to determine the long-term maintenance of remission and safety following cessation of sirukumab treatment, to explore potential requirement for additional sirukumab therapy beyond 52 weeks, and to assess the long-term corticosteroid use and associated toxicities.

Since there is not yet robust evidence of efficacy for sirukumab, or other anti-IL-6 treatments, in GCA, an interim analysis to assess for futility may be included, such that the study can be terminated early if there is no evidence of efficacy.

4.5. Dose Justification

Two doses of sirukumab (100 mg 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 (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.

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with sirukumab can be found in the Investigator's Brochure. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [sirukumab]		
TB reactivation	Cases of TB reactivation have been reported with IL-6 antagonists, such as tocilizumab and sirukumab.	Inclusion only of subjects with no evidence of active or latent TB infection, negative diagnostic TB test at Screening and Screening chest radiograph showing no evidence of current or previous pulmonary TB (Section 5.1 Bullet 4). Evaluation of TB throughout the study by use of a TB questionnaire and a TB test (Section 7.5.7)
Serious/opportunistic infections	IL-6 deficient mice have been noted to be susceptible to infections with *Listeria, monosytogenes, Toxoplasma gondii*, and *Candida albicans* [Dalrymple, 1995; Romani, 1996; Suzuki, 1997]. Serious, life-threatening infections such as septic shock, some of which have been fatal, have occurred in subjects receiving sirukumab.	Exclusion of subjects with an active current or history of recurrent bacterial, viral, fungal, mycobacterial, or other infection or those with a prior episode of major infection (serious infectious event). Monitoring of serious and opportunistic infections by IDMC.
Hypersensitivity	Serious allergic reactions (eg, anaphylaxis) have been reported with the administration of mAbs, including sirukumab, and may occur during or after the administration of the mAbs.	Exclusion of subjects with severe allergic reactions to monoclonal antibodies, human proteins, or excipients. Subjects will be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention. Discontinuation of blinded subcutaneous study drug in the event of a severe allergic reaction. Monitoring of serious allergic reactions by IDMC; adjudication and classification of these events using Sampson criteria (Sampson, 2006) by

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		sponsor safety review team will be implemented.
Gastrointestinal perforation	Upper and lower GI tract perforations occurred in the anti-IL-6 receptor (tocilizumab) & the anti-IL6 (sirukumab) Phase III programs. Sirukumab binds to IL-6 and prevents binding to IL-6 receptor (IL-6R). Tocilizumab binds to IL-6 R to prevent IL-6 signalling. Potential differences in safety between agents that bind to the IL-6 receptor versus ones that bind to the IL-6 ligand (sirukumab) warrants further study.	Exclusion of subjects with a history of diverticulitis, inflammatory bowel disease, or other symptomatic GI tract condition that might predispose to bowel perforation. Investigators should closely monitor for GI perforations with a high degree of suspicion. Monitoring of gastrointestinal perforations by IDMC.
Cytopenias	Neutropenia and thrombocytopenia have occurred in sirukumab studies, including severe thrombocytopenia associated with bleeding. Most patients who developed neutropenia while being treated with sirukumab did not develop infections, and most patients who developed thrombocytopenia did not experience bleeding events. Decreases in platelet counts have also been observed.	Exclusion of subjects with absolute neutrophil count (ANC) $<2x10^9$/L, platelet count $<140x10^9$/L, WBC count $<3.5x10^9$/L, ALC <0.5 $x10^9$/L. Discontinuation of blinded subcutaneous study drug for subjects with 2 confirmed consecutive absolute neutrophil counts of $<0.5 \times 10^9$ cells/L or platelet counts $<50 \times 10^9$ cells/L. Monitoring of cytopenias by IDMC.
Lipid increases	Increases in blood total cholesterol, LDL, HDL, and triglycerides have occurred in sirukumab-treated subjects. No dose response was observed.	Monitor HDL/LDL levels, administer a cholesterol lowering agent if indicated.
Liver enzyme increases	Transient asymptomatic increases (1 to 3 x ULN, sometimes > 5 x ULN but < 8 x ULN) in blood ALT and AST values have been observed in subjects in completed and ongoing studies of sirukumab. Six subjects have had ALT or AST >3 x ULN and bilirubin >2 x ULN; all 6 had received	Exclusion of subjects with AST or ALT >2.0 x ULN, or total bilirubin >ULN with the exception of Gilbert's disease. Inclusion of pre-defined liver chemistry discontinuation criteria (Section 5.4.3). Monitoring of hepatic abnormalities by IDMC.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	sirukumab 100 mg SC q2w. Three subjects had concurrent biliary stones/colic, and 1 subject was concomitantly taking isoniazid. The hepatobiliary laboratory values normalized after surgery or discontinuation of isoniazid in these subjects. A fifth subject with long-standing methotrexate use, who had pre-existing fatty liver disease, developed hyperbilirubinemia (>9 x ULN) and jaundice, as well as elevations in AST (>5 x ULN), after 2 doses of sirukumab 100 mg. A liver biopsy revealed active steatohepatitis. After discontinuation of methotrexate and sirukumab, the hepatobiliary tests improved such that 9 months later AST was 1-1.5 x ULN, and ALT and bilirubin were normal. A sixth subject initially was observed to have ALT and AST >5 x ULN which both increased 2 weeks later to >20 x ULN with bilirubin > 2 x ULN. Notable findings at that time were hepatitis E virus IgM positivity and chronic liver changes by ultrasound. Hepatobiliary abnormalities had resolved 16 weeks after discontinuation of study agent.	
Cardiovascular events	No cardiovascular risk with sirukumab has been identified in clinical studies to date. Most subjects who experienced cardiovascular events in the sirukumab RA Phase 3 program had pre-existing risk factors as well as active RA. There was no association between grade 3 or 4 lipid levels and the development of MACE in the majority of subjects in the sirukumab Phase 3 RA program.	Exclusion of subjects with uncontrolled cardiovascular disease or marked baseline prolongation of QTc interval > 480 msec (QTcB or QTcF) or QTc > 500 msec in subjects with Bundle Branch Block, history of Torsade de Pointes, family history of long QT syndrome, history of second or third degree heart block or subject with major ischemic event unrelated to

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Overall, the data do not support a direct link between sirukumab-induced elevations in lipid levels and MACE. However, this study population is at high risk for CV disease.	GCA. Inclusion of pre-defined QTc discontinuation criteria (Section 5.4.4). Monitoring of CV events by CEC and IDMC
Malignancies	The impact of treatment with tocilizumab on the development of malignancies is not known, but malignancies were observed in clinical studies. As an IL-6 inhibitor, sirukumab may have some effect on the risk of malignancy by affecting immune surveillance. Malignancies have been reported with sirukumab in rheumatoid arthritis (RA) clinical trials.	Exclusion of subjects with active malignancy or history of malignancy within previous 5 years (except basal and squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that has been excised and cured). Monitoring of malignancies by IDMC.
Study Procedures		
Blood draws for safety and biomarker assessments	Fainting, mild pain, bruising, irritation or redness at the site are associated with blood draws.	Experienced site staff will follow standard approaches for managing events related to blood draws.
Use of auto-injector	Mild pain, bruising, irritation or redness at the injection site may be experienced by some patients.	Site staff will be trained and will ensure training and oversight of subjects' capabilities to use the auto-injector.
Rapid steroid taper	Steroid withdrawal symptoms and side effects	Inclusion only of subjects with stable disease who are able to safely participate in the steroid taper. Subjects should have clinically stable disease on steroid therapy prior to randomization. IDMC will monitor all subjects including those in the 3 month taper.

4.6.2. Benefit Assessment

The efficacy of sirukumab in subjects with GCA has yet to be established, but available evidence suggests that inhibition of IL-6 activity may be of therapeutic benefit in the treatment of GCA by interruption of multiple pathogenic pathways. IL-6 inhibition results in improvements in patients with active arthritis and biologic agents targeting the IL-6 cytokine ligand have been shown to be efficacious in RA. Corticosteroids are the treatment of choice but are associated with serious side effects with disease relapse common during the prednisone taper. This study, if successful, will deliver a new therapy for GCA where there remains a clear and significant unmet medical need.

In addition to receiving treatment with prednisone, subjects may be randomized to active treatment with sirukumab that may have clinical utility in the treatment of their GCA. Subjects randomized to placebo will still receive the treatment of choice (corticosteroids) for their GCA disease. All subjects will receive a high standard of care throughout the study and will benefit from physical examinations with frequent monitoring of vital signs, electrocardiograms, and blood tests. A chest radiograph will also be performed at Screening.

4.6.3. Overall Benefit:Risk Conclusion

Although the efficacy of sirukumab in subjects with GCA has yet to be established, it has been shown to be effective in Phase III studies in RA. Furthermore other agents that inhibit IL-6 activity have been shown to be efficacious in RA. All subjects will receive therapy with corticosteroids and will receive a high standard of care for their disease during this study.

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with sirukumab are justified by the anticipated benefits that may be afforded to subjects with GCA. If sirukumab is able to sustain a corticosteroid free remission this would significantly reduce the burden of corticosteroid toxicity that is common in the long term treatment of GCA.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB/IB supplement(s).

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Diagnosis of GCA defined by the following Revised GCA Diagnosis Criteria:

- Age ≥50 years.
- History of ESR ≥ 50 mm/hour or CRP ≥ 2.45 mg/dL.
- Presence of at least **one** of the following:
    - Unequivocal cranial symptoms of GCA (new onset localized headache, scalp or temporal artery tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication).
    - Unequivocal symptoms of PMR, defined as shoulder and/or hip girdle pain associated with inflammatory stiffness.
- Presence of at least **one** of the following:
    - Temporal artery abnormality on biopsy revealing features of GCA.
    - Evidence of large-vessel vasculitis by angiography or cross-sectional imaging, including but not limited to magnetic resonance angiography (MRA), computed tomography angiography (CTA), ultrasound (US) or positron emission tomography-computed tomography (PET-CT).
    - Evidence of temporal artery vasculitis on US (for US imaging qualified centers only).

2. Active GCA within 6 weeks of Randomization (Baseline) where active disease is defined by an ESR ≥30 mm/hr or CRP ≥ 1 mg/dL (≥10 mg/L) AND the presence of at least **one** of the following:

- Unequivocal cranial signs and symptoms of GCA (new onset localized headache, scalp or temporal artery tenderness, reduced or absent pulsation in temporal artery, cord-like thickening of temporal artery, stroke, scalp necrosis, pain over face/scalp arteries or otherwise unexplained mouth or jaw pain upon mastication [i.e., jaw claudication]).
- Visual signs and symptoms associated with GCA, including ischemia-related vision loss [permanent vision loss due to AION, amaurosis fugax, episodic blurry vision], diplopia, scotoma, nerve palsies, relative afferent papillary defects, central retinal artery occlusions.
- Unequivocal symptoms of PMR, defined as shoulder and/or hip girdle pain associated with inflammatory stiffness.
- Other features judged by the clinician investigator to be consistent with GCA or PMR flares (i.e., new or worsened extremity claudication, unexplained systemic symptoms such as fever of unknown origin, weight loss and night sweats).

3. At screening, receiving prednisone treatment with a minimum dose of 20 mg /day for the treatment of active GCA. Subjects not currently receiving prednisone treatment must commence dosing (minimum 20 mg/day of prednisone) at the screening visit.
4. Clinically stable GCA disease at baseline such that the subject is able to safely participate in the blinded prednisone taper regimen in the opinion of the investigator.
5. Practicing acceptable methods of birth control as follows:

   Males:

   Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until 4 months after the last dose of study medication:

   a. Vasectomy with documentation of azoospermia.

   b. Male condom plus female partner use of one of the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Childbearing potential listed in Appendix 2.

   Male subjects should also not donate sperm from the time of first dose of study medication until 4 months after the last dose of study medication.

   Females:

   Female subjects of child-bearing potential must use of one of the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Childbearing potential listed in Appendix 2.

6. No evidence of active or latent infection with Mycobacterium tuberculosis (TB), as defined by all of the following:

   a. No history of active or latent TB infection.

   b. A negative diagnostic TB test at Screening defined as a negative QuantiFERON Gold test (NB: 2 successive indeterminate QuantiFERON tests will be considered as a positive result). In cases where an initial indeterminate QuantiFERON test result may be related to sample processing issues, the second QuantiFERON test may be performed at **either** the local laboratory or the central laboratory at the discretion of the investigator. Re-testing is only permitted for indeterminate results. If the re-test also produces an indeterminate result, further re-testing to determine study eligibility is not permitted either at the local or central laboratory.

   c. Chest radiograph (both posterior-anterior and lateral views unless local guidelines recommend only a single view), taken within 12 weeks prior to baseline or at Screening, and read locally by a qualified radiologist, with no evidence of current active or previous inactive pulmonary tuberculosis.

NB: If there has been recent close contact with persons who have active TB prior to study enrolment the subject will be referred to a TB physician to undergo additional evaluation.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Are pregnant or breastfeeding.
2. Recent (within the past 12 weeks) or planned major surgery that would impact on study procedures or assessments.
3. Organ transplantation recipients (except corneas within 3 months prior to baseline visit).
4. Had prior treatment with any of the following:
    - Systemic immunosuppressives, including azathioprine, oral cyclosporine A, tacrolimus, mycophenolate mofetil, leflunomide, oral or parenteral gold, and IL-1ra (anakinra) within 4 weeks of baseline.
    - Biologic agents targeted at reducing TNFα (including but not limited to infliximab, golimumab, certolizumab pegol, etanercept, yisaipu, and adalimumab) within 4-8 weeks of baseline, depending on the agent *.
    - Anti-IL-6 (tocilizumab or any other anti-IL-6 agent) if:
        - Used within 8 weeks of randomization
        - Associated with a history of intolerance that precluded further treatment
        - Associated with an inadequate response to 3 months of therapy
    - B-cell depleting agents (eg, rituximab) within 12 months prior to baseline or longer if B cell counts have not returned to normal range or baseline levels.
    - Cytotoxic drugs such as cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents within 4 weeks of baseline.
    - Abatacept within 8 weeks of baseline.
    - Tofacitinib within 4 weeks of baseline.
    - Methotrexate use within 2 weeks of baseline.
    - Methylprednisolone > 100 mg/day IV (or equivalent) within 8 weeks of baseline.
5. Regular or continuous systemic corticosteroid use for > 4 years.
6. Requires continued or repeated use of systemic corticosteroids for conditions other than GCA or PMR symptoms associated with GCA.
7. History of severe allergic reactions to monoclonal antibodies, human proteins, or excipients.
8. Evidence of serious concomitant disease, which in the opinion of the investigator makes them unsuitable for participation in the study.
9. Major ischemic event, unrelated to giant cell arteritis, within 12 weeks of screening.

10. Marked baseline prolongation of QTc interval > 480 msec (QTcB or QTcF) or QTc > 500 msec in subjects with Bundle Branch Block**, history of Torsade de Pointes, family history of long QT syndrome, history of second or third degree heart block.
11. Current liver disease that could interfere with the trial as determined by the physician investigator.
12. History of or current active diverticulitis, inflammatory bowel disease, or other symptomatic GI tract condition that might predispose to bowel perforation.
13. History of known demyelinating diseases such as multiple sclerosis or optic neuritis.
14. Active infections, or history of recurrent infections or have required management of acute or chronic infections, as follows:
    - Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria,
    - History or suspicion of chronic infection (e.g joint infection).

    OR

    - Hospitalization for treatment of infection within 60 days of the baseline visit.

    OR

    - Use of parenteral (IV or IM) antimicrobials (antibacterials, antivirals, antifungals, or antiparasitic agents) within 60 days of baseline or oral antimicrobials within 30 days of baseline.
15. Primary or secondary immunodeficiency.
16. HIV infection (positive serology for HIV antibody), hepatitis C (positive serology for hepatitis C antibody confirmed positive by hepatitis C RNA PCR which is reflexively performed)***.
17. Hepatitis B infection (positive test results for hepatitis B surface antigen or hepatitis B core antibody)***.
18. Active malignancy or history of malignancy within previous 5 years (except basal and squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that has been excised and cured).
19. Laboratory abnormalities:
    - AST or ALT >2.0 × upper limit of normal (ULN).
    - Total bilirubin >ULN with the exception of Gilbert's disease.
    - Platelet count <140 × 10^9/L.
    - Hemoglobin <8.5 g/dL.
    - WBC count <3.5 × 10^9/L.
    - ANC <2 × 10^9/L.
    - ALC <0.5 × 10^9/L.

- Serum creatinine ≥ 2.0 mg/dL (SI: positive ≥ 177 µmol/L).

20. Has received, or is expected to receive, any live virus or bacterial vaccination within 3 months before the first administration of study drug, during the study, or within 4 months after the last administration of study drug.
21. Any other autoimmune disease (such as SLE, RA, inflammatory arthritis, other vasculitides, scleroderma, polymyositis, dermatomyositis or other similar systemic connective tissue diseases).
22. Uncontrolled psychiatric or emotional disorder, drug abuse, alcohol abuse within past 3 years.
23. Current history of suicidal ideation or past history of suicide attempt.

*Please refer to Section 6.10.2 Prohibited Medications and Non-Drug Therapies for additional guidance.

**The QTc should be based on averaged QTc values of triplicate ECGs obtained over a brief (e.g., 5-10 minute) recording period.

*** If seropositive, referral of the subject for consultation with a physician with expertise in the treatment of HIV or hepatitis B or C virus infection is recommended.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events.

Re-testing

If a subject has signed the Informed Consent Form (ICF) and failed to meet at least one entry criterion, the site may retest laboratory values or repeat a study entry procedure once only during the screening period. Laboratory parameters can only be re-tested once. If a different laboratory parameter is found to be out of range in the re-test, no further testing is allowed. Re-testing may be performed to determine eligibility within the screening window. Subjects that have laboratory values that do not meet the entry criteria following the re-test are to be deemed a screen failure. Exceptions to re-testing are chest radiograph and a positive result for the QuantiFERON-TB Gold test; these screening tests may not be repeated to meet eligibility criteria. An indeterminate result for the QuantiFERON-TB Gold test may be re-tested and subjects will be eligible upon a negative re-test result). In cases where an initial indeterminate QuantiFERON test result may be related to sample processing issues, the second QuantiFERON test may be performed at **either** the local laboratory or the central laboratory at the discretion of the investigator. Re-testing is only permitted for indeterminate results. If the re-test also

produces an indeterminate result, further re-testing to determine study eligibility is not permitted either at the local or central laboratory.

Re-screening

If a subject is a screen failure but at some point in the future is expected to meet the subject eligibility criteria, the subject may be re-screened on only one occasion and only after consultation with the Sponsor or Sponsor designee. Subjects who are re-screened will be assigned a new subject number, undergo the informed consent process, and then restart a new screening phase.

5.4. Withdrawal/Stopping Criteria

5.4.1. Study Withdrawal

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records. Subjects may also be withdrawn from the study for any of the following reasons:

- Investigator discretion
- Sponsor request
- Use of a new investigational drug
- Protocol violation
- Subject lost to follow-up
- Subject withdraws consent

It should be noted that there is no requirement to withdraw a subject from the study for lack of efficacy. This study is designed to follow subjects over the long-term, irrespective of requirement for rescue treatment or withdrawal of study drug. The investigator should make every reasonable attempt to enable the subject to continue participation in the study and present for visits as scheduled. The investigator should offer treatment with an investigator-defined open-label corticosteroid rescue regimen in combination with double-blind injections of study drug (sirukumab or placebo) for the remainder of the 52 week double-blind treatment period. Methotrexate treatment may also be initiated as part of the rescue regimen at the discretion of the investigator.

The reason for a subject not completing the study will be recorded in the Early Withdrawal Case Report Form (CRF). In the event that a subject withdraws consent to participate further in the study, the investigator must make every reasonable attempt to document the reason for withdrawal of consent in the CRF.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

Subjects who are withdrawn prematurely from the study should attend the Early Withdrawal visit and should also undergo a 16-week Follow-up period for the evaluation of safety. The assessments to be performed at the Early Withdrawal and Follow-up visits are detailed in Section 7.1, Time and Events Tables.

Subjects withdrawn prematurely from the study will not be replaced.

5.4.2. Discontinuation of Study Drug

Permanent discontinuation of study drug will not require the subject to be withdrawn from the study. Subjects should continue where possible to be followed and disease status assessed. Upon permanent discontinuation of subcutaneously-administered blinded sirukumab or matching placebo, corticosteroid dose and treatment will be at the discretion of the investigator.

Study drug (subcutaneously-administered blinded sirukumab or matching placebo) must be permanently discontinued for any of the following:

1. The investigator (in consultation with the medical monitor) believes that for safety reasons (e.g., adverse event) it is in the best interest of the subject to stop treatment.
2. Severe allergic reaction or anaphylactic reaction resulting in bronchospasm with wheezing, or dyspnea requiring ventilatory support, or symptomatic hypotension with a > 40 mmHg decrease in systolic blood pressure that occurs following study drug administration.
3. Reaction suggestive of serum sickness occurring 1-14 days after study drug administration. These may be manifested by symptoms of myalgias, arthralgias, fever, rash, pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.

4. Adverse events (AEs) or laboratory abnormalities indicative of safety concerns which are significant enough to discontinue study drug in the opinion of the investigator.
5. Pregnancy.
6. Liver function abnormalities as specified in Section 5.4.3.
7. Opportunistic infection, ie, an infection by an organism that usually causes disease only in a host whose resistance is lowered (eg, Pneumocystis jirovecii, coccidioidomycosis, Mycobacterium avium).
8. Active or latent TB.
9. Malignancy, excluding nonmelanoma skin cancer.
10. Demyelination, either central or peripheral.
11. Two confirmed consecutive absolute neutrophil counts of $<0.5 \times 10^9$ cells/L.
12. Two confirmed consecutive platelet counts $<50 \times 10^9$ cells/L.
13. Acute diverticulitis requiring antibiotic treatment.
14. Gastrointestinal perforation.

Subjects must **not** receive blinded subcutaneous sirukumab or matching placebo during the course of a serious infection. Subjects who temporarily discontinue blinded sirukumab or matching placebo due to an infection or other reasons should continue to follow the prednisone taper schedule.

Discontinuation of blinded subcutaneous sirukumab or matching placebo must be strongly considered for subjects who develop a serious infection such as sepsis or meningoencephalitis, and considered for subjects who have serious infections requiring hospitalization or IV antibiotic therapy.

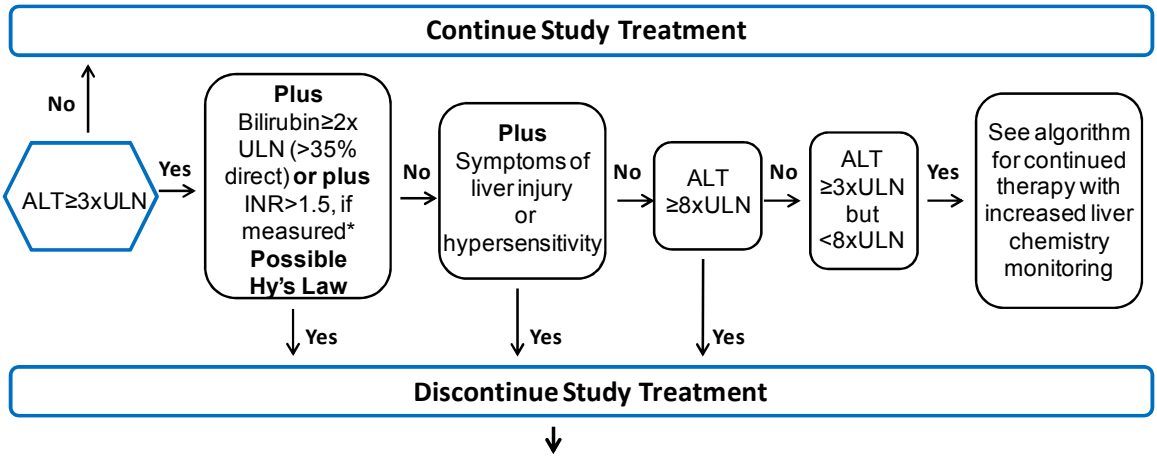
Discontinuation of blinded subcutaneous sirukumab or matching placebo should also be considered for severe injection-site reactions.

5.4.3. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Subjects meeting the liver chemistry stopping and increased monitoring criteria may be required to temporarily or permanently discontinue study treatment.

Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm

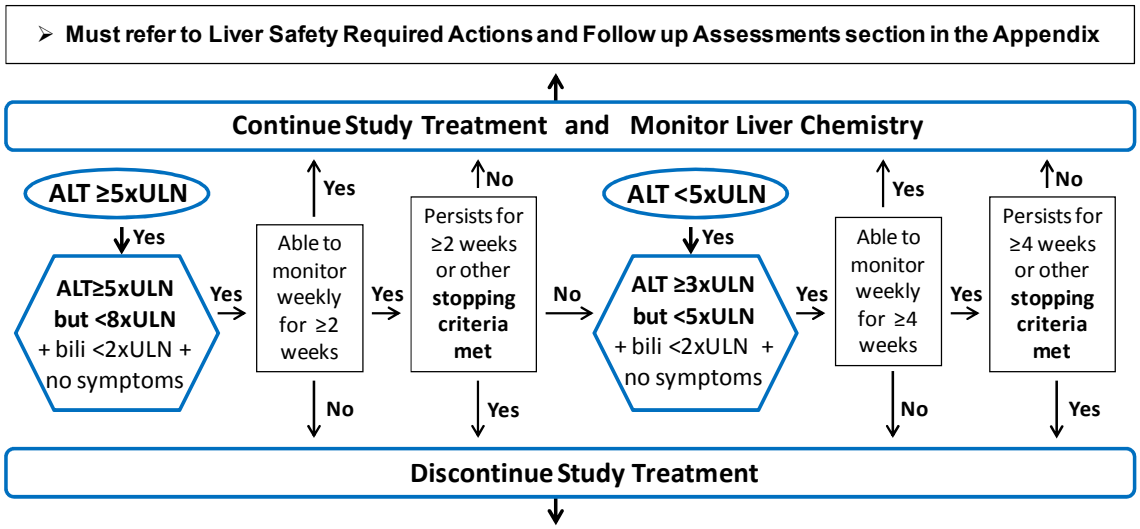


- **Must refer to Liver Safety Required Actions and Follow up Assessments section in the Appendix**
- **Report as an SAE if possible Hy's Law case:** ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) **or** INR>1.5, if measured*

*INR value not applicable to subjects on anticoagulants

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 3

Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



- **Must refer to Liver Safety Required Actions and Follow up Assessments section in the Appendix**
- **Report as an SAE if possible Hy's Law case:** ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) **or** INR>1.5, if measured*

*INR value not applicable to subjects on anticoagulants

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 3

5.4.3.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.4.4. QTc Stopping Criteria

An ECG is required only at screening. If an additional ECG is performed during study participation outside of study requirements and any of the bulleted criteria below are met, study treatment should be discontinued and the Medical Monitor should be contacted. There is no requirement for the subject to be withdrawn from the study.

QTc Stopping Criteria:

- QTc ≥ 530 msec (all subjects)

  OR

- Change from baseline of QTc > 60 msec.

The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.

- For example, if a subject is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual subject as well.
- Once the QT correction formula has been chosen for a subject's eligibility, the *same formula* must continue to be used for that subject *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on averaged QTc values of triplicate ECGs obtained over a brief (e.g., 5-10 minute) recording period.

5.5. Subject and Study Completion

A completed subject is one who has completed both Part A and Part B (and the maximum of a 16-week follow-up upon completion of Part B, if applicable) of the study. As discussed in Section 4.1, the up to 16-week follow-up visit is only for subjects who are withdrawn prematurely from the study or for those subjects in Part B of the study who **complete** open-label treatment with sirukumab 100 mg SC q2w after Week 88.

The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments. Study treatment specifically related to sirukumab and matching placebo is distinguished by the use of the terminology "subcutaneously-administered blinded study drug or treatment (sirukumab and matching placebo)".

Sirukumab and matching placebo will be supplied by the Sponsor. Both sirukumab and matching placebo will be administered subcutaneously using an autoinjector device. The sirukumab drug product provided for this study is supplied in a 1 mL Pre-filled Syringe (PFS) fitted with a spring-powered, disposable autoinjector device for single use SC administration of liquid biologic drug products (SmartJect Autoinjector) that is permanently assembled on the syringe. The sirukumab PFS is aseptically filled to deliver a dose of either 100 mg/1.0 mL or 50 mg/1.0 mL of sirukumab in a Becton-Dickinson (BD) Hypak, 1 mL glass SCF (presiliconized) syringe barrel with a 26 gauge (G) ½ inch fixed needle, an elastomeric needle shield, and a fluoropolymer coated elastomeric plunger stopper. Placebo for sirukumab PFS provided for this study is supplied in a matching presentation.

However, as a contingency, sirukumab may also be supplied as a single-use prefilled syringe-Ultrasafe (PFS-U), which is a ready to use liquid filled 1-mL-long syringe product supplied with a passive safety needle guard (UltraSafe Passive Delivery System, Safety Syringes, Inc.) for SC administration. Placebo for sirukumab PFS-U will also be supplied as appropriate.

The needle shield on the PFS (either assembled into UltraSafe needle guard or autoinjector/prefilled pen) is made with a derivative of natural rubber latex, which may cause allergic reactions in individuals sensitive to latex.

Prednisone for the pre-specified standard blinded taper will be provided by the Sponsor. The prednisone used in the blinded taper of this study is manufactured by Jubilant Cadista (Salisbury, MD) and supplied to the Sponsor by Myoderm (Norristown, PA).

Prednisone for the unblinded (open-label) taper will be provided by the sites or by the Sponsor in certain countries in order to comply with local regulations. Use of standard release prednisone is required for the open-label taper. Prednisone doses between 60 and 20 mg will be administered during the unblinded (open label) taper. Subjects who reach 20 mg will receive the blinded prednisone from that visit. Prednisone doses below 20 mg and/or matching placebo will be provided in blister packs for blinded administration. Subjects should take their prednisone daily dose in one single daily administration in the morning.

	Study Treatment		
Product name:	Sirukumab	Placebo	Prednisone/ prednisone placebo
Dosage form:	1.0 mL Pre-filled syringe	1.0 mL Pre-filled syringe	Tablets
Unit dose strength(s)/Dosage 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)

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 (see Section 6.4).

Instructions for use of the SmartJect autoinjector will be provided to subjects and to the sites. Each step in the instructions is essential to ensure a successful delivery of study drug. It is important that the autoinjector is held against the skin at the injection site with sufficient force to disengage the safety interlock and make the push button actuatable, the actuation button is pressed to begin the injection cycle, and the autoinjector remains in place until the complete dose is delivered (second audible click or 15 seconds).

The investigator and designated site staff will be trained in the use of the SmartJect autoinjector for the SC administration of study drug. The trained site staff will be responsible for training each individual subject in the proper use of the SmartJect autoinjector. The study drug will be administered by the trained site staff during site visits until the subject is trained and confident in the use of the SmartJect auto-injector to self-administer study drug at home. If necessary a family member or carer will be trained in the use of the SmartJect autoinjector in order to administer the injection to the subject.

Study drug will be administered by the trained site staff at the Baseline and Week 2 visits. At the Week 4 visit, subjects will self-administer study drug at the site under the supervision of the trained site staff unless they are unable or unwilling to do so. In this case, study drug will be administered by the trained site staff.

At the relevant site visits, study drug must be withheld until all patient reported outcomes (PROs) questionnaires have been completed and blood samples taken for pharmacokinetic (PK) analysis of sirukumab serum concentrations (in order to collect a pre-dose sample). The visits scheduled for PRO and PK analyses are provided in Section 7.1, Time and Events Tables.

Once these assessments are completed, subjects will self-administer study drug at the site or may have study drug administered by the trained site staff. Subjects will self-administer study drug at home in between site visits. Subjects unable or unwilling to self-administer study drug at home may be able to attend the clinic between scheduled visits for study drug administration.

Subjects who self-administer study drug at home, should be instructed to take the study drug q2w but no more than ± 4 days from the scheduled dosing day. Administrations of study drug must be at least 7 days apart. Subjects will be instructed to contact the investigator promptly in the event of any signs of an allergic reaction, infection or bleeding.

6.2. Treatment Assignment

Central randomization will be implemented in this study. Subjects will be 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 (IRT). Randomization will be stratified by baseline oral prednisone dose (<30 mg/day or ≥30 mg/day. Subjects will be randomized in a ratio of 3:3:2:2:2 to 1 of 5 treatment arms:

1. Treatment Arm A: Sirukumab 100 mg SC q2w for 52 weeks plus a pre-specified maximum of 6-month prednisone taper regimen(n=51)
2. Treatment Arm B: Sirukumab 100 mg SC q2w for 52 weeks plus a pre-specified maximum of 3-month prednisone taper regimen (n=51)
3. Treatment Arm C: Sirukumab 50 mg SC q4w for 52-weeks plus a pre-specified maximum of 6-month prednisone taper regimen (n=34)
4. Treatment Arm D: Placebo SC q2w for 52 weeks plus a pre-specified maximum of 6-month prednisone taper regimen (n=34)
5. Treatment Arm E: Placebo SC q2w for 52 weeks plus a pre-specified maximum of 12-month prednisone taper regimen (n=34).

Once a randomization number has been assigned to a subject, it will not be re-assigned.

6.3. Planned Dose Adjustments

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

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. A pre-specified prednisone tapering schedule outlined in Table 1 begins for all subjects upon randomization at Baseline, (Week 0). 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 pre-specified prednisone taper schedule (Table 1).

- The pre-specified maximum tapering schedule to be followed will depend on the subject's treatment group assignment.

- The prednisone taper will be unblinded (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 q2w or placebo q2w for the full 52 weeks. Subjects should continue to be followed per the protocol-specified assessments while receiving rescue treatment. There is no requirement for these subjects to be withdrawn from the study. 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.

Table 1 Prednisone Taper

	3 Month	6 Month	12 Month
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

	3 Month	6 Month	12 Month
	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
	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

*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.

6.4. Blinding

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 pre-filled syringes in a matching presentation. Blinding to the prednisone dose during the taper will be maintained by providing prednisone dosages 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 patient, 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 value 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 PMR) suggestive of disease activity.

An IDMC may carry out a futility assessment when approximately 30% of subjects have completed 52 weeks, dependent upon the recruitment rates. This committee will consist of clinicians and statisticians who are external to GSK in order to maintain the integrity of the blind during the 52-week double-blind treatment phase of the study.

The CEC, an independent committee composed of external specialists will be blinded to treatment assignment and will therefore not affect the integrity of the blind.

This will be a double-blind study and the following will apply:

- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the GSK Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the

treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.

- The date and reason for the unblinding must be fully documented in the CRF.

A subject may continue in the study if that subject's treatment assignment is unblinded but this must be discussed with the Medical Monitor.

6.5. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.6. Preparation/Handling/Storage/Accountability

Sirukumab and matching placebo should be stored at 2-8°C and protected from light. Do not remove from the outer carton until ready to use. The storage temperature should be monitored and any excursions noted.

Prior to use the SmartJect autoinjector should be removed from the outer carton and allowed to sit at ambient temperature for 30 minutes with the cap in place.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SPM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.7. Compliance with Study Treatment Administration

Subjects will be provided with a worksheet to record the dates when they self-administer study treatments at home. Compliance with sirukumab or matched placebo and prednisone and matched placebo will be assessed through querying the subject's worksheet during the site visits and will be documented in the source documents and CRF. A record of the number of sirukumab or placebo pre-filled syringes and prednisone/placebo tablets dispensed to and taken by each subject must be maintained

and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays will also be recorded in the CRF.

A record of study treatments administered during site visits will be documented in the source documents and CRF.

6.8. Treatment of Study Treatment Overdose

Subjects in clinical studies with sirukumab have received up to 10 mg/kg sirukumab IV q2w and no dose-limiting toxicity has been observed. No clinical information is available for sirukumab doses greater than 10 mg/kg.

For this study, any dose of sirukumab >100 mg within a 7 day period will be considered an overdose.

GSK does not recommend specific treatment for an overdose of sirukumab (see Section 5.22 on overdose in the sirukumab IB).

The investigator should refer to the approved product label for advice on an overdose of prednisone.

In the event of an overdose the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for AEs/serious adverse events (SAEs) and laboratory abnormalities until sirukumab can no longer be detected systemically (at least 70 days for sirukumab).
3. Obtain a plasma sample for PK analysis within 70 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.9. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study. Upon study completion, decisions on treatment options for individual subjects will be at the discretion of the investigator.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

6.10. Concomitant Medications and Non-Drug Therapies

All concomitant medications taken during the study will be recorded in the concomitant medications CRF.

6.10.1. Permitted Medications and Non-Drug Therapies

The following drugs are permitted during the study:

- The use of statins for the treatment of hyperlipidemia is permitted in this study. However, some statins such as simvastatin, atorvastatin, cerivastatin, and lovastatin are metabolized by cytochrome P450 enzymes and caution should be exercised when sirukumab is co-administered with these CYP3A4 substrate drugs.
- Inflammatory cytokines, including IL-6, are known to down regulate activity and expression of multiple cytochrome P450 (CYP) enzymes. Hypothetically, IL-6 inhibition in a patient with an inflammatory condition will restore or increase the CYP enzyme activity, and, in turn, increase the hepatic metabolism and clearance of drugs that are substrates for those enzymes. Therefore, upon initiation or discontinuation of sirukumab in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (eg, warfarin) or drug concentration (eg, theophylline) is recommended and the individual dose of the drug may be adjusted as needed. Caution should also be exercised when sirukumab is coadministered with CYP3A4 substrate drugs such as oral contraceptives, and certain statin medications mentioned above.
- Analgesics, paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, at the usual marketed doses approved in the country in which the study is being conducted.
- The use of topical analgesics including capsaicin and diclofenac.
- Stable doses of inhaled and topical corticosteroids.

6.10.2. Prohibited Medications and Non-Drug Therapies

The following drugs and vaccines are prohibited within the specified time frames and with concomitant SC administration of study drug:

- Systemic immunosuppressives such as azathioprine, oral cyclosporine A, tacrolimus, mycophenolate mofetil, leflunomide, oral or parenteral gold, and IL-1ra (anakinra) within 4 weeks of baseline.
- Biologic agents targeted at reducing TNFα (including but not limited to infliximab, golimumab, certolizumab pegol, etanercept, yisaipu, and adalimumab and/or biosimilar or generic versions of these agents) within the specified time frames.

Anti-TNFα Therapy	**Treatment Prior to First Study Agent Administration (Baseline)**
Infliximab, infliximab biosimilar, golimumab IV	8 Weeks
Golimumab SC, adalimumab, certolizumab pegol	6 Weeks
Etanercept, yisaipu	4 Weeks

- Prior anti-IL-6 (tocilizumab or any other anti-IL-6 agent) if:
  - Used within 8 weeks of randomization
  - Associated with a history of intolerance that precluded further treatment
  - Associated with an inadequate response to 3 months of therapy
- B-cell depleting agents (eg, rituximab) within 12 months prior to baseline or longer if B cell counts have not returned to the normal range or baseline levels.
- Cytotoxic drugs such as cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents within 4 weeks of baseline.
- Abatacept within 8 weeks of baseline.
- Tofacitinib within 4 weeks of baseline.
- Methotrexate within 2 weeks of baseline in Part A of the study only. Methotrexate use in Part B of the study is at the discretion of the investigator and may be used concurrently with open-label sirukumab in Part B.
- Systemic corticosteroids for conditions other than GCA within 8 weeks of baseline or a reasonable possibility of requiring systemic corticosteroids during Part A.
- Use of investigational agents within 12 weeks of baseline.
- Receipt of any live virus or bacterial vaccination within 3 months before the first administration of study drug, during the study, or within 4 months after the last administration of study drug.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Tables, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. It should be noted that for those subjects with disease flare at any visit, the assessments to

be performed are those specified in the Early Withdrawal or Flare visit in all of the following Time and Events Tables.

The assessments for Part A of the study are provided in Time and Events Table 2 in Section 7.1.

Part B assessments are included in separate Time and Events Tables (Table 3, Table 4 and Table 5). It should be noted that the Week 52 visit of Part A also serves as the Week 0 visit of Part B of the study.

Part B Time and Events Tables should be followed as described below:

Time and Events Table 3: Assessments for subjects who will **not** receive open-label treatment with sirukumab during Part B. Dispensing of investigational product is not required. Hematology and clinical chemistry assessments and pregnancy testing from the Week 16 visit onwards are also not required as subjects will have completed the 16-week post-drug follow up assessments.

Time and Events Table 4: Assessments for subjects who initiate open-label sirukumab treatment **at** the baseline visit of Part B (those with disease activity or flare at the Week 52 visit of Part A).

Time and Events Table 5: Assessments for subjects who initiate open-label sirukumab treatment **after** the baseline visit and anytime up to the Week 52 visit of Part B (those who flare during Part B). These subjects will initially be following the assessments in Time and Events Table 3 and will undergo the assessments scheduled for that visit and will include initiation of open-label sirukumab treatment at that same visit.

Subsequent visits will follow the assessments from Time and Events Table 5 starting from the visit labelled 'plus 2 weeks' onwards. It is important that upon initiation of open-label sirukumab therapy, the next visit should occur **2** weeks after treatment start. For these subjects, the last visit in Part B should be scheduled for when they have been in Part B for 104 weeks or upon completion of the 16-week follow-up if applicable.

At the clinic visits where blood samples for lipid analysis are collected, the subjects should be instructed to fast for at least 9 hours (water is permitted) prior to the visit; this will be an overnight fast from the time of going to bed and missing breakfast until after the blood draws in the clinic. It may be preferable to schedule clinic visits in the morning to minimize inconvenience to the subject. Fasting is not required for visits where there is no requirement for lipid analysis.

PRO questionnaires should be completed by subjects before any other assessments and before the administration of study drug. PRO questionnaires should be completed before the completion of the physician reported questionnaires. PRO questionnaires should be completed by the subject in the following order:

1. Patient Global Assessment of disease activity (PtGA).
2. Patient Global Impression of Change (PGIC).

3. Pain Numeric Rating Scale (NRS).
4. HAQ-DI (for subgroup of subjects with PMR).
5. FACIT-fatigue.
6. Steroid Impact PRO.
7. SF-36v2 acute.
8. EQ-5D (5L)
9. Columbia-Suicide Severity Rating Scale (C-SSRS).

Clinician-reported outcome questionnaires include the Physician Global Assessment of disease activity (PhGA), which should be completed after the PRO questionnaires have first been completed by subjects.

7.1. Time and Events Tables

Table 2 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	
Serum chemistry	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	
ESR	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	U
HIV, HBsAg, HBcAb, 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

	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**
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 sub-set of subjects with PMR. PGA assessed using PtGA (subjects) and PhGA (physicians, after subject completion of questionnaires and after conducting patient 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 (see Section 7.5.7). A QuantiFERON-TB Gold Test should be performed at any time during the study if TB 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, Pharm serum samples must be collected prior to study drug administration. Blood collected from one venipuncture will be divided into multiple aliquots of serum for Pharm 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.

Table 3 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 patient 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 (see Section 7.5.7). A QuantiFERON-TB Gold Test should be performed at any time during the study if TB 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 4 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 sub-set of subjects with PMR. PGA assessed using PtGA (subjects) and PhGA (physicians, after subject completion of questionnaires and after conducting patient 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 (see Section 7.5.7). 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 post 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, Pharm serum samples must be collected prior to study drug administration. Blood collected from one venipuncture will be divided into multiple aliquots of serum for Pharm 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.

Table 5 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 3 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 patient 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 (see Section 7.5.7). A QuantiFERON-TB Gold Test should be performed at any time during the study if TB 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 post 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, Pharm serum samples must be collected prior to study drug administration. Blood collected from one venipuncture will be divided into multiple aliquots of serum for Pharm 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.

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at Screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Procedures conducted as part of the subject's routine clinical management (e.g. chest radiograph taken up to 3 months prior to baseline) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

All subjects should be receiving prednisone treatment at Screening. 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 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. Subjects are required to have clinically stable GCA disease at baseline and able to participate in the blinded prednisone taper regimen in the opinion of the investigator. At Baseline (Randomization), doses must be within 20-60 mg prednisone for the starting dose when the pre-specified prednisone taper is initiated.

7.3. Efficacy

Efficacy of sirukumab in GCA will be assessed from the presence of GCA activity including investigator assessment of signs and symptoms of GCA (new onset localized headache, scalp or temporal artery tenderness, reduced or absent pulsation in temporal artery, cord-like thickening of temporal artery, stroke, scalp necrosis, pain over face/scalp arteries, or otherwise unexplained mouth or jaw pain upon mastication [i.e., jaw claudication]); visual signs and symptoms (including but not limited to transient or episodic blurry vision, diplopia, scotoma, ischemia-related vision loss [permanent vision loss due to AION], amaurosis fugax); PMR symptoms [shoulder and/or hip girdle pain associated with inflammatory stiffness]; other features associated with GCA such as new or worsened extremity claudication and fever of unknown origin; and laboratory results for serum ESR and CRP levels (blinded to investigator).

7.3.1. Patient's and Physician's Global Assessment of Disease Activity

The Patient's and Physician's Global Assessments of Disease Activity will be recorded on a VAS. The scale for the subject's assessment ranges from "very well" to "very poor". The scale for the physician's assessment ranges from "no GCA activity" to "extremely active GCA". The evaluating physician and subject must complete the global assessment independently of each other. The physician should preferably be the same person at every study visit for a given subject.

7.4. Health Outcomes

In addition to the Patient's and Physician's Global Assessment of Disease Activity, other health outcome measures used in this study are PGIC, pain assessment using an 11-point numeric rating scale, HAQ-DI, FACIT-fatigue, Steroid Impact questionnaire, SF-36 v2 Acute health survey questionnaire, and EQ5D (5L). These questionnaires should be completed in the order specified in Section 7.

7.4.1. 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. Additionally, the subject rating of change will be used to support the estimation of a minimum clinically meaningful change score for the Steroid Impact PRO. Responses include: Much Better, Better, Slightly Better, No Change, Slightly Worse, Worse, Much Worse.

7.4.2. Pain Assessment

Subjects will be asked to rate the severity of their average pain now on an 11-point numeric rating scale with anchors ranging from 0, "no pain" to 10, "the worst pain imaginable".

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

The functional status of the subgroup of subjects with PMR will be assessed using the HAQ-DI [Fries, 1980]. This 20-question instrument assesses the degree of difficulty encountered in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living). Responses are scored from 0 (no difficulty) to 3 (inability to perform a task in that area).

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

The FACIT-Fatigue is a questionnaire that assesses self-reported tiredness, weakness, and difficulty conducting usual activities due to fatigue [Cella, 2002; Yellen, 1997]. The total FACIT-Fatigue score ranges from 0 to 52, with a higher score indicating less fatigue.

7.4.5. Steroid Impact Questionnaire

The benefits, side effects and impact of steroids on GCA symptoms and subjects will be assessed using a GCA disease specific patient reported questionnaire, the Steroid Impact Questionnaire. The Steroid Impact Questionnaire contains 50 items assessing steroid dose/duration (4 items), general impact (baseline burden; 19 items), benefits (7 items), work/productivity (3 items), side effects (10 items), emotions (6 items), and overall satisfaction (1 item).

7.4.6. 36-item Short Form Version 2 Acute (SF-36v2 Acute)

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

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

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

7.4.7. EuroQoL-5D (EQ-5D) (5L)

The EQ-5D is a standardized measure of health status developed by the EuroQoL Group to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group, 1990). The EQ-5D is applicable to a wide range of health conditions

and treatments. EQ-5D essentially consists of 2 elements: The EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, unable to do. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state which can be converted into a single summary index (EQ-5D index) by applying a formula that attaches values (also called weights) to each of the levels in each dimension. The EQ VAS records the respondent's self-rated health on a vertical line, VAS where the endpoints are 'Best imaginable health state' and 'Worst imaginable health state'. The EQ VAS can be used as a quantitative measure of health outcome as judged by the individual respondents.

7.5. Safety

Safety will be assessed from the documentation of adverse events and review of vital signs and laboratory assessments including complete blood counts, serum chemistry profiles, fasting serum lipids, HbA1c, hepatitis B and C serologies, and markers of bone turnover. The Columbia-Suicide Severity Rating Scale (C-SSRS) will be used to prospectively monitor suicidal ideation and behavior (Section 7.5.7). Adverse events (including serious and opportunistic infections, cardiovascular events, gastrointestinal perforations, hepatic laboratory abnormalities, and cytopenias) will be monitored on a regular and/or event-driven basis by an IDMC throughout the study.

Planned time points for all safety assessments are listed in the Time and Events Tables (Section 7.1).

7.5.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 4.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.5.1.1. Time period and Frequency for collecting AE and SAE information

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.5.1.3), at the time points specified in the Time and Events Tables (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in.

7.5.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.5.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 4.

Other AEs of special interest not defined in Section 4.6.1 are injection site reactions, total or partial blindness, limb claudication, and scalp or tongue necrosis. In addition, severe disease flares, including hospitalizations will be monitored.

Other AEs of special interest for sirukumab are hematologic laboratory abnormalities (decreases in neutrophils and platelets), hepatobiliary laboratory abnormalities, lipid parameter abnormalities, serious CV events, infections, malignancies, and gastrointestinal perforations.

All initial reports of cardiovascular AEs (myocardial infarction, stroke, death, hospitalization for angina, hospitalization for TIA), newly identified malignancies, active TB, hepatobiliary abnormalities (as defined below), and gastrointestinal perforations

must be reported to the Sponsor by the investigational staff within 24 hours of their knowledge of the event even if these events do not meet the definition of an SAE.

Corticosteroid-related AEs such as diabetes mellitus, osteoporosis, fractures, infection, glaucoma, and cataracts among others will be evaluated in relation to steroid exposure and baseline risk. Since subjects participating in this study may be receiving high doses of prednisone for a prolonged period, investigators should consider implementation of the American College of Rheumatology recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis (Grossman, 2010). A summary of these recommendations is included in Section 12.5, Appendix 5. Investigators should also consider whether their subjects may benefit from other approaches for minimizing corticosteroid-related AEs, such as the prophylactic use of proton pump inhibitors for gastroprotection.

7.5.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

In the sirukumab clinical programs, significant changes in lipid laboratory parameters have been observed, as with other agents that block IL-6. The clinical significance of these changes is not known. Nonetheless, serious CV events are considered AEs of special interest and will be closely monitored in the sirukumab program. In order to fully understand CV events in this study, Major Adverse Cardiovascular Events (MACE), defined as myocardial infarction, stroke, death, hospitalization for unstable angina, and hospitalization for TIA, will be collected and prospectively adjudicated by an external CEC. The CEC is an independent committee composed of external specialists, blinded to treatment assignment, who will be commissioned to review case information on serious CV events. This will allow external review of cases and determination of diagnosis prior to analysis.

7.5.1.5. Other Adverse Events of Special Interest for Sirukumab

Laboratory parameter abnormalities

IL-6 is a pleiotropic cytokine necessary for hematopoiesis and IL-6 inhibition has been shown to cause a reduction in both neutrophils and platelets. In addition, IL-6 inhibition has been associated with reversible elevation in liver enzymes. Mechanisms by which

this might occur include inhibition of the hepatoprotective effect of IL-6, leaving hepatocytes susceptible to effects of toxins and other stresses. Lipid abnormalities have also been observed, both in the sirukumab Phase 2 study C1377T04, as well as with other anti-IL-6 agents. The mechanism by which this occurs is not fully understood.

Other Events of Interest

Sirukumab, by its mechanism of action as an IL-6 inhibitor, would be expected to have some properties of immunosuppression. Increased susceptibility to infections is an identified risk of sirukumab. Serious, life-threatening infections such as septic shock, some of which have been fatal, have occurred in subjects receiving sirukumab. IL-6 deficient mice have been found to be susceptible to infections with Listeria monocytogenes, Toxoplasma gondii, and Candida albicans. [Dalrymple, 1995; Romani, 1996; Suzuki, 1997]. In addition, as an IL-6 inhibitor, sirukumab may have some effect on the risk of malignancy by affecting immune surveillance. Further, gastrointestinal perforations have been reported with another anti-IL-6 agent [ACTEMRA Prescribing Information, 2011] and with sirukumab. Please refer to Table 4.6.1 and the Investigator Brochure for additional information.

7.5.1.6. Events That Occur With Biologics

Injection Site Reactions

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. Any adverse reaction (eg, pain, erythema, and/or induration) should be noted on the AE page of the eCRF.

Allergic/Hypersensitivity Reactions

All subjects will be observed carefully for symptoms of allergic reactions for at least 30 minutes after the SC injection of study drug when administered at the study site. If mild or moderate allergic reaction is observed, acetaminophen 650 mg per mouth (PO) or NSAIDS and diphenhydramine 25 mg orally or intravenously may be administered. If the reaction is not severe, subsequent injections at the appropriate treatment intervals may be undertaken with caution.

Subjects with severe reactions following an injection such as bronchospasm with wheezing and/or dyspnea requiring ventilator support, or symptomatic hypotension with a decrease in systolic blood pressure greater than 40 mmHg will not be permitted to receive any additional study drug injections. In the case of such reactions, appropriate medical treatment should be administered.

In cases of serious allergic/hypersensitivity reactions, additional details on the case will be collected via a targeted follow-up questionnaire. An internal safety review team will adjudicate these events to determine if the events meet the Sampson criteria (Sampson, 2006).

7.5.1.7. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs and non-serious AEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.5.2. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until the Follow-up visit.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 2.
- Female subjects who become pregnant during the study must have study drug discontinued immediately. These subjects should continue to follow the protocol-specified visit schedule.

7.5.3. Physical Exams

- A complete physical examination will be conducted at screening and will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will be conducted at all other time points and include, at a minimum assessments of the skin, lungs, CV system, and abdomen (liver and spleen).

- Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.5.4. Vital Signs

Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate.

7.5.5. Electrocardiogram (ECG)

Triplicate 12-lead ECGs will be obtained at the Screening visit using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. The screening ECG will ensure that a comparative ECG is available prior to study drug administration in order to detect any changes should a subject require an ECG for any reason during the study. Refer to Section 5.4.4 for QTc discontinuation criteria and additional QTc readings that may be necessary.

In the event of a suspected cardiac abnormality, the investigator should make every reasonable attempt to obtain the results of the ECG performed in the emergency hospital facility.

7.5.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 6, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedules. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

Pregnancy testing (where applicable) should be conducted every 4 weeks while subjects are receiving study drug and during the 16-week follow-up period. Pregnancy tests may be performed by the subject at home using the test kits provided by the central laboratory when there is no study visit associated with the testing time point.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Hematology, clinical chemistry, and additional parameters to be tested are listed in Table 6.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 112 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not

return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) will be used to grade laboratory abnormalities as appropriate.

The investigators and the Sponsor/study team will remain blinded to the results of the ESR (performed locally), CRP and fasting lipid analyses (see Section 6.4) after the start of treatment during Part A of the study. The central laboratory will send an alert to the investigator for LDL values >160 mg/dL (SI units 4.1 mmol/L) or triglycerides >500 mg/dL (SI units 5.6 mmol/L).

Table 6 Laboratory 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		
Serum Chemistry		
Sodium	Potassium	Chloride
Bicarbonate	Blood urea nitrogen (BUN)	Creatinine
Glucose	Aspartate transaminase	Alanine transaminase
Alkaline phosphatase	Calcium	Phosphate
Albumin	Total protein	Bilirubin, direct, indirect and total
Fasting lipids		
Total cholesterol	Low density lipoprotein (LDL)	High density lipoprotein (HDL)
Triglycerides		
Serum and urine pregnancy test for premenopausal women only		
Serology for HIV, hepatitis B surface antigen, hepatitis B core antibody and hepatitis C antibody [1]		
Other tests		
Hemoglobin A1c	C-reactive protein (CRP) [2,3]	Erythrocyte sedimentation rate (ESR) [2, 3]
QuantiFERON-TB Gold Test		

1. If hepatitis C antibody positive, a hepatitis C RNA PCR assay should be reflexively performed on a fresh sample to confirm the result
2. Investigators will remain blinded to the results of the ESR, CRP and fasting lipids after the start of treatment during Part A of the study (see Section 6.4). ESR will be analyzed at the local laboratory.
3. Required for the evaluation of efficacy.

Values for liver transaminase levels (AST, ALT), absolute neutrophil count (ANC), and platelet count that require study drug interruption and/or permanent discontinuation of study drug administration are listed below in Table 7.

Table 7 Values for Liver Transaminase Levels, Absolute Neutrophil Count, and Platelet Count That Require Study Drug Interruption and/or Permanent Discontinuation of Study Drug

ALT or AST increased	
ALT or AST	**Action**
≥3xULN) for laboratory reference range.	Interrupt study drug administration, assess for symptoms, and repeat ALT/AST test as soon as possible* (see Section 5.4.3). May resume study drug when <3x ULN
Criteria for drug-induced liver injury	Permanent discontinuation of study drug
Low Absolute Neutrophil Count (ANC)	
Neutrophil count	**Action**
0.5 to ≤1.0 x 10^3/μL (SI: 0.5 to ≤1.0 x 10^9 cells/L)	Interrupt study drug administration, repeat ANC test as soon as possible* May resume study drug when >1.0 x 10^3/μL
<0.5 x 10^3/μL (SI: <0.5 x 10^9 cells/L)	Interrupt study drug administration, repeat ANC test as soon as possible* If confirmed to be <0.5 x 103/μL, discontinue study drug permanently (see Section 5.4.2)
Low Platelet Count	
Platelet count	**Action**
50,000 to ≤100,000/μL (SI: 50 to ≤100 x 10^9 cells/L)	Interrupt study drug administration, repeat platelet count test as soon as possible* May resume study drug when platelet count >100,000/μL
<50,000/μL (SI: <50 x 10^9 cells/L)	Interrupt study drug administration, repeat platelet count test as soon as possible* If confirmed to be <50,000/μL, discontinue study drug permanently (see Section 5.4.2)

* Retesting should be performed by Central laboratory

Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. Any RBC evaluation may include abnormalities in the RBC count and/or RBC parameters and/or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.

Any abnormalities in MCH, MCHC and MCV will be reported by the laboratory.

7.5.7. Suicidal Risk Monitoring

Sirukumab is considered to potentially be a CNS-active drug. There has been some concern that some CNS-active drugs may be associated with an increased risk of suicidal thinking or behaviour when given to some patients with certain conditions. Although this drug or other similar drugs in this class have not been shown to be associated with an increased risk of suicidal thinking or behaviour when given to this patient population,

GSK considers it important to monitor for such events before or during clinical studies with compounds such as this.

Subjects being treated with sirukumab should be monitored appropriately for suicidal ideation and behaviour or any other unusual changes in behaviour. Consideration should be given to discontinuing sirukumab in subjects who experience signs of suicidal ideation or behaviour.

Suicidal ideation and behaviour will be assessed at baseline and at the time points indicated in Time and Events Table 2 and in Time and Events Table 3 using the patient-reported outcome version of the C-SSRS [Mundt, 2010].

7.5.8. Tuberculosis Evaluation

A QuantiFERON-TB Gold Test will be performed at Screening. This test can be performed at any time during the study if TB is suspected.

A TB questionnaire will be completed at the times specified in Section 7.1, Time and Events Tables. This questionnaire will evaluate signs and symptoms of active TB in order to aid in the early detection of TB reactivation or new TB infection during the study. The following series of questions is suggested for use during the TB evaluation:

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

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

Investigators should be aware that TB reactivation in immunocompromised subjects may present as disseminated disease or with extrapulmonary features. Subjects with active TB must immediately discontinue study drug and be referred to a physician specializing in TB for appropriate treatment.

Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON-TB Gold test and, if possible, referral to a physician specializing in TB to determine the subject's risk of developing active TB and whether treatment for latent TB is warranted.

Study drug administration should be interrupted during the investigation. A positive QuantiFERON-TB Gold test result should be considered detection of latent TB. If the result is indeterminate, the test should be repeated. If recommended, treatment for latent TB must be initiated prior to the administration of further study drug. Subjects who discontinue treatment for latent TB prematurely or who are noncompliant with therapy must immediately discontinue further administration of study drug and should return for all subsequent scheduled study visits.

7.5.9. Chest Radiograph

A chest radiograph will be performed at the Screening visit only for the detection of TB. A chest radiograph taken up to 3 months prior to Week 0 may be used to qualify as the screening radiograph.

7.6. Pharmacokinetics and Immunogenicity

Blood samples for PK analysis of sirukumab serum concentrations and for analyses of antibodies to sirukumab will be collected at the time points specified in Section 7.1, Time and Events Tables. The actual date and time of each blood sample collection will be recorded. Blood samples for PK analyses of sirukumab serum concentrations must be drawn **prior** to the administration of study drug.

At visits where sirukumab serum concentrations and antibodies to sirukumab will be evaluated, one blood draw of sufficient volume will be used to divide the sample into 3 aliquots, one each for sirukumab serum concentrations and antibodies to sirukumab plus a back-up.

PK analyses of sirukumab serum concentrations and anti-sirukumab antibodies will be performed using validated bioanalytical assays by Janssen Research and Development under the control of PTS-DMPK/Scinovo, GlaxoSmithKline, the details of which will be included in the SPM.

Processing, storage and shipping procedures are provided in the SPM.

7.7. Biomarkers/Pharmacodynamic Markers

7.7.1. Exploratory Biomarkers

Blood samples will be taken at the times indicated in Time and Events Table 2, Section 7.1 for assessment of changes in the biomarkers of bone formation or resorption, CTX1 and P1NP, and for changes in biomarkers indicative of Th1 and Th17 cell function, IFN-γ and IL-17A. An additional sample should be taken at the time of onset of disease flare when applicable for assessment of IFN-γ and IL-17A.

7.7.2. Optional Exploratory Biomarkers

Subjects will also have the option to provide blood and urine samples for future evaluation of biomarkers related to GCA disease activity and transcriptomic analyses to further elucidate the biology of the disease. These samples will be stored in a biobank for a period of up to 5 years. Provision of these samples is optional and is not required for participation in the study.

7.7.3. Pharmacodynamic Markers

Blood samples will be taken at the times indicated in Time and Events Table 2, Section 7.1 for assessment of changes in free and total IL-6 as a pharmacodynamic marker of sirukumab activity. Analyses of serum IL-6 levels will be performed using validated assays by Janssen Research and Development

7.8. Genetics

A blood sample for genetic research will be collected from consenting subjects at the baseline visit. Refusal to participate in the genetic research will not preclude the subject from participating in the study.

7.9. Exploratory Ultrasound Imaging

7.9.1. Background and Rationale

The results of three recent meta-analyses have provided evidence to support the utility of US imaging in the diagnosis of GCA [Ball, 2010; Arrida, 2010; Karassa, 2005]. Additional data from a multicenter study, TABUL (Temporal Artery Biopsy versus ULtrasound), conducted at centers trained in US imaging techniques, also support the diagnostic utility of US in GCA [Luqmani, 2015]. However, the role of US imaging in the assessment of GCA disease activity remains unclear. Available evidence consists of results from a study which found persistent abnormalities suggestive of an association with relapse when GCA patients were assessed by ultrasound imaging every 2-4 weeks [De Miguel, 2012]. Permanent visual loss is also associated with the presence of abnormal sonographic features of cranial and extra-cranial arteries [Schmidt, 2008; Schmidt, 2009; Czihal, 2012]. A recent prospective observational study has demonstrated that ultrasound can be informative in distinguishing potential flares from exacerbations of unrelated headache in patients with diagnosis of GCA [Ponte, 2015]. Taken together, these findings suggest that ultrasound imaging may provide a useful diagnostic and biomarker approach for assessing and monitoring disease activity in GCA.

Currently, no valid biomarkers exist to assess response to therapy and to predict relapse. Changes in the conventional inflammatory markers (CRP and ESR) do not consistently reflect disease activity [Tse, 1998]. Therefore, the utility of US in monitoring disease activity in GCA will be explored in a cohort of study subjects from select participating centers by sonographers trained and/or qualified as proficient in US imaging.

Longitudinal changes in vascular inflammation of the temporal and axillary arteries and the predictive value of US for disease activity will be assessed.

7.9.2. Synopsis

A cohort of subjects with new onset GCA from participating imaging centers who have consented to participate in the US imaging portion of this study will be evaluated. These subjects will undergo US scans of their temporal and axillary arteries at the specified time points for assessment of changes in vascular inflammation.

Only subjects with newly diagnosed GCA are eligible to participate. Due to the exploratory nature of this portion of the study, there is no pre-specified sample size for this cohort. However, it is estimated that up to 50 subjects may participate.

Subjects will have an initial baseline scan at Screening and assessments at Baseline (Week 0), Weeks 12 and 52. Additional US scans should also be conducted in the event of relapses or flares, including flares/relapses that occur during Part B of the study. US scanning for flares/relapses in Part B of the study will conclude when the last subject in the US imaging cohort completes Part A of the study. Thereafter, no additional scans will be taken.

Subjects may also be asked to provide retrospective consent for assessment of their diagnostic US scan. Efforts should be made to conduct the baseline US scan within 3 days of initiating prednisone therapy. However, inability to comply with this time frame does not exclude subjects from participation. Data will be analyzed according to the time frame between prednisone dose and US scan. Detailed information on US imaging in this cohort of study subjects is included in Appendix 8.

8. DATA MANAGEMENT

- For this study (eDM) subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The primary null hypothesis (H0) for this study is that there is no difference between sirukumab 100mg SC q2w plus 6 month prednisone (Treatment Arm A) and placebo plus 6 month prednisone (Treatment Arm D) in the proportions of subjects with sustained disease remission at 52 weeks.

The alternative hypothesis (H1) for this study is that there is a difference in the proportions of subjects with sustained disease remission at 52 weeks.

The hypothesis to be tested for the proportion of subjects in sustained disease remission at 52 weeks using a 2-sided test at α=0.05 will therefore be:

H0: Sirukumab 100mg SC q2w + 6 month prednisone = placebo + 6 month prednisone

Vs.

H1: Sirukumab 100mg SC q2w + 6 month prednisone ≠ placebo + 6 month prednisone

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The sample size has been calculated assuming a 30% sustained remission rate on the placebo plus 6 month prednisone arm, versus a 70% rate on the sirukumab plus 6 month prednisone arms at 52 weeks. To be able to detect that difference using a 5% significance level, the sample size of N=51 on sirukumab 100mg 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 (Treatment Arm B) and placebo plus 6 month prednisone (Treatment 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, see Section 6.2 for more details. The randomisation will be stratified by baseline oral prednisone dose (<30 mg/day or ≥ 30 mg/day).

9.2.2. Sample Size Sensitivity

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%.

Response Rate Sirukumab 100 mg + 6m Pred	Difference Active-Placebo	N Placebo +6m Pred	N Sirukumab 100mg + 6m Pred	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 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.

9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

9.3. Data Analysis Considerations

For statistical analysis, all tests will be two-sided with significance interpreted at the α=0.05 significance level.

9.3.1. Analysis Populations

The analysis populations will include:

Intent to Treat (ITT) population: The ITT population is defined as all subjects who were randomised to treatment and who received at least one dose of study medication. This population will be the primary population for statistical comparisons for efficacy.

Safety population: This population will consist of all randomised subjects who received at least one or a partial dose of study medication. Subjects will be assessed according to the treatment they receive. This population will be used for assessing safety.

Further details of these and any other are included in the Reporting and Analysis Plan (RAP).

9.3.2. Analysis Datasets

Observed: Observed data is the data collected or observed for the subject with no imputation for missing data.

Further details are included in the RAP.

9.3.3. Treatment comparisons

Primary comparison of interest is the comparison between sirukumab 100 mg SC q2w plus 6 month prednisone (Treatment Arm A) and placebo plus 6 month prednisone (Treatment Arm D) for the proportion of subjects in sustained disease remission at Week 52 in the ITT population at the 0.05 significance level. The analysis will be adjusted for the stratification factor applied at randomization.

If the test of the primary endpoint for the primary comparison is statistically significant at α=0.05 (2-sided), the cumulative prednisone dose at week 52 (key secondary endpoint) for the primary comparison (arm A vs arm D) will be tested at a significance level of 0.05 (2-sided). If the statistical significance for the primary endpoint is not met, then the key secondary endpoint in the sequence cannot be deemed statistically significant, although nominal p-values may be reported and considered descriptive but should not be interpreted inferentially.

For the 2 endpoints outlined above the following treatment comparisons will also be evaluated following the same sequential approach provided that the primary endpoint for the primary comparison achieves significance:

- Sirukumab 100mg SC q2w plus 3 month prednisone versus placebo plus 6 month prednisone (Arm B vs. Arm D)
- Sirukumab 100mg SC q2w plus 6 month prednisone versus placebo plus 12 month prednisone (Arm A vs. Arm E)
- Sirukumab 100mg SC q2w plus 3 month prednisone versus placebo plus 12 month prednisone (Arm B vs. Arm E)

Comparisons with Sirukumab 50mg SC q4w (Arm C) will be similarly evaluated.

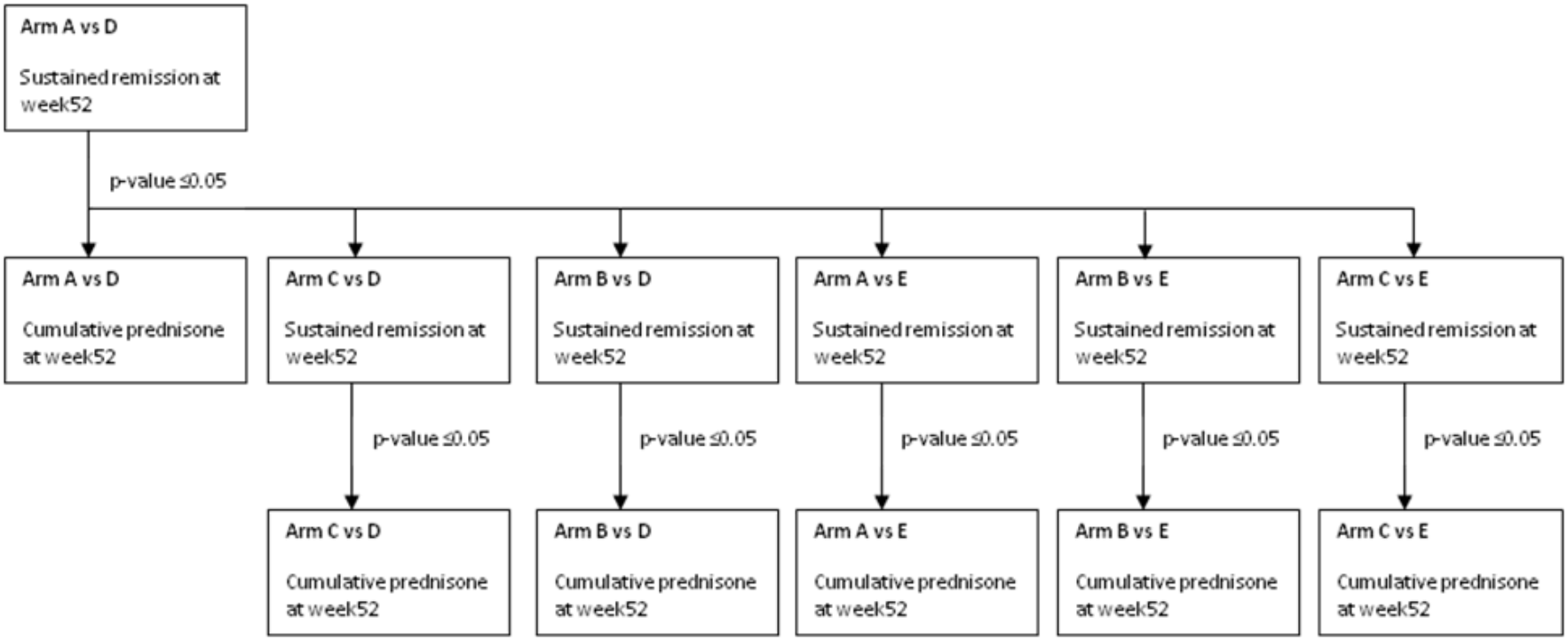
An overview of the multiplicity control is provided in Figure 2.

An alternative testing hierarchy, used to address regional differences in the regulatory requirements for controlling type 1 error, will be specified in the RAP.

Analyses of other efficacy endpoints will not be subject to any multiple comparison procedure. All statistical tests will be 2-sided and performed at an overall significance level of 0.05.

Further details are included in the RAP.

Figure 2 Overview of the Multiplicity control



Treatment arm A = Sirukumab 100 mg SC q2w plus 6-month prednisone taper
Treatment arm B = Sirukumab 100 mg SC q2w plus 3-month prednisone taper
Treatment arm C = Sirukumab 50 mg SC q4w plus 6-month prednisone taper
Treatment arm D = Placebo plus 6-month prednisone taper
Treatment arm E = Placebo plus 12-month prednisone taper

9.3.4. Interim Analysis

Since sirukumab is as yet untested in GCA, the study may employ a futility interim analysis to enable a decision to stop the study early should there be no or little effect of sirukumab. Dependent on the recruitment rate, the interim analysis may be carried out when approximately 30% of subjects have completed 52 weeks. The study will only be stopped for futility (lack of efficacy) if the probability of success of the study (i.e. the conditional power based on the observed interim data) is calculated to be very low. The futility assessment will be carried out by an IDMC, composed of clinicians and statisticians who are external to GSK, such that GSK remains fully blinded to all data and results.

The study will not be stopped early for efficacy to ensure no increase in the risk of a false positive result.

Full details of the process and decision criteria for this interim analysis for futility are included in the RAP.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Efficacy Analyses

The primary endpoint is a proportion of subjects in sustained remission at Week 52, defined as having:

5. Achieved remission (absence of clinical signs and symptoms of GCA and normalization of ESR [<30 mm/hr] and CRP [<1 mg/dL]), by Week 12
6. Absence of disease flare (recurrence of symptoms attributable to active GCA, with or without elevations in ESR and/or CRP) following remission at Week 12 through Week 52
7. Completed the assigned prednisone taper protocol
8. No requirement for rescue therapy at any time through Week 52.

Subjects who do not achieve remission within 12 weeks, require rescue therapy, discontinue treatment during the study or withdraw early from the study for any reason or do not follow the assigned prednisone taper will be recorded as non-responders in the analysis of the primary endpoint.

The proportion of subjects with sustained remission at week 52 in the sirukumab 100 mg SC q2w plus 6 month prednisone (Arm A) versus placebo plus 6 month prednisone (Arm D) will be analysed using a logistic regression model controlling for the stratification factor of baseline prednisone dose. The model will also include the treatment arms. Odds ratios and 95% confidence intervals will be produced.

If however a non-parametric approach is more appropriate then the Cochran-Mantel-Haenszel will be used.

As a supportive of the primary endpoint, the percentage of subjects meeting each of the components of the primary endpoint at Week 52 will be presented and the treatment effect on those components will be evaluated.

Further details of the analysis are included in the RAP.

9.4.2. Secondary Efficacy Analyses

For the analysis of secondary endpoints, all major continuous endpoints such as cumulative prednisone dose in Part A and Part B will be analysed using repeated measures mixed effects model. The analysis will be adjusted for the stratification factors applied at randomisation, as well as the baseline value for the parameter being tested.

The proportion of subjects in sustained remission over time (Part A and Part B) will be analysed using the logistic regression as described for the primary endpoint.

The major secondary endpoints for each comparison of interest will be tested using a step down sequential testing procedure to control the type 1 error.

Further details of the analysis are included in the RAP.

9.4.3. Safety Analyses

Safety in Part A and Part B will be evaluated by adverse events, and changes in laboratory parameters. All safety analyses will be performed on the safety population.

Complete details of the safety analyses are provided in the RAP.

9.4.3.1. Extent of Exposure

The number of day's exposure to study drug will be summarized by treatment group.

9.4.3.2. Adverse Events

The proportion of subjects reporting AEs will be tabulated for each treatment group. The following summaries of AEs will be provided:

- All AEs
- Treatment-related AEs
- AEs leading to withdrawal
- AEs leading to discontinuation of study drug
- Serious AEs
- Serious CV events adjudicated by the CEC.
- AEs of special interest, including corticosteroid-related AEs.

9.4.3.3. Laboratory Parameters

Laboratory data (absolute values and changes from baseline) will be summarized by visit and treatment group. In addition, the number and percent of subjects with values of clinical concern will be summarized by treatment group.

9.4.3.4. Other Safety Measures

Reason for withdrawal/treatment discontinuation will be summarized. Summary statistics for vital signs evaluations at each visit will be presented by treatment group. In addition, summary statistics for change from baseline for vital signs evaluations will be presented by treatment group.

ECG findings will be summarized by treatment group.

Further details are provided in the RAP.

9.4.4. Health Outcomes Analyses

All continuous endpoints such as SF-36 will be analysed using repeated measures mixed effects model. The analysis will be adjusted for the stratification factors applied at randomisation, as well as the baseline value for the parameter being tested.

Health outcomes endpoints will also be summarised appropriately.

Further details are provided in the RAP.

9.4.5. Pharmacokinetic and Immunogenicity Analyses

Serum concentrations of sirukumab in Part A will be summarized descriptively by time and treatment group. All data will be listed.

Possible relationships between serum concentrations and efficacy or safety endpoints may be investigated in an exploratory manner, if appropriate.

Immunogenicity (serum anti-sirukumab antibodies) in Part A and Part B if applicable will be summarized descriptively by time and treatment group.

All data will be listed.

Further details are included in the RAP.

9.4.6. Pharmacodynamic/Exploratory/Biomarker Analyses

Pharmacodynamic and biomarker data in Part A will be presented in graphical and/or tabular form and will be summarised descriptively. As appropriate, exploratory statistical analyses may be conducted where the distribution of biomarker data will be investigated.

Possible relationships between biomarker data and efficacy endpoints may be investigated in an exploratory manner, if appropriate.

Further details are included in the RAP.

9.4.7. Pharmacogenetic Analyses

Any PGx analyses will be described separately from the main clinical study report. GSK may summarize the PGx research results in the clinical study report, or separately, or may publish the results in scientific journal.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.

- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK (or designee) monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK (or designee) will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK (or designee) may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK (or designee) monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK (or designee) will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK (or designee) will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK (or designee) will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK (or designee) will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK [or designee] audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK (or designee) will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK (or designee) of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

10.8. Review Committees

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter which is available upon request.

An independent CEC will be established for this study to review case information on serious CV events (myocardial infarction, stroke, death, hospitalization for angina, hospitalization for transient ischemic attack (TIA). The operations, processes, and definitions to be employed by the committee will be defined in the CEC charter.

11. REFERENCES

Achkar, A.A., Lie, J.T., Hunder, G.G., O'Fallon, W.M., and Gabriel, S.E. (1994). How does previous corticosteroid treatment affect the biopsy findings in giant cell (temporal) arteritis? Annals of Internal Medicine *120*, 987-992.

ACTEMRA [prescribing information]. South San Francisco, CA: Genentech, Inc; 2011.

Arrida, A., Kyprianou, M., Kanakis, M., and Sfikakis, P.P. (2010). The diagnostic value of ultrasonography-derived edema of the temporal artery wall in giant cell arteritis: a second meta-analysis. BMC Musculoskeletal Disorders 11, 44.

Ball, E.L., Walsh, S.R., Tang, T.Y., Gohil, R., and Clarke, J.M. (2010). Role of ultrasonography in the diagnosis of temporal arteritis. The British Journal of Surgery 97, 1765-1771.

Besada, E., and Nossent, J.C. (2012). Ultrasonographic resolution of the vessel wall oedema with modest clinical improvement in a large-vessel vasculitis patient treated with tocilizumab. Clinical Rheumatology *31*, 1263-1265.

Beyer, C., Axmann, R., Sahinbegovic, E., Distler, J.H., Manger, B., Schett, G., and Zwerina, J. (2011). Anti-interleukin 6 receptor therapy as rescue treatment for giant cell arteritis. Annals of the Rheumatic Diseases *70*, 1874-1875.

Cella D, Lai J, Chang C, et al. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer. 2002:94(2):528-538.

Christidis, D., Jain, S., and Das Gupta, B. (2011). Successful use of tocilizumab in polymyalgic onset biopsy positive GCA with large vessel involvement. BMJ case reports *2011*.

Czihal, M., Zanker, S., Rademacher, A., Tato, T.Y., Kuhlencordt, P.J., Schulze-Koops, H., and Hoffman, U. (2012). Sonographic and clinical pattern of extracranial and cranial giant cell arteritis. Scandinavian Journal of Rheumatology 41:231-236.

Dalrymple SA, Lucian LA, Slattery R, et al. Interleukin-6-deficient mice are highly susceptible to Listeria monocytogenes infection: correlation with inefficient neutrophilia. Infect Immun. 1995;63(6):2262-2268.

De Miguel, E., Roxo, A., Castillo, C., Peiteado, D., Villalba, A., and Martin-Mola, E. (2012). The utility and sensitivity of colour Doppler ultrasound in monitoring changes in giant cell arteritis. Clinical and Experimental Rheumatology 30, S34-38.

Emilie, D., Liozon, E., Crevon, M.C., Lavignac, C., Portier, A., Liozon, F., and Galanaud, P. (1994). Production of interleukin 6 by granulomas of giant cell arteritis. Human Immunology *39*, 17-24.

EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. Health Policy. 1990;16:199-208

Flannery, C.R., Little, C.B., Hughes, C.E., Curtis, C.L., Caterson, B., and Jones, S.A. (2000). IL-6 and its soluble receptor augment aggrecanase-mediated proteoglycan catabolism in articular cartilage. Matrix biology : Journal of the International Society for Matrix Biology *19*, 549-553.

Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcomes in arthritis. Arthritis Rheum. 1980;23:137-145.

Gottenberg, J.E., Dayer, J.M., Lukas, C., Ducot, B., Chiocchia, G., Cantagrel, A., Saraux, A., Roux-Lombard, P., and Mariette, X. (2012). Serum IL-6 and IL-21 are associated with markers of B cell activation and structural progression in early rheumatoid arthritis: results from the ESPOIR cohort. Annals of the Rheumatic Diseases *71*, 1243-1248.

Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, Curtis JR, Furst DE, McMahon M, Patkar NM, Volkmann E, Saag KG. (2010). American College of Rheumatology 2010 Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis Care and Research, *62*(11), 1515-1526.

Hachulla, E., Boivin, V., Pasturel-Michon, U., Fauchais, A.L., Bouroz-Joly, J., Perez-Cousin, M., Hatron, P.Y., and Devulder, B. (2001). Prognostic factors and long-term evolution in a cohort of 133 patients with giant cell arteritis. Clinical and Experimental Rheumatology *19*, 171-176.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(a): 24. Table 3-2.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(b): 28.

Hayreh, S.S., and Zimmerman, B. (2003). Management of giant cell arteritis. Our 27-year clinical study: new light on old controversies. Ophthalmologica. Journal International d'Ophtalmologie. International Journal of Ophthalmology. Zeitschrift fur Augenheilkunde *217*, 239-259.

Hoffman, G.S., Cid, M.C., Rendt-Zagar, K.E., Merkel, P.A., Weyand, C.M., Stone, J.H., Salvarani, C., Xu, W., Visvanathan, S., Rahman, M.U., and Infliximab, G.C.A.S.G. (2007). Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. Annals of Internal Medicine *146*, 621-630.

ICH Topic M 3 (R2) Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. Note 5. 2009. CPMP/ICH/286/95."

Isik, M., Kilic, L., Dogan, I., and Calguneri, M. (2013). Tocilizumab for giant cell arteritis: an amazing result. Rheumatology International *33*, 2961-2962.

Karassa, F.B., Matsagas, M.I., Schmidt, W.A., and Ioannidis, J.P. (2005). Meta-analysis: test performance of ultrasonography for giant-cell arteritis. Annals of Internal Medicine 142, 359-369.

Lipsky, P.E. (2006). Interleukin-6 and rheumatic diseases. Arthritis Research & Therapy *8 Suppl 2*, S4.

Luqmani R, Lee E, Singh S, Gillett M, Schmidt WA, Bradburn M, Dasgupta B, Diamantopoulos AP, Forrester-Barker W, Hamilton W, Masters S, McDonald B, McNally E, Pease CT, Piper J, Salmon J, Wailoo A, Wolfe K, Hutchings A. Inter-Rater Analysis of Ultrasound and Histological Findings in Patients with Suspected Giant Cell Arteritis [abstract]. Arthritis Rheumatol. 2015; 67 (suppl 10).

Lurati, A., Bertani, L., Re, K.A., Marrazza, M., Bompane, D., and Scarpellini, M. (2012). Successful treatment of a patient with giant cell vasculitis (Rheuma arteritis) with tocilizumab a humanized anti-interleukin-6 receptor antibody. Case Reports in Rheumatology *2012*, 639612.

Martinez-Taboada VM, Rodriguez-Valverde V, Carreno L, et al (2008). A double-blind placebo controlled trial of etanercept in patients with giant cell arteritis and corticosteroid side effects. Annals of the Rheumatic Diseases 67, 625-630.

Mundt JC, Greist JH, Gelenberg AJ, Katzelnick DJ, Jefferson JW, Modell JG. Feasibility and validation of a computer-automated Columbia-Suicide Severity Rating Scale using interactive voice response technology. J Psychiat Res. 2010; 44(16):1224-1228.

Nemeth, E., Rivera, S., Gabayan, V., Keller, C., Taudorf, S., Pedersen, B.K., and Ganz, T. (2004). IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. The Journal of Clinical Investigation *113*, 1271-1276.

Nesher, G. (2014). The diagnosis and classification of giant cell arteritis. Journal of Autoimmunity *48-49*, 73-75.

Ponte C, Vaggers S, Sznajd J, O'Neill L, Piper J, Gunn J, Mankia K, Luqmani R. How Can We Use Ultrasound in the Diagnosis and Management of Patients with Giant Cell Arteritis? [abstract]. Arthritis Rheumatol. 2015; 67 (suppl 10).

Proven, A., Gabriel, S.E., Orces, C., O'Fallon, W.M., and Hunder, G.G. (2003). Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis and Rheumatism *49*, 703-708.

Rincon, M. (2012). Interleukin-6: from an inflammatory marker to a target for inflammatory diseases. Trends in Immunology *33*, 571-577.

Roche, N.E., Fulbright, J.W., Wagner, A.D., Hunder, G.G., Goronzy, J.J., and Weyand, C.M. (1993). Correlation of interleukin-6 production and disease activity in polymyalgia rheumatica and giant cell arteritis. Arthritis and Rheumatism *36*, 1286-1294.

Romani L, Mencacci A, Cenci E, et al. Impaired neutrophil response and CD4+ T helper cell 1 development in interleukin 6-deficient mice infected with Candida albicans. J Exp Med. 1996;183(4):1345-1355.

Salvarani, C., Crowson, C.S., O'Fallon, W.M., Hunder, G.G., and Gabriel, S.E. (2004). Reappraisal of the epidemiology of giant cell arteritis in Olmsted County, Minnesota, over a fifty-year period. Arthritis and Rheumatism *51*, 264-268.

Salvarani, C., Magnani, L., Catanoso, M., Pipitone, N., Versari, A., Dardani, L., Pulsatelli, L., Meliconi, R., and Boiardi, L. (2012). Tocilizumab: a novel therapy for patients with large-vessel vasculitis. Rheumatology (Oxford, England) *51*, 151-156.

Sampson HA, Munoz-Furlong A, Campbell RL, et.al. (2006). Second symposium on the definition and management of anaphylaxis: Summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol.117, 391-397.

Schmidt WA, Krause E, Schicke B, Kuchenbecker J, Gromnica-Ihle E. Do temporal artery duplex ultrasound findings correlate with ophtalmic complications in giant cell arteritis? Rheumatology (Oxford). 2009 Apr; 48(4):383-5.

Schmidt WA, Moll A, Seifert A, Schicke B, Gromnica-Ihle E, Krause A. Prognosis of large-vessel giant cell arteritis. Rheumatology (Oxford). 2008 Sep;47(9):1406-8.

Sciascia, S., Rossi, D., and Roccatello, D. (2011). Interleukin 6 blockade as steroid-sparing treatment for 2 patients with giant cell arteritis. The Journal of Rheumatology 38, 2080-2081.

Seitz, M., Reichenbach, S., Bonel, H.M., Adler, S., Wermelinger, F., and Villiger, P.M. (2011). Rapid induction of remission in large vessel vasculitis by IL-6 blockade. A case series. Swiss Medical Weekly *141*, w13156.

Seror, R., Baron, G., Hachulla, E., Debandt, M., Larroche, C., Puechal, X., Maurier, F., de Wazieres, B., Quemeneur, T., Ravaud, P., and Mariette, X. (2013). Adalimumab for steroid sparing in patients with giant-cell arteritis: results of a multicentre randomised controlled trial. Annals of the Rheumatic Diseases.

Spies, C.M., Burmester, G.R., and Buttgereit, F. (2010). Methotrexate treatment in large vessel vasculitis and polymyalgia rheumatic. Clinical and Experimental Rheumatology *28*, S172-177.

Suzuki Y, Rani S, Liesenfeld O, et al. Impaired resistance to the development of toxoplasmic encephalitis in interleukin-6-deficient mice. Infect Immun. 1997;65(6):2339-2345.

Swaak, A.J., van Rooyen, A., Nieuwenhuis, E., and Aarden, L.A. (1988). Interleukin-6 (IL-6) in synovial fluid and serum of patients with rheumatic diseases. Scandinavian Journal of Rheumatology *17*, 469-474.

Tse, W.Y., Cockwell, P., and Savage, C.O. (1998). Assessment of disease activity in systemic vasculitis. Postgraduate Medical Journal 74, 1-6.

Unizony, S., Arias-Urdaneta, L., Miloslavsky, E., Arvikar, S., Khosroshahi, A., Keroack, B., Stone, J.R., and Stone, J.H. (2012). Tocilizumab for the treatment of large-vessel vasculitis (giant cell arteritis, Takayasu arteritis) and polymyalgia rheumatica. Arthritis Care & Research *64*, 1720-1729.

Unizony, S.H., Dasgupta, B., Fisheleva, E., Rowell, L., Schett, G., Spiera, R., Zwerina, J., Harari, O., and Stone, J.H. (2013). Design of the tocilizumab in giant cell arteritis trial. International Journal of Rheumatology *2013*, 912562.

Vinit, J., Bielefeld, P., Muller, G., and Besancenot, J.F. (2012). Efficacy of tocilizumab in refractory giant cell arteritis. Joint, Bone, Spine : Revue du Rhumatisme *79*, 317-318.

Waldman, C.W., Waldman, S.D., and Waldman, R.A. (2013). Giant cell arteritis. The Medical Clinics of North America *97*, 329-335.

Ware JE Jr, Sherbourne CD. The MOS 36 item short form health survey (SF 36), I: conceptual framework and item selection. Med Care. 1992;30(6):473 483.

Ware JE, Kosinski M, Keller SD. Interpretation: Norm-Based. In: SF-36 Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute; 1994:8:1-8:42.

Weyand, C.M., and Goronzy, J.J. (2013). Immune mechanisms in medium and large-vessel vasculitis. Nature Reviews. Rheumatology *9*, 731-740.

Weyand, C.M., Fulbright, J.W., Hunder, G.G., Evans, J.M., and Goronzy, J.J. (2000). Treatment of giant cell arteritis: interleukin-6 as a biologic marker of disease activity. Arthritis and Rheumatism *43*, 1041-1048.

Weyand, C.M., Younge, B.R., and Goronzy, J.J. (2011). IFN-gamma and IL-17: the two faces of T-cell pathology in giant cell arteritis. Current Opinion in Rheumatology *23*, 43-49.

Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue sand other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Sympt Manage. 1997;13;63-74.

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACR	American College of Rheumatology
AE	Adverse Event
AION	Acute Ischemic Optic Neuropathy
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase
BCG	Bacille Calmette-Guérin
BD	Becton-Dickinson
bili	Bilirubin
CEC	Clinical Events Committee
CONSORT	Consolidated Standards of Reporting Trials
COX-2	Cyclooxygenase-2
CRF	Case Report Form
CRP	C-reactive Protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CTA	Computed Tomography Angiography
CTX	Carboxyterminal Cross-linked Telopeptide of Bone Collagen
CV	Cardiovascular
DBL	Database lock
dL	Deciliter
DMARD	Disease Modifying Antirheumatic Drugs
ECG	Electrocardiogram
eDM	Electronic Data Management
EQ VAS	EuroQoL Visual Analogue Scale
EQ-5D	EuroQoL-5 Dimensions
ESR	Erythrocyte Sedimentation Rate
EudraCT	European Clinical Trials Database
FACIT-Fatigue	Functional assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
G	gauge
GCA	Giant Cell Arteritis
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GI	Gastrointestinal
gr	Gram
GSK	GlaxoSmithKline
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen

HIV	Human Immunodeficiency Virus
hr	Hour
IB	Investigator's Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgG1	Immunoglobulin G1
IL-1	Interleukin-1
IL-1ra	Anakinra
IL-6	Interleukin-6
IL-17A	Interleukin-17A
IRB	Institutional Review Board
IV	Intravenous
IRT	Interactive Response Technology
LOCF	Last Observation Carried Forward
LTBI	Latent Tuberculosis Infection
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
μmol	Micromoles
mg	Milligrams
Mm	Millimeters
MMF	Mycophenolate Mofetil
MRA	Magnetic Resonance Angiography
MSDS	Material Safety Data Sheet
msec	Milliseconds
MTX	Methotrexate
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NRS	Numeric Rating Scale
NSAID	Nonsteroidal anti-inflammatory drug
PGIC	Patient Global Impression of Change
PhGA	Physician Global Assessment
P1NP	Procollagen Type 1 N-propeptide
PET-CT	Positron Emission Tomography-computed Tomography
PFS	Pre-filled Syringe
PFS-U	Prefilled Syringe-Ultrasafe
PK	Pharmacokinetic
PMR	Polymyalgia Rheumatic
po	Per os (by mouth)
PRO	Patient Reported Outcomes
PtGA	Patient Global Assessment
q2w	Every 2 Weeks
q4w	Every 4 Weeks
RA	Rheumatoid Arthritis
RAP	Reporting and Analysis Plan

SAE	Serious Adverse Event
SC	Subcutaneous
SF-36v2	36-item Short Form Health Survey Version 2
SI	International System of Units
SLE	Systemic Lupus Erythematosus
SPM	Study Procedures Manual
TIA	Transient Ischemic Attack
TST	Tuberculin Skin Test
TB	Tuberculosis
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
US	Ultrasound
VAS	Visual Analogue Scale
vs	Versus

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
ACTEMRA
Hypak
QuantiFERON
RIBA
SCF
SmartJect (Autoinjector)
UltraSafe Passive

12.2. Appendix 2: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) and Collection of Pregnancy Information

12.2.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a]
- Injectable progestogen [Hatcher, 2007a]
- Contraceptive vaginal ring [Hatcher, 2007a]
- Percutaneous contraceptive patches [Hatcher, 2007a]
- Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007a].
- Male condom plus partner use of one of the contraceptive options below:
    - Contraceptive subdermal implant
    - Intrauterine device or intrauterine system
    - Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a] Injectable progestogen [Hatcher, 2007a]
    - Contraceptive vaginal ring [Hatcher, 2007a]
    - Percutaneous contraceptive patches [Hatcher, 2007a]

If using hormonal contraceptives, including oral, injections and patches, a secondary method of contraception must be used.

This is an all inclusive list of those methods that meet the GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and, correctly and, when applicable, in accordance with the product label. For non-product methods (e.g. male sterility), the investigator determines what is consistent and correct use. The GSK definition is based on the definition provided by the ICH [ICH, M3 (R2) 2009].

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.2.2. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject or female partner of male study subject who becomes pregnant while participating in or while partner is participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating in this study will discontinue study drug. There is no requirement to be withdrawn from the study.

12.3. Appendix 3: Liver Safety Required Actions and Follow up Assessments

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase III-IV liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below)	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]. • Blood sample for PK analysis, obtained within 24 hours after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

• **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding**

studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants

3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.

Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

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

12.4. Appendix 4: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.4.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's

condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.4.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.4.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension

- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.4.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.4.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort

and not interfering with everyday activities.

- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests

or investigations, histopathological examinations or consultation with other health care professionals.

- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.4.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the SAE coordinator.
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the SAE coordinator by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5: American College of Rheumatology Standard of Care Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis*

Recommended Monitoring for Patients Receiving Prevalent Glucocorticoid Therapy for a Duration >3 Months

- Consider serial bone mineral density testing
- Consider annual serum 25-hydroxyvitamin D measurement
- Annual height measurement
- Assessment of incident fragility fracture
- Assessment of osteoporosis medication compliance

Pharmacologic Recommendations for Postmenopausal Women and Men age >50 Years Starting Glucocorticoid Therapy with an Anticipated Duration of >3 Months, or Prevalent Glucocorticoid Therapy of a Duration of at Least 3 months

Low-risk patient
Alendronate for _7.5 mg/day prednisone
OR
Risedronate for _7.5 mg/day prednisone
OR
Zoledronic acid for _7.5 mg/day prednisone

Medium-risk patient
Alendronate for any dose of glucocorticoids
OR
Risedronate for any dose of glucocorticoids
OR
Zoledronic acid for _7.5 mg/day prednisone

High-risk patient
Alendronate
OR
Risedronate
OR
Zoledronic acid
OR
Teriparatide

* Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, Curtis JR, Furst DE, McMahon M, Patkar NM, Volkmann E, Saag KG. (2010). American College of Rheumatology 2010 Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis Care and Research, *62*(11), 1515-1526.

12.6. Appendix 6: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including sirukumab, prednisone or any concomitant medicines;
- GCA susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to

the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample

reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.7. Appendix 7 - Country Specific Requirements

In Germany, subcutaneous administration of sirukumab or matching placebo **must** be discontinued for subjects with a clinically important, active infection. This treatment must be withheld until serious and/or severe infections have been completely resolved. This includes all opportunistic infections, sepsis or meningoencephalitis.

In the Netherlands, no subject will be enrolled in the extension phase (Part B) of the study. Subjects will discontinue the study upon completion Part A and the 16-week follow-up phase.

In Australia and New Zealand, the investigator will be notified of the value of the ESR result when an ESR value is > 40 mm/hr or in the event of a increase from baseline or previous visit of > 10 mm/hr in order to determine if a treatment change is warranted.

12.8. Appendix 8: Exploratory US Imaging

The utility of US in monitoring disease activity in GCA will be investigated in a cohort of subjects with new onset GCA. Longitudinal changes in vascular inflammation of the temporal and axillary arteries will be characterized. Only subjects with new onset GCA will participate in order to optimize the ability to detect inflammatory changes on US, based on the potential likelihood that these subjects would not have been receiving corticosteroids prior to diagnosis.

12.8.1. Objectives and Endpoints

The objectives and endpoints of this exploratory US imaging cohort are as follows:

Objectives	Endpoints
• 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 ultrasound for clinical efficacy in GCA	• 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.

12.8.2. Type and Number of Subjects

Only subjects with new onset GCA are eligible to participate in the exploratory imaging portion of this study. These subjects will have a diagnosis of GCA based on the Revised GCA Diagnosis Criteria, and present with new onset GCA disease, defined as having a diagnosis within 6 weeks of baseline. Subjects should have either initiated prednisone treatment upon entry into Screening **and after** their Screening US scan has been performed **or** corticosteroid therapy should have only been recently initiated, optimally within 3 days of the Screening scan. However, inability to comply with this time frame does not exclude subjects from participation.

As this is an exploratory study, there is no pre-specified sample size. However it is estimated that up to 50 subjects may participate.

12.8.3. Assessments and Procedures

12.8.3.1. Sonographer Training

All sonographers participating in this study must have undergone training with documented approval to qualify as a participating site. Sites previously trained for participation in the TABUL study will not be required to participate in the training sessions, but may certify through a separate process. Processes and procedures for training and qualification are outlined in the Imaging Acquisition Guidelines.

Sonographers participating in the training course will US scan a requisite number of healthy volunteers/non-GCA subjects and at least one patient volunteer with active GCA as per the protocol definition for qualification. All volunteers recruited to participate in the sonographer training will be required to provide consent prior to participation. GCA patients who participate in the sonographer training may be eligible to enroll in Study 201677, but they are excluded from participating in the imaging cohort portion of the study. Detailed information on the sonographer training process is contained in the training manual.

12.8.3.2. Subject Eligibility

Study subjects consenting to participate in the exploratory US imaging cohort are eligible only if they have newly diagnosed GCA (within 6 weeks of baseline), based on the Revised GCA Diagnosis Criteria as described in Section 5.1. At Baseline, subjects must have fulfilled all of the eligibility criteria for Study 201677 and be randomized into the study to continue participation in the exploratory imaging cohort. Screen failures for Study 201677 will not be eligible to participate in this cohort.

Optimally, the study baseline scan (Screening) would be performed prior to the initiation of prednisone treatment. If this is not possible, then efforts should be made to perform the US scan within 3 days of initiating prednisone treatment. However, the inability to comply with this time frame is not exclusionary. The number of days between initiation of prednisone treatment and the US scan will be recorded.

12.8.3.3. Ultrasound Scanning

Participating subjects will undergo US scans at the following time points:

1. Screening, or after consent has been provided to participate in the imaging cohort. Optimally (but not required), this scan would be performed within 3 days of initiating corticosteroid therapy for GCA disease activity:

2. Week 0 (Randomization)

3. Week 12

4. Week 52

5. Any time point of disease relapse/flare during Part A or Part B of the study, with every effort made to conduct the US scan within 3 days of rescue prednisone administration. The number of days between the US scan and rescue prednisone administration will be recorded. Scanning in the event of relapse/flare during Part B will conclude when the last subject in the exploratory US imaging cohort completes Part A. No additional Part B scans will be taken after this time point.

The timings of the US assessments are included in Section 7.1, Time and Events Tables, Table 2, Table 3, Table 4 and Table 5.

The scans will be sent for independent review by a central reader. Full details on the US scanning process, training requirements, image transfer and de-identification, assessments and data collection are provided in the Imaging Acquisition Guidelines.

12.8.4. Blinding

The central reader will remain blinded to the subject's treatment group. Investigators and sponsor will remain blinded to the central US results. No clinical findings will be communicated by the central reader to investigators. Scans may be reviewed at the site according to local policy.

12.8.5. Statistical Considerations and Data Analyses

12.8.5.1. Hypotheses

The objectives of the evaluations in the US imaging cohort are exploratory and observational. There are no formal statistical hypotheses planned.

Exploratory comparisons will be made between the sirukumab and placebo arms, if appropriate.

12.8.5.2. Sample Size Considerations

There are no formal calculations of power or sample size for this cohort. There is no pre-specified upper or lower limit for subject enrolment in this cohort. Therefore, no sample size sensitivity was performed and there are no plans for sample size re-estimation .

12.8.5.3. Data Analysis Considerations

No formal analyses are planned for this cohort.

12.8.5.4. Key Elements of Analysis Plan

Data from the US imaging cohort may be reported separately from the main 201677 clinical study report.

Data will be analyzed according to the timeframe between prednisone dose and US scan.

Graphics and/or descriptive statistics will be used to describe the time course and magnitude of changes in key markers (e.g. halo). If data permits, analyses assessing the associations between these key markers and some disease activity and health outcomes indicators (e.g. GCA disease activity, ESR, CRP, fatigue and pain) will be carried out using descriptive statistics and graphics.

Full details of the approaches will be described separately from the main clinical study report.

12.9. Appendix 9: Protocol Changes

Amendment 01 15 October 2015

1. Clarification of the secondary objective and endpoint relating to characterization of disease remission. Characterization of disease flare over time has been delineated as a separate secondary objective.

   Rationale: Sustained remission will be assessed at various time points throughout the 52-week treatment period and will not include subjects who are in remission but have not been able to follow the protocol taper and/or received rescue therapy.

Section 1 and Section 3: Objective(s)/Endpoint(s)

Part A: 52-week double-blind treatment phase

• To characterize ~~remission~~ **sustained** remission ~~and disease flare~~ over time	• Proportion of subjects in **sustained** remission ~~over~~ **at each time point of assessment from Week 12 to Week 52, where sustained remission is defined as having achieved all of the following:** • **Remission at Week 12 and** • **Absence of disease flare following remission at Week 12 and** • **Adherence to the assigned prednisone taper protocol and** • **No requirement for rescue therapy at any time**
• **To characterize disease flare over time**	• Time to first GCA flare after clinical remission • Number of disease flares per patient over time • Proportion of subjects requiring hospitalizations for disease flare and number of hospitalizations for disease flare over time

2. Clarification of the objectives and endpoints related to patient and physician reported health outcomes.

   Rationale: To provide additional details for clarification and correction of errors in the original protocol.

Section 1 and Section 3: Objective(s)/Endpoint(s)

Part A: 52-week double-blind treatment phase

• 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**	• Patient reported outcomes including SF-36v2, EQ-5D (~~3~~**5**L), FACIT-Fatigue, Pain ~~**VAS**~~**Numeric Rating Scale (NRS)**, Steroid Impact PRO, HAQ-DI, **Patient Global Impression of Change** (PGIC), **Patient Global Assessment of disease activity (PtGA)** • **Clinician reported outcomes including Physician Global Assessment of disease activity (PhGA)**

3. Amendment of the endpoints for evaluation of maintenance of disease remission and patient and physician reported outcomes in Part B.

   Rationale: Clarification that the key secondary endpoint in Part B is proportion of subjects who had achieved sustained remission at the end of Part A and remained in sustained remission without a treatment change at Week 24 of Part B. Subjects who received 12 months of sirukumab treatment during Part B will also be evaluated for sustained remission 6 months post cessation of treatment. It is also clarified that hospitalizations over time will be assessed. Additional details on objectives and assessment of patient and physician reported outcomes have been included for clarification purposes and for correction of errors in the original protocol.

Section 1 and Section 3: Objective(s)/Endpoint(s)

Part B: 104-week long-term extension phase

Objectives	Endpoints
• To evaluate the long-term maintenance of disease remission on cessation of 12 months of sirukumab treatment	• Proportion of subjects who remained in sustained remission ~~6 months post cessation of 12-month sirukumab treatment~~ **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 GCA flare for subjects in sustained remission at baseline of Part B • Number of disease flares per patient

Objectives	Endpoints
	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 post cessation of 12-month 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	• Patient reported outcomes including SF-36v2, EQ-5D (~~3~~**5**L), FACIT-Fatigue, Pain ~~VAS~~**NRS**, Steroid Impact PRO, HAQ-DI **and PtGA** • **Clinician reported outcomes including PhGA**

4. Clarification of the signs and symptoms of GCA.

   Rationale: To provide additional detail and clarifications for investigator guidance and consideration.

   Section 4.1 Overall Design

Signs and symptoms of GCA may include ~~PMR symptoms,~~ new onset headache; jaw claudication (jaw or mouth pain upon chewing); **visual signs and** symptoms including but not limited to amaurosis fugax, transient or episodic blurry vision, diplopia, permanent vision loss due to acute ischemic optic neuropathy (AION); temporal artery tenderness; scalp tenderness; **reduced or absent pulsation in temporal artery; cord-like thickening of temporal artery; stroke; scalp necrosis; pain over face/scalp arteries; new or worsened extremity claudication**; fever of unknown origin; **PMR symptoms**; or other symptoms that in the investigator's experience are associated with GCA.

5. Clarification and correction of wording around prednisone during Screening and initiation of the open-label and blinded prednisone taper.

   Rationale: Prednisone dose during Screening should be determined by investigator to ensure disease activity is stable at Randomization when prednisone taper is initiated. It is clarified that the first decrease in prednisone dose per the taper regimen occurs at Week 1.

   Section 4.1 Overall Design

The prednisone dose for all subjects **at Screening** will be determined by the Investigator and ~~starting doses must be within 20-60 mg prednisone at Baseline (Randomization).~~**may be adjusted in an open manner based on the subject's disease status per investigator discretion. At Baseline (Randomization), doses must be within 20-60 mg prednisone for the starting dose when the pre-specified prednisone taper is initiated. Subjects will remain on the prednisone dose they are receiving at Baseline for one week and then will decrease the dose at Week 1, as specified in the taper regimen. Subjects will follow the open-label prednisone taper regimen until they reach a 20 mg dose of prednisone when the blinded prednisone taper regimen begins. Subjects receiving a 20 mg prednisone dose at Baseline will continue the 20 mg dose for one week and at Week 1 will initiate the blinded taper.**

6. Addition of details regarding the imaging sub-study.

   Rationale: To add the study number and clarify that it will be conducted at select centers.

   Section 4.1 Overall Design

A separate exploratory sub-study **(Study 205028)** will be conducted **at selected centers** to assess the utility of imaging assessment of inflammation as an indicator of disease activity in a cohort of study subjects. The details of this exploratory sub-study will be provided in a separate protocol.

7. Clarifications of circumstances for receiving open-label sirukumab in Part B.

   Rationale: To clarify that open-label sirukumab and corticosteroid use and corticosteroid dose adjustments are determined by the investigator based on their assessment of the subject's disease activity. Guidance is provided to investigators to consider appropriate use of sirukumab in subjects with continued disease activity or with persistent flares to help ensure that sirukumab therapy is discontinued in individual circumstances where it is ineffective.

   Section 4.2.2 Part B: 104-week extension phase

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

- Subjects in remission at the primary 52-week endpoint. These subjects will discontinue blinded study drug treatment on entry into Part B and will be followed for maintenance of response. However, **in the event of a flare**. they will have the option to receive, **at the discretion of their Investigator**, open-label sirukumab 100 mg SC q2w for a maximum of 52 weeks during the first 52 weeks of Part B ~~in the event of a flare~~.
- Subjects ~~with disease activity~~ **not in remission** at the primary 52-week endpoint or subjects who have not been able to ~~follow the prednisone taper~~ **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 1st 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~~ **Adjustments in corticosteroid dose** 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 that continue to experience flares or persistent disease activity following the start of open label treatment.

8. Clarification of the risk mitigation strategies for hypersensitivity and GI perforations, including the addition of information regarding sponsor classification of hypersensitivity reactions using the Sampson criteria. Amendment of the wording to clarify that subjects with hypersensitivity reactions, cytopenias, liver enzyme increases and cardiovascular events should discontinue study treatment without requirement to withdraw from the study. Clarification of wording on disease stability for initiating the prednisone taper.

   Rationale: To help ensure subject safety, additional wording has been added around subject awareness of the nature and risks of hypersensitivity reactions and investigator vigilance in monitoring for signs of GI perforations due to the potential for these to be masked by prednisone use. Sponsor adjudication of hypersensitivity reactions using the Sampson criteria will be implemented to further characterize any such events. Risk mitigation strategies include discontinuation of study drug but not subject withdrawal from the study.

   Section 4.6.1 Risk Assessment

Hypersensitivity	Serious allergic reactions (eg, anaphylaxis) have been reported with the administration of mAbs, including sirukumab, and may occur during or after the administration of the mAbs.	Exclusion of subjects with severe allergic reactions to monoclonal antibodies, human proteins, or excipients. ~~Withdrawal of study drug in the event of a severe allergic reaction.~~ **Subjects will be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention.** **Discontinuation of blinded subcutaneous study drug in the event of a severe allergic**

		reaction. **Monitoring of serious allergic reactions by IDMC; adjudication and classification of these events using Sampson criteria (Sampson, 2006) by sponsor safety review team will be implemented.**
Gastrointestinal perforation	Upper and lower GI tract perforations occurred in the anti-IL-6 receptor (tocilizumab) Phase III program. Sirukumab binds to IL-6 and prevents binding to IL-6 receptor (IL-6R). Tocilizumab binds to IL-6 R to prevent IL-6 signalling. Potential differences in safety between agents that bind to the IL-6 receptor versus ones that bind to the IL-6 ligand (sirukumab) warrants further study.	Exclusion of subjects with a history of diverticulitis, inflammatory bowel disease, or other symptomatic GI tract condition that might predispose to bowel perforation. **Investigators should closely monitor for GI perforations with a high degree of suspicion.** Monitoring of gastrointestinal perforations by IDMC.
Cytopenias	Neutropenia and thrombocytopenia have occurred in sirukumab studies, including severe thrombocytopenia associated with bleeding. Decreases in platelet counts have also been observed.	Exclusion of subjects with absolute neutrophil count (ANC) $<2x10^9$/L, platelet count $<140x10^9$/L, WBC count $<3.5x10^9$/L, ALC <0.5 x10^9/L. ~~Withdrawal of~~ **Discontinuation of blinded subcutaneous study drug for** subjects with 2 confirmed consecutive absolute neutrophil counts of $<0.5 \times 10^9$ cells/L or platelet counts <50 x 10^9 cells/L. Monitoring of cytopenias by IDMC.
Liver enzyme increases	Transient asymptomatic increases (1 to 3 x ULN, sometimes > 5 x ULN but < 8 x ULN) in blood ALT and AST values have been observed in subjects in completed and ongoing studies of sirukumab. These changes were not associated with an increase in bilirubin.	Exclusion of subjects with AST or ALT >2.0 x ULN, or total bilirubin >ULN with the exception of Gilbert's disease. Inclusion of pre-defined liver chemistry ~~withdrawal~~ **discontinuation** criteria (Section 5.4.3). Monitoring of hepatic abnormalities by IDMC.

Cardiovascular events	No cardiovascular risk with sirukumab has been identified in clinical studies to date. However, the study population is at high risk for CV disease.	Exclusion of subjects with uncontrolled cardiovascular disease or marked baseline prolongation of QTc interval ≥ 450 msec (QTcB or QTcF), history of Torsade de Pointes, family history of long QT syndrome, history of second or third degree heart block or subject with major ischemic event unrelated to GCA. Inclusion of pre-defined QTc ~~withdrawal~~ **discontinuation** criteria (Section 5.4.4). Monitoring of CV events by CEC and IDMC
Rapid steroid taper	Steroid withdrawal symptoms and side effects	Inclusion only of subjects with stable disease who are able to safely participate in the steroid taper. Subjects should ~~be stabilized~~ **have clinically stable disease** on steroid therapy prior to randomization. IDMC will monitor all subjects including those in the 3 month taper.

9. Clarification of the wording describing the mechanism of IL-6 inhibition.

   Rationale: Sirukumab does not target the IL-6 receptor but inhibits IL-6 activity by binding to the molecule itself.

   Section 4.6.3 Overall Benefit:Risk Conclusion

   Although the efficacy of sirukumab in subjects with GCA has yet to be established, it has been shown to be effective in Phase II studies in RA. Furthermore other agents that ~~target the IL-6 receptor~~ **inhibit IL-6 activity** have been shown to be efficacious in RA.

10. Clarification of inclusion criteria related to diagnosis of GCA and signs and symptoms of active GCA.

    Rationale: To provide additional guidance to investigators regarding qualifications for a diagnosis of GCA on biopsy and imaging and for signs and symptoms of GCA to ensure inclusion of appropriate patients in the study.

    Section 5.1 Inclusion Criteria

1. Diagnosis of GCA defined by the following Revised GCA Diagnosis Criteria:

- Presence of at least **one** of the following:
  - Temporal artery **abnormality on** biopsy revealing features of GCA.
  - Evidence of large-vessel vasculitis by angiography or cross-sectional imaging, including but not limited to magnetic resonance angiography (MRA), computed tomography angiography (CTA), **ultrasound (US) or** positron emission tomography-computed tomography (PET-CT) ~~or evidence of large-vessel or temporal artery vasculitis by ultrasound (US)~~.

2. Active GCA within 6 weeks of Randomization (Baseline) where active disease is defined by an ESR ≥30 mm/hr or CRP ≥ 1 mg/dL AND the presence of at least **one** of the following:

- Unequivocal cranial **signs and** symptoms of GCA (new onset localized headache, scalp or temporal artery tenderness, ~~ischemia-related vision loss [permanent vision loss due to AION, amaurosis fugax, episodic blurry vision], diplopia, or~~ **reduced or absent pulsation in temporal artery, cord-like thickening of temporal artery, stroke, scalp necrosis, pain over face/scalp arteries** or otherwise unexplained mouth or jaw pain upon mastication [i.e., jaw claudication]).
- **Visual signs and symptoms associated with GCA, including ischemia-related vision loss [permanent vision loss due to AION, amaurosis fugax, episodic blurry vision], diplopia, scotoma, nerve palsies, relative afferent papillary defects, central retinal artery occlusions.**

11. Amendment of inclusion criteria for TB testing.

Rationale: All sites are capable of conducting the QuantiFERON Gold test. To ensure consistency of testing across the study for TB, the options for T spot and skin testing have been removed.

6. No evidence of active or latent infection with Mycobacterium tuberculosis (TB), as defined by all of the following:

a. No history of active or latent TB infection.

b. A negative diagnostic TB test at Screening defined as: ~~–~~a negative QuantiFERON Gold test (NB: 2 successie indeterminate QuantiFERON tests will be considered as a positive result).

~~OR~~

- ~~If QuantiFERON gold or T-spot test is not approved or registered in country of participation, then a negative tuberculin skin test (TST) reaction as per local guidelines is required (it is strongly recommended that patients with a history of BCG vaccination be tested with QuantiFERON gold test).~~

12. Correction of time frames for biologic use and reference to section for additional guidance.

    Rationale: Based on the pharmacokinetic profile of anti-TNFα therapies, a minimum of a 4 week wash out period is required.

    Section 5.2 Exclusion Criteria

4. Had prior treatment with any of the following:
    - Biologic agents targeted at reducing TNFα (including but not limited to infliximab, golimumab, certolizumab pegol, etanercept, yisaipu, and adalimumab) within ~~2~~**4**-8 weeks of baseline, depending on the agent *.

Please refer to ~~the Study Procedures Manual (SPM) for~~ ~~**guidance**~~ **Section 6.10.2 Prohibited Medications and Non-Drug Therapies for additional guidance.**

13. Addition of exclusion criteria related to prolonged use or requirement for continued use of systemic corticosteroids.

    Rationale: Patients who have used systemic corticosteroids for more than 4 years represent a refractory population who are unlikely to tolerate a steroid taper, such as that included in this trial. Patients who require continued use of systemic corticosteroids for conditions other than GCA are not suitable candidates for a steroid taper.

    Section 5.2 Exclusion Criteria

5. **Regular or continuous systemic corticosteroid use for > 4 years.**
6. **Requires continued or repeated use of systemic corticosteroids for conditions other than GCA.**

14. Clarification of requirements for eligibility based on results of the QuantiFERON-TB Gold test and for re-screening.

    Rationale: A single indeterminate result is not sufficient to exclude patients who may benefit from this study due to the relatively high rate of occurrence in patients who may not carry a risk of tuberculosis. An indeterminate result followed by a negative re-test result is sufficient to exclude patients with a risk of tuberculosis.

    Section 5.3 Screening/Baseline/Run-in Failures

Re-testing

Exceptions to re-testing are chest radiograph, ECG, and **a positive result for the** QuantiFERON-TB Gold test; these screening tests may not be repeated to meet eligibility

criteria. **An indeterminate result for the QuantiFERON-TB Gold test may be re-tested and subjects will be eligible upon a negative re-test result.**

Re-screening

If a subject is a screen failure but at some point in the future is expected to meet the subject eligibility criteria, the subject may be re-screened on only one occasion **and** only after consultation with the Sponsor or Sponsor designee. Subjects who are re-screened will be assigned a new subject number, undergo the informed consent process, and then restart a new screening phase

15. Clarification of circumstances related to withdrawal from the study and discontinuation of study drug.

    Rationale: This study is designed to collect information on disease status even when study drug has been discontinued. To ensure subject safety, events which require withdrawal of study drug are described, but it is clarified that study withdrawal is not required and subjects should continue to be followed.

    Section 5.4 Withdrawal/Stopping Criteria

5.4.1 Study Withdrawal

A subject may withdraw from ~~study treatment~~ **the study** at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records. Subjects may also be withdrawn from the study for any of the following reasons:

- Investigator discretion
- Sponsor request
- ~~Adverse events (AEs) or laboratory abnormalities indicative of safety concerns~~
- ~~Pregnancy~~
- Use of a new investigational drug
- Protocol violation
- Subject lost to follow-up
- Subject withdraws consent

5.4.~~1~~**2** ~~Withdrawal~~**Discontinuation** of Study Drug

Permanent ~~withdrawal~~**discontinuation** of study drug will not require the subject to be withdrawn from the study.

2. **Severe allergic reaction or a**~~A~~naphylactic reaction resulting in bronchospasm with wheezing, or dyspnea requiring ventilatory support, or symptomatic hypotension with a > 40 mmHg decrease in systolic blood pressure that occurs following study drug administration.

4. **Adverse events (AEs) or laboratory abnormalities indicative of safety concerns which are significant enough to discontinue study drug in the opinion of the investigator.**
5. **Pregnancy.**
6. **Liver function abnormalities as specified in Section 5.4.3.**
8. Active or ~~subject with~~ latent TB ~~who discontinues treatment for latent TB prematurely or is not compliant with treatment for latent TB~~.

16. Clarification of requirements for subjects meeting liver chemistry stopping and monitoring criteria.

    Rationale: Subjects may be required to discontinue study treatment for safety reasons, but are not required to withdraw from the study.

    Section 5.4.3 Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Subjects meeting the liver chemistry stopping and increased monitoring criteria may be required to temporarily or permanently discontinue study treatment.

17. Clarification of ECG criteria.

    Rationale: To clarify that QTC stopping criteria requiring discontinuation of study drug are applicable only when ECGs are performed outside of study requirements, as only a screening ECG is required.

    Section 5.4.4 QTc Stopping Criteria

~~A subject who meets either of the bulleted criteria below will be withdrawn from the study:~~**An ECG is required only at screening. If an additional ECG is performed during study participation outside of study requirements and any of the bulleted criteria below are met, study treatment should be discontinued and the Medical Monitor should be contacted. There is no requirement for the subject to be withdrawn from the study.**

18. Clarification that sponsor may supply the open-label prednisone is some countries.

    Rationale: Compliance with local regulations.

    Section 6.1 Investigational Product and Other Study Treatment

Prednisone for the pre-specified standard blinded taper will be provided by the Sponsor. Prednisone for the unblinded (open-label) taper will be provided by the sites **or by the Sponsor in certain countries in order to comply with local regulations**. **Use of standard release prednisone is required for the open-label taper.**

19. Clarification of method for randomization.

    Rationale: Provide appropriate terminology for randomization system.

    Section 6.2 Treatment Assignment

Randomization will be performed by an ~~Interactive Voice Recognition System (IVRS)~~**Interactive Response Technology System (IRT).**

20. Provision of guidance to investigators for situations in which a small increase in prednisone dose is warranted.

    Rationale: Changes in prednisone dose should be considered only in situations representative of a GCA flare.

    Section 6.3 Planned Dose Adjustments

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 q2w or placebo q2w for the full 52 weeks. Subjects should continue to be followed per the protocol-specified assessments while receiving rescue treatment. There is no requirement for these subjects to be withdrawn from the study. **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.**

21. Clarification of notifications of ESR results.

    Rationale: ESR alert values may be needed for investigators to make informed decisions regarding the clinical management of subjects experiencing a GCA disease flare and should be considered in the context of the presenting clinical symptoms.

    Section 6.4 Blinding

Investigators will remain blinded to the results of the fasting lipids, CRP and ESR laboratory tests. 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~~ **value** 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 PMR) suggestive of disease activity.**

22. Clarification of permitted NSAID use.

Rationale: There is no basis for restrictions on NSAID use.

Section 6.10.1 Permitted Medications and Non-Drug Therapies

- ~~Subjects treated with NSAIDs, including aspirin and selective COX-2 inhibitors, and other analgesics should receive the usual marketed doses approved in the country in which the study is being conducted. Prescriptions of NSAIDs and other analgesics generally should not be adjusted for at least 4 weeks prior to the first administration of the study drug to Week 52 if possible. The dose and the type of NSAIDs or other analgesics may be changed (reduced or temporally discontinued) at the discretion of the investigator if the subject develops unacceptable side effects or a contraindication to their use. When the reason to reduce or temporarily discontinue the NSAID or analgesic has ceased, the dose should be adjusted back to the approved level. Acetaminophen/paracetamol dosed no more than 3.0 gm/day and/or an opioid not exceeding the potency equivalent of 30 mg of orally administered morphine are allowable as rescue medication for no more than 10 consecutive days.~~ **Analgesics, paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, at the usual marketed doses approved in the country in which the study is being conducted.**

23. Clarification of wash out periods for prior use of anti-TNFα therapies.

Rationale: Biologics have long drug half-lives. Details on the wash out period for specific anti-TNFα therapies are provided based on their pharmacokinetic profile.

Section 6.10.2 Prohibited Medications and Non-Drug Therapies

- Biologic agents targeted at reducing TNFα (including but not limited to infliximab, golimumab, certolizumab pegol, etanercept, yisaipu, and adalimumab) within the specified time frames.

Anti-TNFαTherapy	**Treatment Prior to First Study Agent Administration (Baseline)**
Infliximab, infliximab biosimilar, golimumab IV	**8 Weeks**
Golimumab SC, adalimumab, certolizumab pegol	**6 Weeks**
Etanercept, yisaipu	**4 Weeks**

24. Addition of restrictions for systemic corticosteroid use.

    Rationale: Subjects who require systemic corticosteroid use for conditions other than GCA may be negatively impacted by the prednisone requirements for this trial.

    Section 6.10.2 Prohibited Medications and Non-Drug Therapies

- **Systemic corticosteroids for conditions other than GCA within 8 weeks of baseline or a reasonable possibility of requiring systemic corticosteroids during Part A.**

25. Clarification of requirements for laboratory assessments and pregnancy testing for subjects not receiving open-label sirukumab in Part B.

    Rationale: Less stringent safety monitoring is acceptable for subjects not receiving open-label sirukumab in Part B.

    Section 7: Study Assessments and Procedures

Time and Events Table 3: Assessments for subjects who will **not** receive open-label treatment with sirukumab during Part B. Dispensing of investigational product-is ~~and hematology, and clinical chemistry assessments from the Week 76 visit onwards are~~ not required. **Hematology and clinical chemistry assessments and pregnancy testing from the Week 16 visit onwards are also not required as subjects will have completed the 16-week post-drug follow up assessments.**

26. Clarification and correction of PRO questionnaires.

    Rationale: To provide additional details on the questionnaires.

    Section 7: Study Assessments and Procedures

PRO questionnaires should be completed by subjects before any other assessments and before the administration of study drug. PRO questionnaires should be completed before the completion of the physician reported questionnaires. PRO questionnaires should be completed by the subject in the following order:

1. Patient Global Assessment of disease activity (PtGA).
2. **Patient Global Impression of Change** (PGIC).
3. Pain ~~VAS~~**Numeric Rating Scale (NRS).**
4. HAQ-DI (for subgroup of subjects with PMR).
5. FACIT-fatigue.
6. Steroid **Impact** PRO.
7. SF-36v2 acute.
8. EQ-5D (~~3~~**5**L).

Clinician-reported outcome questionnaires include the Physician Global Assessment of disease activity (PhGA), which should be completed after the PRO questionnaires have first been completed by subjects.

27. Changes in Time and Events Tables and correction of typographical errors.

    Rationale: Consistency with the protocol specifications and requirements.

    Section 7.1 Time and Events Tables

Table 2 Time and Events Table for Part A of the Study (52-week Double-blind Treatment Phase)

	Screening (~Wk -6)	**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 ~~or Flare~~**	**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	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[4], 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 ~~VAS~~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 (~~3~~5L)[4]		x				x			x			x				x	x	x	
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

	Screening (~Wk -6)	**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 ~~or Flare~~**	**Follow Up**
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
Laboratory Assessments																			
Hematology	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	
CRP	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	
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, HBcAb, Hepatitis C[11]	x																		
PK[12]		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																	
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																	

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. To be completed by subjects before any other assessments and before the administration of study drug**. HAQ-DI administered only to sub-set of subjects with PMR. PGA assessed using PtGA (subjects) and PhGA (physicians, after subject completion of questionnaires)**.
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 suspected heart attack.
8. Suggested questions (see Section 7.5.7**). A QuantiFERON-TB Gold Test should be performed at any time during the study if TB is suspected.**
9. ~~If a QuantiFERON-TB Gold Test is not approved at a site, a tuberculin skin test should be performed. In addition, to be performed at any time during the study if TB is suspected~~. 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, Pharm serum samples must be collected prior to study drug administration. Blood collected from one venipuncture will be divided into multiple aliquots of serum for Pharm 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

Table 3 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 ~~or Flare~~**
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 ~~VAS~~**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 (~~3~~5L) [2]	x			x		x		x	x	x	x	x
Safety Assessments												
Physical Examination[1,3]	x							x		x	x	x
Vital Signs[2,4]	x	x	x	x	x	x	x	x	x	x	x	x
TB evaluation[3,5]	x	x	x	x	x	~~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
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
ESR	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 ~~or Flare~~**
Lipid panel (fasting)	**x**			**x**	**x**	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	**x**[6]	**x**[6]
Hemoglobin A1c	**x**			**x**	**x**	~~x~~	~~x~~	~~x~~	~~x~~	~~x~~	**x**[6]	**x**[6]
Pregnancy Test[7]	**U**	**U**	**U**	**U**	**U**	~~U~~		~~U~~		~~U~~		**U**[6]
~~Immunogenicity~~	~~x~~			~~x~~				~~x~~		~~x~~	~~x~~	
Exploratory Lab Assessments												
Blood Biomarkers & exploratory markers	**x**											
Blood and Urine Markers, Transcriptomics (optional)	**x**											

1. ~~Complete physical exam at Screening and brief physical exam at other time points~~. **Assessment from Week 52 visit of Part A.**
2. ~~Measure in a semi-supine position after 5 minutes rest; includes blood pressure, temperature and heart rate.~~**To be completed by subjects before any other assessments. HAQ-DI administered only to sub-set of subjects with PMR. PGA assessed using PtGA (subjects) and PhGA (physicians, after subjects complete their questionnaires).**
3. ~~Suggested questions (see Section 7.5.7). 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~~**Brief physical exam.**
4. Measure in a semi-supine position after 5 minutes rest; includes blood pressure, temperature and heart rate.
5. Suggested questions (see Section 7.5.7). 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. **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.

Table 4 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[4]	**wk 48±5d[1]**	**wk 52±5d**	wk 78~~6~~±5d	**wk 104±5d**	**Flare**	**Early Withdrawal ~~or Flare~~**	**Follow Up**
Dispense Investigational Product	x	x	x	x	x	x	x	x	x	~~x~~	~~x~~				~~x~~
Assess Invest.Product compliance	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
Efficacy Assessments															
GCA disease activity	x	x	x	x	x	x	x	x		x	x	x	x	x	
PGA[4] (patient, physician)~~[2]~~	x	x	x	x	x	x	x	x		x	x	x	x	x	
Health Outcomes															
Pain ~~VAS~~**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 (~~3~~**5**L) [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
Chest radiograph															
TB evaluation[5]	x	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
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[4]	**wk 48±5d[1]**	**wk 52±5d**	wk 78±5d	**wk 104±5d**	**Flare**	**Early Withdrawal ~~or Flare~~**	**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	~~U~~
Hemoglobin A1c	x				x	x	x	x		x	x	x	x	x	~~x~~
Pregnancy Test[6]	U		U	U	U	U	U			U		U		U	U
Immunogenicity[7]	x				x					x		x	x	x	x
Exploratory Lab Assessments															
Blood Biomarkers & exploratory markers	x														
Blood and Urine Markers, Transcriptomics (optional)	x														

1. ~~Additional visits will be scheduled at Wk 48, Wk 66, and Wk 90 to dispense open-label sirukumab as appropriate.~~ **Visit only to dispense IP; no assessments are required.**
2. To be completed by subjects before any other assessments and before the administration of open-label sirukumab as applicable. **HAQ-DI administered only to sub-set of subjects with PMR. PGA assessed using PtGA (subjects) and PhGA (physicians, after subjects complete their questionnaires))**
3. ~~Complete~~ **Brief** physical exam ~~at Screening and brief physical exam at other time points~~
4. Measure in a semi-supine position after 5 minutes rest; includes blood pressure, temperature and heart rate.
5. Suggested questions (see Section 7.5.7). 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.
7. **On study drug administration days, serum samples to measure antibodies to sirukumab must be collected prior to study drug administration.**

Table 5 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**[2]	**PLUS 48 Wks±5d**[2]	**PLUS 52 Wks±5d**	PLUS 78**6** WKS±5d	**PLUS 104 Wks±5d** [3]	**Flare**	**Early Withdrawal ~~or Flare~~**	**Follow Up**
Dispense Investigational Product		x	x	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[4], physician)[4]		x	x	x	x	x	x	x		x	x	x	x	x	
Health Outcomes															
Pain ~~VAS~~**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 (~~3~~**5**L)[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
Chest radiograph															
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
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**[2]	**PLUS 48 Wks±5d**[2]	**PLUS 52 Wks±5d**	PLUS 78~~6~~ WKS±5d	**PLUS 104 Wks±5d** [3]	**Flare**	**Early Withdrawal ~~or Flare~~**	**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**
Immunogenicity[9]					**x**					**x**		**x**	**x**	**x**	**x**

1. Upon the initiation of open-label sirukumab, perform the assessments from Time and Events Table 3 at the visit the subject was scheduled to undergo when study drug is started.
2. ~~Additional visits will be scheduled at Wk 48, Wk 66, and Wk 90 to dispense open-label sirukumab as appropriate.~~.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. To be completed by subjects before any other assessments and before the administration of open-label sirukumab as applicable. **HAQ-DI administered only to sub-set of subjects with PMR. PGA assessed using PtGA (subjects) and PhGA (physicians, after subjects complete their questionnaires).**
5. ~~Complete~~ **Brief** 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. Suggested questions (see Section 7.5.7). 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.
8. Pregnancy test: urine = U, serum = S. Premenopausal women only.
9. **On study drug administration days, serum samples to measure antibodies to sirukumab must be collected prior to study drug administration.**

28. Clarification of requirements for prednisone starting dose at Screening and Baseline.

    Rationale: To clarify that the investigator should determine the prednisone dose during screening and adjust accordingly so that subject is receiving a dose consistent with protocol requirements at Baseline.

    Section 7.2 Screening and Critical Baseline Assessments

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 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. Subjects are required to have clinically stable GCA disease at baseline and able to participate in the blinded prednisone taper regimen in the opinion of the investigator. **At Baseline (Randomization), doses must be within 20-60 mg prednisone for the starting dose when the pre-specified prednisone taper is initiated.**

29. Provision of details on GCA signs and symptoms

    Rationale: Investigator guidance for consideration when assessing GCA activity.

    Section 7.3 Efficacy

Efficacy of sirukumab in GCA will be assessed from the presence of GCA activity including investigator assessment of signs and symptoms of GCA (new onset localized headache, scalp or temporal artery tenderness~~, ischemia-related vision loss [permanent vision loss due to AION, amaurosis fugax, episodic blurry vision], diplopia,~~ **reduced or absent pulsation in temporal artery, cord-like thickening of temporal artery, stroke, scalp necrosis, pain over face/scalp arteries**, or otherwise unexplained mouth or jaw pain upon mastication [i.e., jaw claudication]); **visual signs and symptoms (including but not limited to transient or episodic blurry vision, diplopia, scotoma, ischemia-related vision loss [permanent vision loss due to AION], amaurosis fugax)**; PMR symptoms [shoulder and/or hip girdle pain associated with inflammatory stiffness]**;** ~~and~~ other features **associated with GCA** such as new or worsened extremity claudication and fever of unknown origin); and laboratory results for serum ESR and CRP levels **(blinded to investigator).**

30. Corrections, clarifications and additional details of PRO instruments.

    Rationale: A numeric rating scale for pain assessment is a more sensitive scale.

    Section 7.4 Health Outcomes

In addition to the Patient's and Physician's Global Assessment of Disease Activity, other health outcome measures used in this study are PGIC, pain assessment using ~~a VAS~~ **an 11-point numeric rating scale**, HAQ-DI, FACIT-fatigue, Steroid Impact questionnaire, SF-36 v2 Acute health survey questionnaire, and EQ5D (~~3~~**5**L). These questionnaires should be completed in the order specified in Section 7.

Section 7.4.2 Pain Assessment

Subjects will be asked to ~~assess~~ **rate the severity of** their average pain now on ~~a visual analogue scale (VAS) ranging from "no pain" to "the worst possible pain~~ **an 11-point numeric rating scale with anchors ranging from 0, "no pain" to 10, "the worst pain imaginable".**

Section 7.4.5 Steroid Impact Questionnaire

The **benefits,** side effects and impact of steroids on GCA symptoms and subjects will be assessed using a GCA disease specific patient reported questionnaire, the Steroid Impact Questionnaire. **The Steroid Impact Questionnaire contains 50 items assessing steroid dose/duration (4 items), general impact (baseline burden; 19 items), benefits (7 items), work/productivity (3 items), side effects (10 items), emotions (6 items), and overall satisfaction (1 item).**

Section 7.4.7 EuroQoL-5D (EQ-5D) (~~3~~**5**L)

The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. **Each dimension has** ~~3 levels: no problems, some problems, extreme problems.~~ **5 levels: no problems, slight problems, moderate problems, severe problems, unable to do.**

31. Addition of the American College of Rheumatology recommendations for prevention and treatment of osteoporosis and guidance for investigators to consider prophylactic use of proton pump inhibitors.

    Rationale: Since study subjects may be on high doses of prednisone, investigator guidance is provided for management of corticosteroid-induced osteoporosis and gastroprotection.

    Section 7.5.1.3 Follow-up of AEs and SAEs

Corticosteroid-related AEs such as diabetes mellitus, osteoporosis, fractures, infection, glaucoma, and cataracts among others will be evaluated in relation to steroid exposure and baseline risk. ~~Further information on assessment of specific events will be available in the SPM.~~ **Since subjects participating in this study may be receiving high doses of prednisone for a prolonged period, investigators should consider implementation of the American College of Rheumatology recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis (Grossman, 2010). A summary of these recommendations is included in Section 12.5, Appendix 5. Investigators should also consider whether their subjects may benefit from other approaches for**

minimizing corticosteroid-related AEs, such as the prophylactic use of proton pump inhibitors for gastroprotection.

32. Addition of wording to specify requirement to collect additional details on cases of serious allergic/hypersensitivity reactions.

    Rationale: Cases will be adjudicated by the Sponsor and classified according to the Sampson criteria.

    Section 7.5.1.6 Allergic/**Hypersensitivity** Reactions

All subjects will be observed carefully for symptoms of allergic reactions for at least 30 minutes after the SC injection of study drug **when administered** at the study site. If mild or moderate allergic reaction is observed, acetaminophen 650 mg per mouth (PO) or NSAIDS and diphenhydramine 25 mg orally or intravenously may be administered. If the reaction is not severe, subsequent injections at the appropriate treatment intervals may be undertaken with caution.

Subjects with severe reactions following an injection such as bronchospasm with wheezing and/or dyspnea requiring ventilator support, or symptomatic hypotension with a decrease in systolic blood pressure greater than 40 mmHg will not be permitted to receive any additional study drug injections. In the case of such reactions, appropriate medical treatment should be administered.

In cases of serious allergic/hypersensitivity reactions, additional details on the case will be collected via a targeted follow-up questionnaire. An internal safety review team will adjudicate these events to determine if the events meet the Sampson criteria (Sampson, 2006).

33. Amendment of requirement to withdraw from study in the event of pregnancy.

    Rationale: The study is designed to collect information on disease status after discontinuing therapy. This is applicable even in cases of pregnancy.

    Section 7.5.2 Pregnancy

- Female subjects who become pregnant during the study must have study drug ~~withdrawn~~ **discontinued** ~~immediately and be withdrawn from the study. Complete the assessments for the Early Withdrawal visit at the time of withdrawal and the Follow-up visit 16 weeks later (see Section 5.4).~~ **These subjects should continue to follow the protocol-specified visit schedule.**

34. Amendment of QTC withdrawal criteria to discontinuation criteria.

    Rationale: To provide clarification on requirement to discontinue study drug versus study withdrawal.

Section 7.5.5 Electrocardiogram (ECG)

Triplicate 12-lead ECGs will be obtained at the Screening visit using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. The screening ECG will ensure that a comparative ECG is available prior to study drug administration in order to detect any changes should a subject require an ECG for any reason during the study. Refer to Section 5.4.4 for QTc ~~withdrawal~~ **discontinuation** criteria and additional QTc readings that may be necessary.

35. Amendment of clinical laboratory assessment withdrawal criteria to discontinuation criteria.

    Rationale: To provide clarification on requirement to discontinue study drug versus study withdrawal.

    Section 7.5.6 Clinical Safety Laboratory Assessments

Values for liver transaminase levels (AST, ALT), absolute neutrophil count (ANC), and platelet count that require study drug interruption and/or permanent ~~withdrawal~~ **discontinuation** of study drug administration are listed below in Table 7.

Table 7 Values for Liver Transaminase Levels, Absolute Neutrophil Count, and Platelet Count That Require Study Drug Interruption and/or Permanent ~~Withdrawal~~ **Discontinuation** of Study Drug

36. Amendment of the requirements for TB testing to allow only testing using QuantiFERON-TB Gold Test.

    Rationale: QuantiFERON-TB Gold Test is available in all countries and should be used at all sites to ensure consistency of testing.

    Section 7.5.7 Tuberculosis Evaluation

A QuantiFERON-TB Gold Test will be performed at Screening. ~~If a QuantiFERON-TB Gold Test is not approved at a site, a PPD skin test should be performed instead. These~~ This test~~s~~ can be performed at any time during the study if TB is suspected.

Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON-TB Gold test, ~~a repeat tuberculin skin test in countries in which the QuantiFERON-TB Gold test is not approved/registered,~~ and, if possible, referral to a physician specializing in TB to determine the subject's risk of developing active TB and whether treatment for latent TB is warranted. Study drug administration should be interrupted during the investigation. A positive QuantiFERON-TB Gold ~~(or tuberculin skin)~~ test result should be considered detection of latent TB.

37. Clarification of protocol-specified exploratory biomarkers and optional exploratory biomarkers.

    Rationale: To provide additional clarifications on the two approaches for biomarker assessment.

    Section 7.7 Biomarker(s)

Section 7.7.1 Optional Exploratory Biomarkers

Subjects will **also** have the option to provide blood and urine samples for future evaluation of biomarkers related to GCA disease activity and transcriptomic analyses to further elucidate the biology of the disease.

38. Amendment of the sample size sensitivity analysis.

    Rationale: The sensitivity analysis was carried out for the response rate for sirukumab and not for the placebo arm as there is more uncertainty around the response rate for sirukumab than for placebo.

    Section 9.2.2 Sample Size Sensitivity

A sample size sensitivity analysis was performed to assess the effect on power if the ~~placebo~~ **sirukumab** plus 6 month prednisone response rate was ~~higher~~ **lower** than expected at~~35~~ **65**%, ~~40~~**60**% or ~~45~~**55**%.

39. Addition of subjects who discontinue study treatment as non-responders in the primary endpoint analysis and update of the approach for analysis of primary and secondary endpoints.

    Rationale: Subjects who discontinue treatment will not fulfil the requirements for a responder. Logistic regression model is preferred approach for analysis.

    Section 9.4.1 Primary Efficacy Analyses

Subjects who do not achieve remission within 12 weeks, require rescue therapy, **discontinue treatment during the study** or withdraw early from the study for any reason or do not follow the assigned prednisone taper will be recorded as non-responders in the analysis of the primary endpoint.

The proportion of subjects with sustained remission at week 52 in the sirukumab 100 mg SC q2w plus 6 month prednisone (Arm A) versus placebo plus 6 month prednisone (Arm D) will be analysed using a ~~generalised estimating equations~~ **logistic regression** model controlling for the stratification factor of baseline prednisone dose. The model will **also** include **the** treatment~~, week, and treatment-by-week interaction and subject within week as a random effect~~ **arms**. Odds ratios and 95% confidence intervals will be produced.

If however a non-parametric approach is more appropriate then the Cochran-Mantel-Haenszel will be used.

Section 9.4.2 Secondary Efficacy Analyses

The proportion of subjects in sustained remission over time (Part A and Part B) will be analysed using the ~~generalised estimating equations~~ **logistic regression** as described for the primary endpoint.

40. Addition of AEs leading to discontinuation of study drug and summaries of reasons for treatment discontinuation.

    Rationale: To further characterize the safety profile of sirukumab as treatment discontinuation may be frequently based on an adverse event.

    Section 9.4.3.2 Adverse Events

The proportion of subjects reporting AEs will be tabulated for each treatment group. The following summaries of AEs will be provided:

- All AEs
- Treatment-related AEs
- AEs leading to withdrawal
- **AEs leading to discontinuation of study drug**

Section 9.4.3.4 Other Safety Measures

Reason for withdrawal**/treatment discontinuation** will be summarized.

41. Addition of requirement for a secondary method of contraception for females using hormonal contraception.

    Rationale: There is a hypothetical risk for sirukumab to decrease the effectiveness of oral contraceptives. Therefore, additional precautions should be taken.

Appendix 2, Section 12.2.1 Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

If using hormonal contraceptives, including oral, injections and patches, a secondary method of contraception must be used.

42. Clarification that pregnancy does not require withdrawal from the study.

    Rationale: The study is designed to collect information on disease status after discontinuing therapy. This is applicable even in cases of pregnancy.

Appendix 2, Section 12.2.2 Collection of Pregnancy Information

Any female subject who becomes pregnant while participating in this study will discontinue study drug ~~and be withdrawn from the study~~. There is no requirement to be withdrawn from the study.

43. Addition of details on the American College of Rheumatology Standard of Care Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

    Rationale: For investigator guidance as subjects may be on high doses of prednisone for prolonged periods.

    Section 12.5, Appendix 5 American College of Rheumatology Standard of Care Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis*

Recommended Monitoring for Patients Receiving Prevalent Glucocorticoid Therapy for a Duration >3 Months

- **Consider serial bone mineral density testing**
- **Consider annual serum 25-hydroxyvitamin D measurement**
- **Annual height measurement**
- **Assessment of incident fragility fracture**
- **Assessment of osteoporosis medication compliance**

Pharmacologic Recommendations for Postmenopausal Women and Men age >50 Years Starting Glucocorticoid Therapy with an Anticipated Duration of >3 Months, or Prevalent Glucocorticoid Therapy of a Duration of at Least 3 months

Low-risk patient
Alendronate for 7.5 mg/day prednisone
OR
Risedronate for 7.5 mg/day prednisone
OR
Zoledronic acid for 7.5 mg/day prednisone

Medium-risk patient
Alendronate for any dose of glucocorticoids
OR
Risedronate for any dose of glucocorticoids
OR
Zoledronic acid for 7.5 mg/day prednisone

High-risk patient
Alendronate

OR
Risedronate
OR
Zoledronic acid
OR
Teriparatide

*** Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, Curtis JR, Furst DE, McMahon M, Patkar NM, Volkmann E, Saag KG. (2010). American College of Rheumatology 2010 Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis Care and Research, *62*(11), 1515-1526.**

44. Correction of typographical errors and administrative changes related to amendment of protocol.

Title Page

Updated author list

Author (s): PPD

Medical Monitor/Sponsor Information Page

Regulatory Agency Identifying Number(s): EudraCT number 2015-001758-14, **IND 101073**

Updated Table of Contents

Section 1, Protocol Synopsis for Study 201677, Overall Design

Subjects will be randomized to receive sirukumab ~~(~~100 mg subcutaneous [SC] every 2 weeks [q2w] or 50 mg SC every 4 weeks [q4w] or matching placebo.

Type and Number of Subjects

Subjects are required to have active GCA disease within 6 weeks of baseline where active disease is defined as the presence of unequivocal clinical signs and symptoms attributable to GCA and increased levels of inflammatory markers (ESR ≥ 30 mm/hr **and/**or CRP ≥ 1 mg/dL).

Section 9.3.4 Interim Analysis

Full details of the process and decision criteria for this interim analysis for futility are included in the ~~IDMC charter~~**RAP.**

Addition of new protocol references

Section 11 References

Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, Curtis JR, Furst DE, McMahon M, Patkar NM, Volkmann E, Saag KG. (2010). American College of Rheumatology 2010 Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis Care and Research, *62*(11), 1515-1526.

Sampson HA, Munoz-Furlong A, Campbell RL, et.al. (2006). Second symposium on the definition and management of anaphylaxis: Summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol.*117*, 391-397.

Updates to Appendix 1, Abbreviations and Trademarks

~~IVRS~~	~~Interactive Voice Recognition System~~
IRT	**Interactive Response Technology**
NRS	**Numeric Rating Scale**
NSAID	**Nonsteroidal anti-inflammatory drug**
PhGA	**Physician Global Assessment**
PtGA	**Patient Global Assessment**

Addition of Appendix 5 and Appendix 8, Protocol Changes and re-numbering of subsequent appendices.

Amendment 02 31 March 2016

1. Inclusion of the pharmacodynamic measurement enabling evaluation of sirukumab effects on blood IL-6 levels.

Rationale: IL-6 is a pharmacodynamic marker directly related to the mechanism of action of sirukumab. Assay development has progressed to enable the assessment of total and free IL-6, thus enabling a more robust and accurate measurement of the pharmacodynamic effect of sirukumab on IL-6 levels.

Section 1 and Section 3: Objective(s)/Endpoint(s)

Objectives	Endpoints
Pharmacodynamic	
• **To characterize the effect of sirukumab on IL-6 levels in the blood**	• **Change from baseline in free and total IL-6 over time**

Section 7.7.Biomarkers/**Pharmacodynamic Markers**

Section 7.7.3 Pharmacodynamic Markers

Blood samples will be taken at the times indicated in Time and Events Table 2, Section 7.1 for assessment of changes in free and total IL-6 as a pharmacodynamic marker of sirukumab activity.. **Analyses of serum IL-6 levels will be performed using validated assays by Janssen Research and Development.**

Section 9.4.6 **Pharmacodynamic/**Exploratory/Biomarker Analyses

Pharmacodynamic and ~~B~~biomarker data in Part A will be presented in graphical and/or tabular form and will be summarised descriptively.

2. Inclusion of the information and relevant details regarding the new exploratory US imaging cohort.

Rationale: Protocol has been amended to include the exploratory US imaging sub-study as a cohort of Study 201677 rather than conducting as a separate sub-study.

Section 1 and Section 3: Objective(s)/Endpoint(s)

Objectives	Endpoints
Exploratory	
• **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**	• **Change over time of the following measurements of vascular inflammation in temporal and axillary arteries:** – **Presence/absence of occlusion** – **Presence/absence and maximum diameter of halo** – **Presence/absence of stenosis**
• **To explore the predictive value of ultrasound for clinical efficacy in GCA**	• **Correlation of clinical endpoints with changes in vascular inflammation.** • **Correlation of changes in vascular inflammation on US with clinical markers such as GCA disease activity, CRP and ESR** • **Correlation of changes in vascular inflammation on US with health-related quality of life outcomes**

Section 4.1 Overall Design

~~A separate exploratory sub-study (Study 205028) will be conducted at selected centers to assess the utility of imaging assessment of inflammation as an indicator of disease activity in a cohort of study subjects. The details of this exploratory sub-study will be provided in a separate protocol.~~

The utility of US in monitoring disease activity in GCA will be explored in a cohort of subjects from select centers who have qualified as US imaging centers. Longitudinal changes in vascular inflammation of the temporal and axillary arteries will be assessed and changes will also be correlated with clinical markers. Additional details on the exploratory US imaging cohort are contained in Section 7.9 and Appendix 8.

Section 7.9 Exploratory Ultrasound Imaging

7.9 Exploratory Ultrasound Imaging

7.9.1 Background and Rationale

The results of three recent meta-analyses have provided evidence to support the utility of US imaging in the diagnosis of GCA [Ball, 2010; Arida, 2010; Karassa,

2005]. Additional data from a multicenter study, TABUL (Temporal Artery Biopsy versus ULtrasound), conducted at centers trained in US imaging techniques, also support the diagnostic utility of US in GCA [Luqmani, 2015]. However, the role of US imaging in the assessment of GCA disease activity remains unclear. Available evidence consists of results from a study which found persistent abnormalities suggestive of an association with relapse when GCA patients were assessed by ultrasound imaging every 2-4 weeks [de Miguel, 2012]. Permanent visual loss is also associated with the presence of abnormal sonographic features of cranial and extra-cranial arteries [Schmidt, 2008; Schmidt, 2009; Czihal, 2012]. A recent prospective observational study has demonstrated that ultrasound can be informative in distinguishing potential flares from exacerbations of unrelated headache in patients with diagnosis of GCA [Ponte, 2015]. Taken together, these findings suggest that ultrasound imaging may provide a useful diagnostic and biomarker approach for assessing and monitoring disease activity in GCA.

Currently, no valid biomarkers exist to assess response to therapy and to predict relapse. Changes in the conventional inflammatory markers (CRP and ESR) do not consistently reflect disease activity [Tse, 1998]. Therefore, the utility of US in monitoring disease activity in GCA will be explored in a cohort of study subjects from select participating centers by sonographers trained and/or qualified as proficient in US imaging. Longitudinal changes in vascular inflammation of the temporal and axillary arteries and the predictive value of US for disease activity will be assessed.

7.9.2 Synopsis

A cohort of subjects with new onset GCA from participating imaging centers who have consented to participate in the US imaging portion of this study will be evaluated. These subjects will undergo US scans of their temporal and axillary arteries at the specified time points for assessment of changes in vascular inflammation.

Only subjects with newly diagnosed GCA are eligible to participate. Due to the exploratory nature of this portion of the study, there is no pre-specified sample size for this cohort. However, it is estimated that up to 50 subjects may participate.

Subjects will have an initial baseline scan at Screening and assessments at Weeks 12 and 52. Additional US scans should also be conducted in the event of relapses or flares, including flares/relapses that occur during Part B of the study. Subjects may also be asked to provide retrospective consent for assessment of their diagnostic US scan. Efforts should be made to conduct the baseline US scan within 3 days of initiating prednisone therapy. However, inability to comply with this time frame does not exclude subjects from participation. Data will be analyzed according to the time frame between prednisone dose and US scan. Detailed information on US imaging in this cohort of study subjects is included in Appendix 8.

Appendix 8

12.8 Appendix 8: Exploratory US Imaging

The utility of US in monitoring disease activity in GCA will be investigated in a cohort of subjects with new onset GCA. Longitudinal changes in vascular inflammation of the temporal and axillary arteries will be characterized. Only subjects with new onset GCA will participate in order to optimize the ability to detect inflammatory changes on US, based on the potential likelihood that these subjects would not have been receiving corticosteroids prior to diagnosis.

12.8.1 Objectives and Endpoints

The objectives and endpoints of this exploratory US imaging cohort are as follows:

Objectives	Endpoints
• 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	• Change over time of the following measurements of vascular inflammation in temporal and axillary arteries: – Presence/absence of occlusion – Presence/absence and maximum diameter of halo – Presence/absence of stenosis
• To explore the predictive value of ultrasound for clinical efficacy in GCA	• Correlation of clinical endpoints with changes in vascular inflammation. • Correlation of changes in vascular inflammation on US with clinical markers such as GCA disease activity, CRP and ESR • Correlation of changes in vascular inflammation on US with health-related quality of life outcomes

12.8.2 Type and Number of Subjects

Only subjects with new onset GCA are eligible to participate in the exploratory imaging portion of this study. These subjects will have a diagnosis of GCA based on the Revised GCA Diagnosis Criteria, and present with new onset GCA disease, defined as having a diagnosis within 6 weeks of baseline. Subjects should have either initiated prednisone treatment upon entry into Screening and after their Screening US scan has been performed or corticosteroid therapy should have only been recently initiated, optimally within 3 days of the Screening scan. However, inability to comply with this time frame does not exclude subjects from participation.

As this is an exploratory study, there is no pre-specified sample size. However it is estimated that up to 50 subjects may participate.

12.8.3 Assessments and Procedures

12.8.3.1 Sonographer Training

All sonographers participating in this study must have undergone training with documented approval to qualify as a participating site. Sites previously trained for participation in the TABUL study will not be required to participate in the training sessions, but may certify through a separate process. Processes and procedures for training and qualification are outlined in the Imaging Acquisition Guidelines.

Sonographers participating in the training course will US scan a requisite number of healthy volunteers/non-GCA subjects and at least one patient volunteer with active GCA as per the protocol definition for qualification. All volunteers recruited to participate in the sonographer training will be required to provide consent prior to participation. GCA patients who participate in the sonographer training may be eligible to enroll in Study 201677, but they are excluded from participating in the imaging cohort portion of the study. Detailed information on the sonographer training process is contained in the training manual.

12.8.3.2 Subject Eligibility

Study subjects consenting to participate in the exploratory US imaging cohort are eligible only if they have newly diagnosed GCA (within 6 weeks of baseline), based on the Revised GCA Diagnosis Criteria as described in Section 5.1. At Baseline, subjects must have fulfilled all of the eligibility criteria for Study 201677 and be randomized into the study to continue participation in the exploratory imaging cohort. Screen failures for Study 201677 will not be eligible to participate in this cohort.

Optimally, the study baseline scan (Screening) would be performed prior to the initiation of prednisone treatment. If this is not possible, then efforts should be made to perform the US scan within 3 days of initiating prednisone treatment. However, the inability to comply with this time frame is not exclusionary. The number of days between initiation of prednisone treatment and the US scan will be recorded.

12.8.3.3 Ultrasound Scanning

Participating subjects will undergo US scans at the following time points:

1. **Screening, or after consent has been provided to participate in the imaging cohort. Optimally (but not required), this scan would be performed within 3 days of initiating corticosteroid therapy for GCA disease activity:**
2. **Week 0 (Randomization)**
3. **Week 12**

4. **Week 52**

5. **Any time point of disease relapse/flare during Part A or Part B of the study, with every effort made to conduct the US scan within 3 days of rescue prednisone administration. The number of days between the US scan and rescue prednisone administration will be recorded.**

The timings of the US assessments are included in Section 7.1, Time and Events Tables, Table 2, Table 3, Table 4 and Table 5.

The scans will be sent for independent review by a central reader. Full details on the US scanning process, training requirements, image transfer and de-identification, assessments and data collection are provided in the Imaging Acquisition Guidelines.

12.8.4 Blinding

The central reader will remain blinded to the subject's treatment group. Investigators and sponsor will remain blinded to the central US results. No clinical findings will be communicated by the central reader to investigators. Scans may be reviewed at the site according to local policy.

12.8.5 Statistical Considerations and Data Analyses

12.8.5.1 Hypotheses

The objectives of the US imaging cohort are exploratory and observational. There are no formal statistical hypotheses planned.

Exploratory comparisons will be made between the sirukumab and placebo arms, if appropriate.

12.8.5.2 Sample Size Considerations

There are no formal calculations of power or sample size for this cohort. There is no pre-specified upper or lower limit for subject enrolment in this cohort. Therefore, no sample size sensitivity was performed and there are no plans for sample size re-estimation .

12.8.5.3 Data Analysis Considerations

No formal analyses are planned for this cohort.

12.8.5.4 Key Elements of Analysis Plan

Data from the US imaging cohort may be reported separately from the main 201677 clinical study report.

Data will be analyzed according to the timeframe between prednisone dose and US scan.

Graphics and/or descriptive statistics will be used to describe the time course and magnitude of changes in key markers (e.g. halo and stenosis sizes, presence of occlusions). If data permits, analyses assessing the associations between these key markers and some disease activity and health outcomes indicators (e.g. GCA disease activity, ESR, CRP, fatigue and pain) will be carried out using descriptive statistics and graphics.

Full details of the approaches will be described separately from the main clinical study report.

3. Updated inclusion criteria to allow for diagnosis of GCA by US imaging in centers who are participating in the exploratory US imaging portion of the study.

Rationale: US imaging has been shown to be an accurate technique for diagnosis of GCA for sonographers trained in the TABUL method. Therefore, trained and qualified centers participating in the exploratory US portion of the study may also qualify subjects for this study by confirming a diagnosis of GCA by US imaging.

Section 5.1 Inclusion Criteria #1

- Presence of at least **one** of the following:
  - Temporal artery abnormality on biopsy revealing features of GCA.
  - Evidence of large-vessel vasculitis by angiography or cross-sectional imaging, including but not limited to magnetic resonance angiography (MRA), computed tomography angiography (CTA), ultrasound (US) or positron emission tomography-computed tomography (PET-CT).
  - **Evidence of temporal artery vasculitis on US (for US imaging qualified centers only).**

4. Further clarification of the inclusion criteria for active GCA by including additional details on features associated with GCA.

Rationale: To provide additional guidance to investigators on features of GCA that may present clinically as systemic symptoms.

Section 5.1 Inclusion Criteria #2

- Other features judged by the clinician investigator to be consistent with GCA or PMR flares (i.e., new or worsened extremity claudication, **unexplained systemic symptoms such as** fever of unknown origin, **weight loss and night sweats**).

5. Additional clarification of the prednisone dose at screening.

Rationale: The prednisone dose at screening must be a minimum of 20 mg/day but there is no requirement to limit the dose to 60 mg/day during the screening period.

Section 5.1 Inclusion Criteria #3

At screening, receiving or able to ~~receive~~ **initiate** prednisone ~~20-60mg/day~~ **treatment with a minimum dose of 20 mg /day** for the treatment of active GCA.

6. Addition of wording to clarify requirements for chest radiographs to exclude infection with TB.

Rationale: Single views of chest radiographs are acceptable according to local guidance in some countries, such as Germany. The protocol has been amended to clarify the acceptability of local practices/guidance.

Section 5.1 Inclusion Criteria #6

c. Chest radiograph (both posterior-anterior and lateral views **unless local guidelines recommend only a single view**), taken within 12 weeks prior to baseline or at Screening, and read locally by a qualified radiologist, with no evidence of current active or previous inactive pulmonary tuberculosis.

7. Addition of details to clarify that physicians with hepatitis B expertise should be consulted in the event of positive results for hepatitis B testing.

Rationale: To include guidance to investigators for clinical follow up in the event of positive findings for hepatitis B testing.

Section 5.2 Exclusion Criteria # 16

Hepatitis B infection (positive test results for hepatitis B surface antigen or hepatitis B core antibody)**.

** If seropositive, consultation with a physician with expertise in the treatment of HIV or hepatitis **B or** C virus infection is recommended.

8. Amendment of wording describing the needle shield for the sirukumab PFS.

Rationale: To correct the description for the needle shield for consistency with the updated IB, including the information on the potential risk of allergic reaction in latex-sensitive individuals.

Section 6.1 Investigational Product and Other Study Treatment

The sirukumab PFS is aseptically filled to deliver a dose of either 100 mg/1.0 mL or 50 mg/1.0 mL of sirukumab in a Becton-Dickinson (BD) Hypak, 1 mL glass SCF

(presiliconized) syringe barrel with a 26 gauge (G) ½ inch fixed needle, ~~a non-latex-based~~ **an** elastomeric needle shield, and a fluoropolymer coated elastomeric plunger stopper.

The needle shield on the PFS (either assembled into UltraSafe needle guard or autoinjector/prefilled pen) is made with a derivative of natural rubber latex, which may cause allergic reactions in individuals sensitive to latex.

9. Addition of wording to clarify that the prednisone dose should be taken as a single daily administration in the morning.

Rationale: To ensure consistency of prednisone dosing in the study to minimize any variation in prednisone pharmacokinetics.

Section 6.1 Investigational Product and Other Study Treatment

Prednisone doses below 20 mg and/or matching placebo will be provided in blister packs for blinded administration. **Subjects should take their prednisone daily dose in one single daily administration in the morning.**

10. Update the Time and Events Tables to include additional time points for PK assessments and additional samples for IL-6 measurements, to include the assessments for the exploratory US imaging cohort, and to amend the footnote wording for requirement for ECG .

Rationale: For consistency with protocol changes.

Section 7.1 Time and Events Tables

Table 2 Time and Events Table for Part A of the Study (52-week Double-blind Treatment Phase)

	Screening (~Wk -6)	**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**
Laboratory Assessments																			
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			x																
Ultrasound imaging[15]	x[16]					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. To be completed by subjects before any other assessments and before the administration of study drug. HAQ-DI administered only to sub-set of subjects with PMR. PGA assessed using PtGA (subjects) and PhGA (physicians, after subject completion of questionnaires).
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 suspected ~~heart attack~~ **cardiac abnormality**.
8. Suggested questions (see Section 7.5.7). A QuantiFERON-TB Gold Test should be performed at any time during the study if TB 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, Pharm serum samples must be collected prior to study drug administration. Blood collected from one venipuncture will be divided into multiple aliquots of serum for Pharm 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.**

Table 3 Time and Events Table for Part B (104-week Extension) of the Study: 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**
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. To be completed by subjects before any other assessments. HAQ-DI administered only to sub-set of subjects with PMR. PGA assessed using PtGA (subjects) and PhGA (physicians, after subjects complete their questionnaires).
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 (see Section 7.5.7). A QuantiFERON-TB Gold Test should be performed at any time during the study if TB 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. **Ultrasound scan to be performed only in the event of disease flare or relapse in Part B for subjects participating in the exploratory US imaging cohort.**

Table 4 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)	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**
Laboratory Assessments												
PK[7]	x				x					x		x
Immunogenicity[7]	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. To be completed by subjects before any other assessments and before the administration of open-label sirukumab as applicable. HAQ-DI administered only to sub-set of subjects with PMR. PGA assessed using PtGA (subjects) and PhGA (physicians, after subjects complete their questionnaires))
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 (see Section 7.5.7). 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.
7. **On study drug administration days, Pharm serum samples must be collected prior to study drug administration. Blood collected from one venipuncture will be divided into multiple aliquots of serum for Pharm serum (sirukumab concentration and antibodies to sirukumab) and backup samples..**
8. **Ultrasound scan to be performed only in the event of disease flare or relapse in Part B for subjects participating in the exploratory US imaging cohort.**

Table 5 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**
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	
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
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 3 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. To be completed by subjects before any other assessments and before the administration of open-label sirukumab as applicable. HAQ-DI administered only to sub-set of subjects with PMR. PGA assessed using PtGA (subjects) and PhGA (physicians, after subjects complete their questionnaires).
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 (see Section 7.5.7). A QuantiFERON-TB Gold Test should be performed at any time during the study if TB is suspected.

8. Pregnancy test: urine = U, serum = S. Premenopausal women only.
9. **On study drug administration days, Pharm serum samples must be collected prior to study drug administration. Blood collected from one venipuncture will be divided into multiple aliquots of serum for Pharm serum (sirukumab concentration and antibodies to sirukumab) and backup samples.**
10. **Ultrasound scan to be performed only in the event of disease flare or relapse in Part B for subjects participating in the exploratory US imaging cohort.**

11. Modify the wording related to when the results of an ECG should be obtained.

Rationale: The results of an ECG performed for any suspected cardiac abnormality should be obtained.

Section 7.5.5 Electrocardiogram (ECG)

In the event of a suspected ~~myocardial infarction~~ **cardiac abnormality**, the investigator should make every reasonable attempt to obtain the results of the ECG performed in the emergency hospital facility. ~~at the time of the suspected myocardial infarction.~~

12. Correct typographical error in time frame for assessment of cumulative prednisone dose.

Section 9.3 Data Analysis Considerations, Section 9.3.3 Treatment comparisons

3. Cumulative prednisone dose over 7~~8~~6 week period

13. Include additional references for the exploratory US imaging portion of the study.

Section 11

Arrida, A., Kyprianou, M., Kanakis, M., and Sfikakis, P.P. (2010). The diagnostic value of ultrasonography-derived edema of the temporal artery wall in giant cell arteritis: a second meta-analysis. BMC Musculoskeletal Disorders 11, 44.

Ball, E.L., Walsh, S.R., Tang, T.Y., Gohil, R., and Clarke, J.M. (2010). Role of ultrasonography in the diagnosis of temporal arteritis. The British Journal of Surgery 97, 1765-1771.

Czihal, M., Zanker, S., Rademacher, A., Tato, T.Y., Kuhlencordt, P.J., Schulze-Koops, H., and Hoffman, U. (2012). Sonographic and clinical pattern of extracranial and cranial giant cell arteritis. Scandinavian Journal of Rheumatology 41:231-236.

De Miguel, E., Roxo, A., Castillo, C., Peiteado, D., Villalba, A., and Martin-Mola, E. (2012). The utility and sensitivity of colour Doppler ultrasound in monitoring changes in giant cell arteritis. Clinical and Experimental Rheumatology 30, S34-38.

Karassa, F.B., Matsagas, M.I., Schmidt, W.A., and Ioannidis, J.P. (2005). Meta-analysis: test performance of ultrasonography for giant-cell arteritis. Annals of Internal Medicine 142, 359-369.

Luqmani R, Lee E, Singh S, Gillett M, Schmidt WA, Bradburn M, Dasgupta B, Diamantopoulos AP, Forrester-Barker W, Hamilton W, Masters S, McDonald B, McNally E, Pease CT, Piper J, Salmon J, Wailoo A, Wolfe K, Hutchings A. Inter-

Rater Analysis of Ultrasound and Histological Findings in Patients with Suspected Giant Cell Arteritis [abstract]. Arthritis Rheumatol. 2015; 67 (suppl 10).

Ponte C, Vaggers S, Sznajd J, O'Neill L, Piper J, Gunn J, Mankia K, Luqmani R. How Can We Use Ultrasound in the Diagnosis and Management of Patients with Giant Cell Arteritis? [abstract]. Arthritis Rheumatol. 2015; 67 (suppl 10).

Schmidt WA, Moll A, Seifert A, Schicke B, Gromnica-Ihle E, Krause A. Prognosis of large-vessel giant cell arteritis. Rheumatology (Oxford). 2008 Sep;47(9):1406-8.

Schmidt WA, Krause E, Schicke B, Kuchenbecker J, Gromnica-Ihle E. Do temporal artery duplex ultrasound findings correlate with ophtalmic complications in giant cell arteritis? Rheumatology (Oxford). 2009 Apr; 48(4):383-5.

14. Inclusion of information in Appendix 7 for Country Specific Amendments

Rationale: To reflect changes requested by central ethics committees in Germany and the Netherlands to include additional measures regarding subject safety and for consistency with local guidelines with respect to chest radiographs.

Section 12.7 Appendix 7 Country Specific Requirements

In Germany, subcutaneous administration of sirukumab or matching placebo must be discontinued for subjects with a clinically important, active infection. This treatment must be withheld until serious and/or severe infections have been completely resolved. This includes all opportunistic infections, sepsis or meningoencephalitis.

In the Netherlands, no subject will be enrolled in the extension phase (Part B) of the study. Subjects will discontinue the study upon completion Part A and the 16-week follow-up phase.

In Australia and New Zealand, the investigator will be notified of the value of the ESR result when an ESR value is > 40 mm/hr or in the event of a increase from baseline or previous visit of > 10 mm/hr in order to determine if a treatment change is warranted.

15. Administrative changes

Updated author list, Table of Contents, name and contact information for GSK medical monitor and correction of typographical error in Abbreviations.

Amendment 03 17 November 2016

1. Clarification of the endpoints for the ultrasound imaging cohort.

Rationale: Occlusion and stenosis will not be assessed by sonographers. Since this is an exploratory cohort of the study, the analyses related to changes in vascular information will be detailed in a separate RAP.

Section 1 Protocol Synopsis for Study 201677, Objective(s)/Endpoint(s)

Section 3 Objectives and Endpoints

Section 12.8 Appendix 8: Exploratory US Imaging, Section 12.8.1 Objectives and Endpoints

Objectives	Endpoints
• 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	• Change over time ~~of the following~~ **in** measurements of vascular inflammation in temporal and axillary arteries~~:~~ ~~– Presence/absence of occlusion~~ ~~– Presence/absence and maximum diameter of halo~~ ~~– Presence/absence of stenosis~~
• To explore the predictive value of ultrasound for clinical efficacy in GCA	• Correlation of clinical endpoints with changes in vascular inflammation • Correlation of changes in vascular inflammation on US with clinical ~~markers such as GCA disease~~ **activity,** CRP and ESR • Correlation of changes in vascular inflammation on US with health-related quality of life outcomes

GCA = giant cell arteritis; ESR – erythrocyte sedimentation rate; CRP = C-reactive protein; SF-36 v2 = 36-item short form health survey version 2; EQ-5D (3L) = EuroQoL-5 dimensions; FACIT-fatigue = functional assessment of chronic illness therapy-fatigue; PRO = patient reported outcomes; HAQ-DI = health assessment questionnaire-disability index; PGIC = Patient Global Impression of Change; P1NP = procollagen type 1 N-propeptide; CTX = carboxyterminal cross-linked telopeptide of bone collagen; IL = interleukin; **US=ultrasound**.

2. Inclusion on information on the 3 time points when the database will be locked and the data to be included.

Rationale: The results from Parts A and B will be analyzed separately. The results of Part A will be analyzed when the last subject completes Week 52 of treatment and the data reported. The data for the 1st 6 months of Part B will also comprise a separate data set and report.

Section 1 Protocol Synopsis for Study 201677, Overall Design

Section 4 Study Design, Section 4.1 Overall Design

Three primary database locks (DBLs) are planned for reporting of the results:

- **The first DBL for the primary analysis will occur after all subjects have completed the Week 52 visit assessments in Part A or have withdrawn prematurely from the study. Treatment-level data will be unblinded to Sponsor personnel.**
- **The second DBL for the 6-month follow-up will occur after all subjects have completed the Week 24 visit in Part B, or have withdrawn prematurely from the study. The data from subjects undergoing the 16-week follow-up assessments at the end of Part A will also be included and will potentially comprise a separate data set/report if applicable.**
- **The third planned DBL will occur after all subjects have completed the last visit in Part B, or have withdrawn prematurely from the study. The Part B DBL will include the data from all visits associated with Part B of the study, including the 16-week follow-up assessments of Part B if applicable.**

All subjects and study site personnel will remain blinded to the treatment group assignment until all subjects of Part B have completed the Week 24 visit assessments of Part B.

3. Additional clarification regarding requirements for implementation of the prednisone taper.

Rationale: To include additional details for investigator understanding of how to implement the prednisone taper for their study subjects.

Section 1 Protocol Synopsis for Study 201677, Treatment Arms and Duration

The prednisone tapering schedule begins for all subjects upon randomization (Baseline, Week 0) as follows:

- **Subjects will remain on the prednisone dose they are currently receiving at Baseline for one week.**
- **At Week 1, the prednisone dose will be decreased in accordance with the pre-specified prednisone taper schedule.**
- **The pre-specified maximum tapering schedule to be followed will depend on the subject's treatment group assignment.**
- **The prednisone taper will be unblinded (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.**

Section 4 Study Design, Section 4.2 Treatment Arms and Duration, Section 4.2.1 Part A: 52-week, double-blind treatment phase

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. The prednisone tapering schedule (summarized in Section 6.3) will be initiated at randomization for all subjects. **Subjects should remain on the prednisone dose they are currently receiving at Baseline (randomization) for one week. At Week 1, the prednisone dose should be decreased in accordance with the pre-specified prednisone taper schedule.** The pre-specified maximum tapering schedule to be followed will depend on the subject's treatment group assignment. The standardized prednisone taper regimen will be unblinded (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 for the pre-specified differences in duration of the prednisone tapering**. Subjects who are receiving a prednisone dose of open-label 20 mg/day at randomization should continue taking the 20 mg daily dose for one week. At Week 1, these subjects will initiate the blinded taper regimen.**

Section 6 Study Treatment, Section 6.3 Planned Dose Adjustments

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

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. A pre-specified prednisone tapering schedule outlined in Table 1 ~~will be initiated at randomization, depending on the subject's treatment group assignment~~ **begins for all subjects upon randomization at Baseline, (Week 0).** 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 pre-specified prednisone taper schedule (Table 1).**
- **The pre-specified maximum tapering schedule to be followed will depend on the subject's treatment group assignment.**

- **The prednisone taper will be unblinded (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.**

Section 7 Study Assessments and Procedures, Section 7.2 Screening and Critical Baseline Assessments

All subjects should be receiving prednisone treatment at Screening. Prednisone treatment must be initiated at Screening for subjects not currently receiving steroid treatment.

4. Addition of values for CRP units in mg/L.

Rationale: To specify the unit in mg/L for consistency with results from the central laboratory.

Section 1 Protocol Synopsis for Study 201677, Type and Number of Subjects

Section 4 Study Design, Section 4.1 Overall Design

Subjects are required to have active GCA disease within 6 weeks of baseline where active disease is defined as the presence of unequivocal clinical signs and symptoms attributable to GCA and increased levels of inflammatory markers ~~([~~ESR ≥ 30 mm/hr and/or CRP ≥ 1 mg/dL **(10 mg/L)]**.

Section 4 Study Design, Section 4.1 Overall Design

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 ESR ≥30 mm/hr and/or serum CRP ≥1 mg/dL **(10 mg/L)**.

Section 5 Selection of Study Population and Withdrawa Criteria, Section 5.1 Inclusion Criteria

1. Diagnosis of GCA defined by the following Revised GCA Diagnosis Criteria:

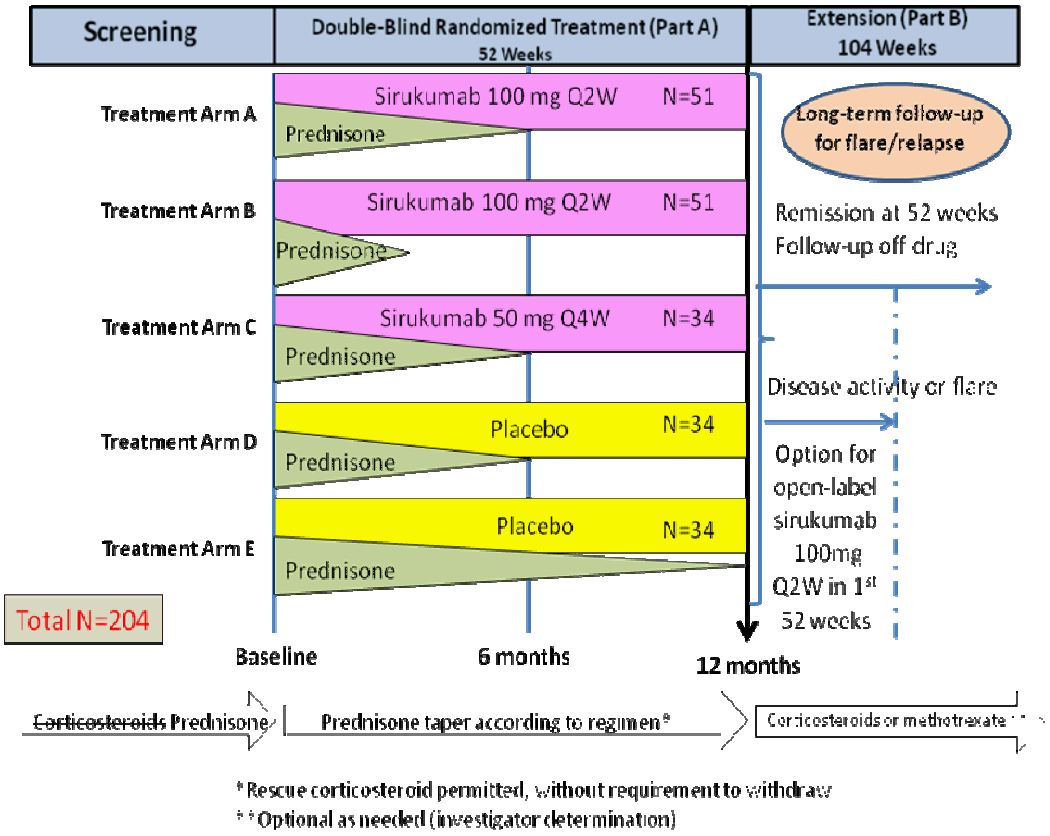
- Age ≥50 years.
- History of ESR ≥ 50 mm/hour or CRP ≥ 2.45 mg/dL **(≥ 24.5 mg/L)**

2. Active GCA within 6 weeks of Randomization (Baseline) where active disease is defined by an ESR ≥30 mm/hr or CRP ≥ 1 mg/dL **(≥10 mg/L)** AND the presence of at least **one** of the following:

5. Update of study schematic to clarify that prednisone should be taken during Screening.

Rationale: To specify that prednisone should be taken during Screening.

Section 4 Study Design, Section 4.1 Overall Design



6. Update of risk assessment table and modification of events of special interest for sirukumab.

Rationale: To incorporate the findings from the Phase III sirukumab study in rheumatoid arthritis and for consistency with the updated investigator brochure

Section 4: Study Design, Section 4.6 Benefit:Risk Assessment, Section 4.6.1 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [sirukumab]		
TB reactivation	Cases of TB reactivation have been reported with ~~other~~ IL-6 antagonists, such as tocilizumab **and sirukumab**.	Inclusion only of subjects with no evidence of active or latent TB infection, negative diagnostic TB test at Screening and Screening chest radiograph showing no evidence of current or previous pulmonary TB (Section 5.1 Bullet 4). Evaluation of TB throughout the study by use of a TB questionnaire and a TB test (Section 7.5.7)
Serious/opportunistic infections	IL-6 deficient mice have been noted to be susceptible to infections with *Listeria, monosytogenes, Toxoplasma gondii*, and *Candida albicans* [Dalrymple, 1995; Romani, 1996; Suzuki, 1997]. Serious, life-threatening infections such as septic shock, some of which have been fatal, have occurred in subjects receiving sirukumab.	Exclusion of subjects with an active current or history of recurrent bacterial, viral, fungal, mycobacterial, or other infection or those with a prior episode of major infection (serious infectious event). Monitoring of serious and opportunistic infections by IDMC.
Hypersensitivity	Serious allergic reactions (eg, anaphylaxis) have been reported with the administration of mAbs, including sirukumab, and may occur during or after the administration of the mAbs.	Exclusion of subjects with severe allergic reactions to monoclonal antibodies, human proteins, or excipients. Subjects will be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention. Discontinuation of blinded subcutaneous study drug in the event of a severe allergic reaction. Monitoring of serious allergic reactions by IDMC; adjudication and classification of these events using Sampson criteria (Sampson, 2006) by sponsor safety review team will be implemented.
Gastrointestinal perforation	Upper and lower GI tract perforations occurred in	Exclusion of subjects with a history of

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	the anti-IL-6 receptor (tocilizumab) **& the anti-IL6 (sirukumab)** Phase III program**s**. Sirukumab binds to IL-6 and prevents binding to IL-6 receptor (IL-6R). Tocilizumab binds to IL-6 R to prevent IL-6 signalling. Potential differences in safety between agents that bind to the IL-6 receptor versus ones that bind to the IL-6 ligand (sirukumab) warrants further study.	diverticulitis, inflammatory bowel disease, or other symptomatic GI tract condition that might predispose to bowel perforation. Investigators should closely monitor for GI perforations with a high degree of suspicion. Monitoring of gastrointestinal perforations by IDMC.
Cytopenias	Neutropenia and thrombocytopenia have occurred in sirukumab studies, including severe thrombocytopenia associated with bleeding. ~~Decreases in platelet counts have also been observed.~~ **Most patients who developed neutropenia while being treated with sirukumab did not develop infections, and most patients who developed thrombocytopenia did not experience bleeding events.**	Exclusion of subjects with absolute neutrophil count (ANC) <$2x10^9$/L, platelet count <$140x10^9$/L, WBC count <$3.5x10^9$/L, ALC <0.5 $x10^9$/L. Discontinuation of blinded subcutaneous study drug for subjects with 2 confirmed consecutive absolute neutrophil counts of <0.5×10^9 cells/L or platelet counts <50×10^9 cells/L. Monitoring of cytopenias by IDMC.
Lipid increases	Increases in blood total cholesterol, LDL, HDL, and triglycerides have occurred in sirukumab-treated subjects. No dose response was observed.	Monitor HDL/LDL levels, administer a cholesterol lowering agent if indicated.
Liver enzyme increases	Transient asymptomatic increases (1 to 3 x ULN, sometimes > 5 x ULN but < 8 x ULN) in blood ALT and AST values have been observed in subjects in completed and ongoing studies of sirukumab. ~~These changes were not associated with an increase in bilirubin.~~ **Six subjects have had ALT or AST >3 x ULN and bilirubin >2 x ULN; all 6 had received sirukumab 100 mg SC**	Exclusion of subjects with AST or ALT >2.0 x ULN, or total bilirubin >ULN with the exception of Gilbert's disease. Inclusion of pre-defined liver chemistry discontinuation criteria (Section 5.4.3). Monitoring of hepatic abnormalities by IDMC.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	q2w. Three subjects had concurrent biliary stones/colic, and 1 subject was concomitantly taking isoniazid. The hepatobiliary laboratory values normalized after surgery or discontinuation of isoniazid in these subjects. A fifth subject with long-standing methotrexate use, who had pre-existing fatty liver disease, developed hyperbilirubinemia (>9 x ULN) and jaundice, as well as elevations in AST (>5 x ULN), after 2 doses of sirukumab 100 mg. A liver biopsy revealed active steatohepatitis. After discontinuation of methotrexate and sirukumab, the hepatobiliary tests improved such that 9 months later AST was 1-1.5 x ULN, and ALT and bilirubin were normal. A sixth subject initially was observed to have ALT and AST >5 x ULN which both increased 2 weeks later to >20 x ULN with bilirubin > 2 x ULN. Notable findings at that time were hepatitis E virus IgM positivity and chronic liver changes by ultrasound. Hepatobiliary abnormalities had resolved 16 weeks after discontinuation of study agent.	
Cardiovascular events	No cardiovascular risk with sirukumab has been identified in clinical studies to date. **Most subjects who experienced cardiovascular events in the sirukumab RA Phase 3 program had pre-existing risk factors as well as active RA. There was no association between grade**	Exclusion of subjects with uncontrolled cardiovascular disease or marked baseline prolongation of QTc interval ≥ 450 msec (QTcB or QTcF), history of Torsade de Pointes, family history of long QT syndrome, history of second or third degree heart block or subject with major

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	3 or 4 lipid levels and the development of MACE in the majority of subjects in the sirukumab Phase 3 RA program. Overall, the data do not support a direct link between sirukumab-induced elevations in lipid levels and MACE. However, the study population is at high risk for CV disease.	ischemic event unrelated to GCA. Inclusion of pre-defined QTc discontinuation criteria (Section 5.4.4). Monitoring of CV events by CEC and IDMC
Malignancies	**The impact of treatment with tocilizumab on the development of malignancies is not known, but malignancies were observed in clinical studies.** **As an IL-6 inhibitor, sirukumab may have some effect on the risk of malignancy by affecting immune surveillance. Malignancies have been reported with sirukumab in rheumatoid arthritis (RA) clinical trials.**	**Exclusion of subjects with active malignancy or history of malignancy within previous 5 years (except basal and squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that has been excised and cured). Monitoring of malignancies by IDMC.**
Study Procedures		
Blood draws for safety and biomarker assessments	Fainting, mild pain, bruising, irritation or redness at the site are associated with blood draws.	Experienced site staff will follow standard approaches for managing events related to blood draws.
Use of auto-injector	Mild pain, bruising, irritation or redness at the injection site may be experienced by some patients.	Site staff will be trained and will ensure training and oversight of subjects' capabilities to use the auto-injector.
Rapid steroid taper	Steroid withdrawal symptoms and side effects	Inclusion only of subjects with stable disease who are able to safely participate in the steroid taper. Subjects should have clinically stable disease on steroid therapy prior to

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		randomization. IDMC will monitor all subjects including those in the 3 month taper.

Section 7 Study Assessments and Procedures, Section 7.5 Safety, Section 7.5.1 Adverse Events (AE) and Serious Adverse Events (SAEs), Section 7.5.1.5 Other Adverse Events of Special Interest for Sirukumab

Other Events of Interest

Sirukumab, by its mechanism of action as an IL-6 inhibitor, would be expected to have some properties of immunosuppression. ~~As such, increased susceptibility to certain infections is a potential risk.~~ . **Increased susceptibility to infections is an identified risk of sirukumab. Serious, life-threatening infections such as septic shock, some of which have been fatal, have occurred in subjects receiving sirukumab.** IL-6 deficient mice have been found to be susceptible to infections with Listeria monocytogenes, Toxoplasma gondii, and Candida albicans. [Dalrymple, 1995; Romani, 1996; Suzuki, 1997]. In addition, as an IL-6 inhibitor, sirukumab may have some effect on the risk of malignancy by affecting immune surveillance. Further, gastrointestinal perforations have been reported with another anti-IL-6 agent [ACTEMRA Prescribing Information, 2011] **and with sirukumab. Please refer to Table 4.6.1 and the Investigator Brochure for additional information.**

7. To update the benefit:risk conclusion.

Rationale: To clarify that the efficacy has been demonstrated in Phase III trials in RA.

Section 4.6 Benefit:Risk Assessment, Section 4.6.3 Overall Benefit:Risk Conclusion

Although the efficacy of sirukumab in subjects with GCA has yet to be established, it has been shown to be effective in Phase ~~II~~ **III** studies in RA.

8. To update the Inclusion Criteria to clarify prednisone requirements at Screening.

Rationale: To clarify that subjects should be receiving prednisone at the start of Screening.

Section 5 Selection of Study Population and Withdrawa Criteria, Section 5.1 Inclusion Criteria

3. At screening, receiving ~~or able to initiate~~ prednisone treatment with a minimum dose of 20 mg /day for the treatment of active GCA. **Subjects not currently receiving prednisone treatment must commence dosing (minimum 20 mg/day of prednisone) at the screening visit.**

9. To include information on requirements for contraception and sperm donation.

Rationale: Use of male contraception and restrictions on sperm donation have been included for consistency with Janssen's requirements for safety monitoring

Section 5 Selection of Study Population and Withdrawa Criteria, Section 5.1 Inclusion Criteria

5. Practicing acceptable methods of birth control ~~Acceptable methods of birth control are provided in Appendix 2.~~**as follows:**

Males:

Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until 4 months after the last dose of study medication:

h. Vasectomy with documentation of azoospermia.

i. Male condom plus female partner use of one of the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Childbearing potential listed in Appendix 2.

Male subjects should also not donate sperm from the time of first dose of study medication until 4 months after the last dose of study medication.

Females:

Female subjects of child-bearing potential must use of one of the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Childbearing potential listed in Appendix 2.

10. To modify the requirements for QuantiFERON Gold TB testing.

Rationale: An indeterminate result may be a consequence of issues with sample processing; therefore, allowance for local laboratory testing after an initial indeterminate result from the central laboratory is permissible.

Section 5 Selection of Study Population and Withdrawa Criteria, Section 5.1 Inclusion Criteria

6. No evidence of active or latent infection with Mycobacterium tuberculosis (TB), as defined by all of the following:
    a. No history of active or latent TB infection.
    b. A negative diagnostic TB test at Screening defined as a negative QuantiFERON Gold test (NB: 2 successive indeterminate QuantiFERON tests will be considered as a positive result). **In cases where an initial indeterminate QuantiFERON test result may be related to sample processing issues, the second QuantiFERON test may be performed at either the local laboratory or the central laboratory at the discretion of the investigator. Re-testing is only permitted for indeterminate results. If the re-test also produces an indeterminate result, further re-testing to determine study eligibility is not permitted either at the local or central laboratory.**
    c. Chest radiograph (both posterior-anterior and lateral views unless local guidelines recommend only a single view), taken within 12 weeks prior to baseline or at Screening, and read locally by a qualified radiologist, with no evidence of current active or previous inactive pulmonary tuberculosis.

11. To modify the Exclusion Criteria and Prohibited Medications sections regarding prior use of anti-IL-6 agents.

Rationale: Sirukumab efficacy can reasonably be evaluated in study subjects who previously used an anti-IL-6 agent without evidence of an inadequate response or intolerance to the agent used.

Section 5 Selection of Study Population and Withdrawal Criteria, Section 5.2 Exclusion Criteria

4. Had prior treatment with any of the following:
    - ~~Any prior use of tocilizumab or other anti-IL-6 agents.~~
    - **Anti-IL-6 (tocilizumab or any other anti-IL-6 agent) if:**

- **Used within 8 weeks of randomization**
- **Associated with a history of intolerance that precluded further treatment**
- **Associated with an inadequate response to 3 months of therapy**

Section 6.10 Concomitant Medications and Non-Drug Therapies, Section 6.10.2 Prohibited Medications and Non-Drug Therapies

The following drugs and vaccines are prohibited within the specified time frames and with concomitant SC administration of study drug:

- ~~Any prior use of tocilizumab or other anti-IL-6 agents.~~
- **Anti-IL-6 (tocilizumab or any other anti-IL-6 agent) if:**
  - **Used within 8 weeks of randomization**
  - **Associated with a history of intolerance that precluded further treatment**
  - **Associated with an inadequate response to 3 months of therapy**

12. To modify the requirements for ECG test results for study eligibility and stopping criteria and to clarify ECG testing requirements.

Rationale: Sirukumab use is not associated with a QTc liability. The elderly patient population in this study is more likely to have excursions outside of the previous requirements in the absence of increased risk; therefore, the QTc requirements for eligibility were amended to be less restrictive.

Section 5 Selection of Study Population and Withdrawa Criteria, Section 5.2 Exclusion Criteria

10. Marked baseline prolongation of QTc **interval** ~~≥ 450~~ **> 480 msec** (QTcB or QTcF) **or QTc > 500 msec in subjects with Bundle Branch Block****, history of Torsade de Pointes, family history of long QT syndrome, history of second or third degree heart block.

****The QTc should be based on averaged QTc values of triplicate ECGs obtained over a brief (e.g., 5-10 minute) recording period.**

Section 5.4 Withdrawal/Stopping Criteria, 5.4.4 QTc Stopping Criteria

QTc Stopping Criteria:

- QTc > ~~500~~ **530** msec ~~OR Uncorrected QT > 600 msec~~ **(all subjects)**

  OR
- Change from baseline of QTc > 60 msec.

~~For patients with underlying~~ **~~bundle branch block~~**~~, follow the discontinuation criteria listed below:~~

~~Baseline QTc with Bundle Branch Block~~	**~~Discontinuation QTc with Bundle Branch Block~~**
~~< 450 msec~~	~~> 500 msec~~
~~450 – 480 msec~~	~~≥ 530 msec~~

13. To clarify testing procedures for hepatitis C.

Rationale: To ensure that subject eligibility is based on a confirmed positive result for hepatitis C.

Section 5: Selection of Study Population and Withdrawal Criteria, Section 5.2 Exclusion Criteria

16. HIV infection (positive serology for HIV antibody), hepatitis C (positive serology for hepatitis C **antibody confirmed positive by hepatitis C RNA PCR which is reflexively performed)*****.

*** If seropositive, **referral of the subject for** consultation with a physician with expertise in the treatment of HIV or hepatitis B or C virus infection is recommended.

14. To include wording to clarify exclusion requirements for continued or repeated use of corticosteroids.

Rationale: To clarify that subjects receiving corticosteroid treatment for symptoms of PMR are eligible.

Section 5: Selection of Study Population and Withdrawal Criteria, Section 5.2 Exclusion Criteria

6. Requires continued or repeated use of systemic corticosteroids for conditions other than GCA **or PMR symptoms associated with GCA.**

15. To include behaviors related to suicidality as an exclusion.

Rationale: Per GSK policy, prospective monitoring of suicidal ideation and behavior is implemented in clinical trials for investigational agents with potential activity on the central nervous system, including sirukumab. This exclusion has been included to decrease the likelihood of enrolment of patients at risk of suicidal behaviors.

Section 5: Selection of Study Population and Withdrawa Criteria, Section 5.2 Exclusion Criteria

23. Current history of suicidal ideation or past history of suicide attempt.

16. To clarify requirements for re-testing for ECG assessment and QuantiFERON-TB Gold test.

Section 5.3 Screening/Baseline/Run-in Failures

Re-testing

If a subject has signed the Informed Consent Form (ICF) and failed to meet at least one entry criterion, the site may retest laboratory values or repeat a study entry procedure once only during the screening period. Laboratory parameters can only be re-tested once. If a different laboratory parameter is found to be out of range in the re-test, no further testing is allowed. Re-testing may be performed to determine eligibility within the screening window. Subjects that have laboratory values that do not meet the entry criteria following the re-test are to be deemed a screen failure. Exceptions to re-testing are chest radiograph, ~~ECG,~~ and a positive result for the QuantiFERON-TB Gold test; these screening tests may not be repeated to meet eligibility criteria. An indeterminate result for the QuantiFERON-TB Gold test may be re-tested and subjects will be eligible upon a negative re-test result). **In cases where an initial indeterminate QuantiFERON test result may be related to sample processing issues, the second QuantiFERON test may be performed at either the local laboratory or the central laboratory at the discretion of the investigator. Re-testing is only permitted for indeterminate results. If the re-test also produces an indeterminate result, further re-testing to determine study eligibility is not permitted either at the local or central laboratory.**

17. To clarify methotrexate use as a rescue therapy.

Rationale: Investigators may use either corticosteroids and/or methotrexate in the event of a flare.

Section 5.4 Withdrawal/Stopping Criteria, Section 5.4.1 Study Withdrawal

It should be noted that there is no requirement to withdraw a subject from the study for lack of efficacy. This study is designed to follow subjects over the long-term, irrespective of requirement for rescue treatment or withdrawal of study drug. The investigator should make every reasonable attempt to enable the subject to continue participation in the study and present for visits as scheduled. The investigator should offer treatment with an investigator-defined open-label corticosteroid rescue regimen in combination with double-blind injections of study drug (sirukumab or placebo) for the remainder of the 52 week double-blind treatment period. **Methotrexate treatment may also be initiated as part of the rescue regimen at the discretion of the investigator.**

18. To clarify requirements for discontinuation of study drug.

Rationale: To provide guidance to the investigator on management of corticosteroid treatment in the event of discontinuation of blinded sirukumab or matching placebo and to clarify the requirements for study drug discontinuation (blinded sirukumab or matching placebo only) in the event of infection.

Section 5.4 Withdrawal/Stopping Criteria, Section 5.4.2 Discontinuation of Study Drug

Permanent discontinuation of study drug will not require the subject to be withdrawn from the study. Subjects should continue where possible to be followed and disease status assessed. **Upon permanent discontinuation of subcutaneously-administered blinded sirukumab or matching placebo, corticosteroid dose and treatment will be at the discretion of the investigator.**

Study drug **(subcutaneously-administered blinded sirukumab or matching placebo)** must be permanently discontinued for any of the following:

Subjects must **not** receive ~~study drug~~ **blinded subcutaneous sirukumab or matching placebo** during the course of a serious infection. **Subjects who temporarily discontinue blinded sirukumab or matching placebo due to an infection or other reasons should continue to follow the prednisone taper schedule.**

Discontinuation of ~~study drug~~ **blinded subcutaneous sirukumab or matching placebo** must be strongly considered for subjects who develop a serious infection such as sepsis or meningoencephalitis, and considered for subjects who have serious infections requiring hospitalization or IV antibiotic therapy.

Discontinuation of ~~study drug~~ **blinded subcutaneous sirukumab or matching placebo** should also be considered for severe injection-site reactions.

19. To clarify terminology for study treatment.

Rationale: Since both blinded sirukumab or matching placebo and prednisone may be considered study treatment, the terminology has been clarified to distinguish them.

Section 6 Study Treatment, Section 6.1 Investigational Product and Other Study Treatment

The term ‘study treatment’ is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments. **Study treatment specifically related to sirukumab and matching placebo is distinguished by the use of the terminology “subcutaneously-administered blinded study drug or treatment (sirukumab and matching placebo)”.**

20. To clarify administration of sirukumab and matching placebo.

Rationale: To clarify that blinded sirukumab or matching placebo will be administered using an autoinjector device.

Section 6 Study Treatment, Section 6.1 Investigational Product and Other Study Treatment

Sirukumab and matching placebo will be supplied by the Sponsor. **Both sirukumab and matching placebo will be administered subcutaneously using an autoinjector device.**

21. To include information on the sourcing of the blinded prednisone.

Rationale: As the Sponsor provides the blinded prednisone, the manufacturer was included for informational purposes.

Section 6 Study Treatment, Section 6.1 Investigational Product and Other Study Treatment

Prednisone for the pre-specified standard blinded taper will be provided by the Sponsor. **The prednisone used in the blinded taper of this study is manufactured by Jubilant Cadista (Salisbury, MD) and supplied to the Sponsor by Myoderm (Norristown, PA).**

22. To clarify the method of blinding of prednisone and laboratory values for CRP and ESR.

Rationale: To provide additional information on how the study blind is maintained for the prednisone taper, and to clarify that CRP and ESR values prior to the start of study treatment are not blinded to the investigator nor the Sponsor/study team as there is no impact on the integrity of the study blind prior to the start of sirukumab treatment.

Section 6: Study Treatment, Section 6.4 Blinding

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 pre-filled syringes in a matching presentation. Blinding to the prednisone dose during the taper will be maintained by providing prednisone dosages 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 patient, 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.

Section 7 Study Assessments and Procedures, Section 7.5 Safety, Section 7.5.6 Clinical Safety Laboratory Assessments

The investigators **and the Sponsor/study team** will remain blinded to the results of the **ESR (performed locally),** CRP and fasting lipid analyses (see Section 6.4) **after the start of treatment during Part A of the study.**

23. To include biosimilar/generic versions of biologics in prohibited medications.

Rationale: Biosimilar/generic versions of anti-TNF agents may be available for use with similar restrictions to other marketed agents.

Section 6.10 Concomitant Medications and Non-Drug Therapies, Section 6.10.2 Prohibited Medications and Non-Drug Therapies

Biologic agents targeted at reducing TNFα (including but not limited to infliximab, golimumab, certolizumab pegol, etanercept, yisaipu, and adalimumab **and/or biosimilar or generic versions of these agents**) within the specified time frames.

24. Addition of the assessment of the C-SSRS

Rationale: Per GSK policy, prospective monitoring of suicidal ideation and behavior is implemented in clinical trials for investigational agents with potential activity on the central nervous system, including sirukumab.

Section 7: Study Assessments and Procedures

1. Patient Global Assessment of disease activity (PtGA).
2. Patient Global Impression of Change (PGIC).
3. Pain Numeric Rating Scale (NRS).
4. HAQ-DI (for subgroup of subjects with PMR).
5. FACIT-fatigue.
6. Steroid Impact PRO.
7. SF-36v2 acute.
8. EQ-5D (5L)

9. **Columbia-Suicide Severity Rating Scale (C-SSRS).**

Section 7 Study Assessments and Procedures, Section 7.5 Safety

Safety will be assessed from the documentation of adverse events and review of vital signs and laboratory assessments including complete blood counts, serum chemistry profiles, fasting serum lipids, HbA1c, hepatitis B and C serologies, and markers of bone turnover. **The Columbia-Suicide Severity Rating Scale (C-SSRS) will be used to prospectively monitor suicidal ideation and behavior (Section 7.5.7).**

Section 7: Study Assessments and Procedures, Section 7.5 Safety, Section 7.5.7 Suicidal Risk Monitoring

Sirukumab is considered to potentially be a CNS-active drug. There has been some concern that some CNS-active drugs may be associated with an increased risk of suicidal thinking or behaviour when given to some patients with certain conditions. Although this drug or other similar drugs in this class have not been shown to be associated with an increased risk of suicidal thinking or behaviour when given to this patient population, GSK considers it important to monitor for such events before or during clinical studies with compounds such as this.

Subjects being treated with sirukumab should be monitored appropriately for suicidal ideation and behaviour or any other unusual changes in behaviour. Consideration should be given to discontinuing sirukumab in subjects who experience signs of suicidal ideation or behaviour.

Suicidal ideation and behaviour will be assessed at baseline and at the time points indicated in Time and Events Table 2 and in Time and Events Table 3 using the patient-reported outcome version of the C-SSRS [Mundt, 2010].

25. To clarify requirements for assessment of subjects for injection site reactions.

Rationale: Assessments may only be conducted when subjects receive injections at the study center.

Section 7 Study Assessments and Procedures, Section 7.5 Safety, Section 7.5.1 Adverse Events (AE) and Serious Adverse Events (SAEs), Section 7.5.1.6 Events that Occur with Biologics

Injection Site Reactions

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. Any adverse reaction (eg, pain, erythema, and/or induration) should be noted on the AE page of the eCRF.

26. To update the requirements for collection of pregnancy information.

Rationale: To clarify that pregnancy details of female partners of male study subjects will be collected.

Section 7 Study Assessments and Procedures, Section 7.5 Safety, Section 7.5.2 Pregnancy

- Details of all pregnancies in female subjects **and female partners of male subjects** will be collected after the start of dosing and until the Follow-up visit.

Section 12 Appendices, Section 12.2 Appendix 2: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) and Collection of Pregnancy Information, Section 12.2.2 Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject **or female partner of male study subject** who becomes pregnant while participating in **or while partner is participating** in this study.

27. To include the requirement for pregnancy testing at additional time points during the study.

Rationale: Pregnancy testing (when applicable) should be conducted every 4 weeks while receiving study treatment.

Section 7 Study Assessments and Procedures, Section 7.5 Safety, Section 7.5.6 Clinical Safety Laboratory Assessments

Pregnancy testing (where applicable) should be conducted every 4 weeks while subjects are receiving study drug and during the 16-week follow-up period. Pregnancy tests may be performed by the subject at home using the test kits provided by the central laboratory when there is no study visit associated with the testing time point.

28. Clarification of ultrasound scanning in the event of flare for Part B of the study.

Rationale: For logistical purposes, scanning in the event of flare in Part B will conclude when the last subject in the exploratory imaging cohort completes Part A of the study.

Section 7.9 Exploratory Ultrasound Imaging, 7.9.2 Synopsis

Subjects will have an initial baseline scan at Screening and assessments at Baseline (Week 0), Weeks 12 and 52. Additional US scans should also be conducted in the event of relapses or flares, including flares/relapses that occur during Part B of the study. **US scanning for flares/relapses in Part B of the study will conclude when the last subject in the US imaging cohort completes Part A of the study. Thereafter, no additional scans will be taken.**

Section 12.8 Appendix 8, Section 12.8.3 Assessments and Procedures, Section 12.8.3 Ultrasound Scanning

5. Any time point of disease relapse/flare during Part A or Part B of the study, with every effort made to conduct the US scan within 3 days of rescue prednisone administration. The number of days between the US scan and rescue prednisone administration will be recorded. **Scanning in the event of relapse/flare during Part B will conclude when the last subject in the exploratory US imaging cohort completes Part A. No additional Part B scans will be taken after this time point.**

29. To include updated information on the statistical plans. for treatment comparisons and an overview of the multiplicity control.

Rationale: To provide additional details on the statistical plans for treatment comparisons and an overview of the multiplicity control.

Section 9 Statistical Considerations and Data Analysis, Section 9.3 Data Analysis Considerations, Section 9.3.3 Treatment comparisons

Primary comparison of interest is the comparison between sirukumab 100 mg SC q2w plus 6 month prednisone (Treatment Arm A) and placebo plus 6 month prednisone (Treatment Arm D) for the proportion of subjects ~~with~~ **in** sustained disease remission at ~~52 weeks~~ **Week 52** in the ITT population at the 0.05 significance level. ~~The observed dataset will be used for this comparison.~~ The analysis will be adjusted for the stratification factor applied at randomization. ~~as well as the baseline value for the parameter being tested.~~

If the test of the primary endpoint **for the primary comparison** is statistically significant at α=0.05~~, the following major secondary endpoints for the primary comparison will be tested in the sequential order:~~ **(2-sided), the cumulative prednisone dose at week 52 (key secondary endpoint) for the primary comparison (arm A vs arm D) will be tested at a significance level of 0.05 (2-sided). If the statistical significance for the primary endpoint is not met, then the key secondary endpoint in the sequence cannot be deemed statistically significant, although nominal p-values may be reported and considered descriptive but should not be interpreted inferentially.**

- ~~Cumulative prednisone dose over 52 week period~~
- ~~Proportions of subjects with sustained disease remission at 6 months post cessation of 12-month sirukumab treatment~~
- ~~Cumulative prednisone dose over 76 week period~~

For the **2** endpoints outlined above, the following treatment comparisons will also be evaluated following the same sequential approach provided that the primary endpoint for the primary comparison achieves significance:

- Sirukumab 100mg SC q2w plus 3 month prednisone versus placebo plus 6 month prednisone (Arm B vs. Arm D)
- Sirukumab 100mg SC q2w plus 6 month prednisone versus placebo plus 12 month prednisone (Arm A vs. Arm E)
- Sirukumab 100mg SC q2w plus 3 month prednisone versus placebo plus 12 month prednisone (Arm B vs. Arm E)

Comparisons with Sirukumab 50mg SC q4w (Arm C) will be similarly evaluated.
~~Comparisons of interest for other secondary efficacy endpoints will also be assessed.~~

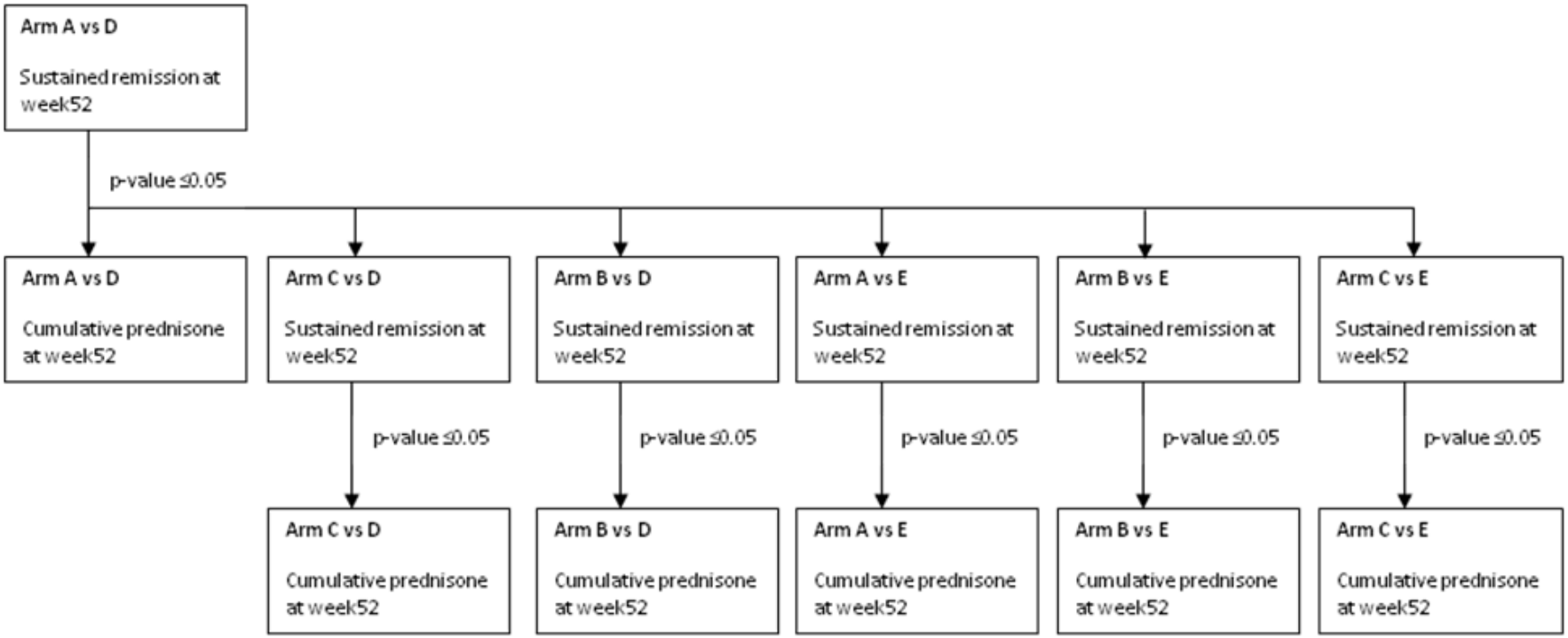
An overview of the multiplicity control is provided in Figure 2.

An alternative testing hierarchy, used to address regional differences in the regulatory requirements for controlling type 1 error, will be specified in the RAP.

Analyses of other efficacy endpoints will not be subject to any multiple comparison procedure. All statistical tests will be 2-sided and performed at an overall significance level of 0.05.

Further details are included in the RAP.

Figure 1: Overview of the Multiplicity control



Treatment arm A = Sirukumab 100 mg SC q2w plus 6-month prednisone taper
Treatment arm B = Sirukumab 100 mg SC q2w plus 3-month prednisone taper
Treatment arm C = Sirukumab 50 mg SC q4w plus 6-month prednisone taper
Treatment arm D = Placebo plus 6-month prednisone taper
Treatment arm E = Placebo plus 12-month prednisone taper

30. To update the Time and Events Tables to incorporate and reflect the changes in the protocol amendment.

Section 7 Study Assessments, Section 7.1 Time and Events Tables

Table 2 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	

	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**
EQ-5D (5L)[4]		x				x			x			x				x	x	x	
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	
Serum chemistry	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	
ESR	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	U
HIV, HBsAg, HBcAb, 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

	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**
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** ~~T~~to be completed by subjects before ~~any~~ 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 patient 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 (see Section 7.5.7). A QuantiFERON-TB Gold Test should be performed at any time during the study if TB 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, Pharm serum samples must be collected prior to study drug administration. Blood collected from one venipuncture will be divided into multiple aliquots of serum for Pharm 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.

Table 3 Time and Events Table for Part B (104-week Extension) of the Study: 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** ~~T~~to be completed by subjects before ~~any~~ 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 patient 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 (see Section 7.5.7). A QuantiFERON-TB Gold Test should be performed at any time during the study if TB 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 scan to be performed only in the event of disease flare or relapse in Part B ~~for subjects participating in the exploratory US imaging cohort~~ **Part B scans will conclude when the last subject in the US imaging cohort completes Part A.**

Table 4 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** ~~T~~to be completed by subjects before ~~any~~ 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 patient 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 (see Section 7.5.7). 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 post 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, Pharm serum samples must be collected prior to study drug administration. Blood collected from one venipuncture will be divided into multiple aliquots of serum for Pharm serum (sirukumab concentration and antibodies to sirukumab) and backup samples..
8. **For subjects participating in the exploratory US imaging cohort.** Ultrasound scan to be performed only in the event of disease flare or relapse in Part B ~~for subjects participating in the exploratory US imaging cohort~~ **Part B scans will conclude when the last subject in the US imaging cohort completes Part A.**

Table 5 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															

	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**
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**	
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 3 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** ~~T~~to be completed by subjects before ~~any~~ 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 patient 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 (see Section 7.5.7). A QuantiFERON-TB Gold Test should be performed at any time during the study if TB 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 post 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, Pharm serum samples must be collected prior to study drug administration. Blood collected from one venipuncture will be divided into multiple aliquots of serum for Pharm serum (sirukumab concentration and antibodies to sirukumab) and backup samples..
10. **For subjects participating in the exploratory US imaging cohort.** Ultrasound scan to be performed only in the event of disease flare or relapse in Part B ~~for subjects participating in the exploratory US imaging cohort~~ **Part B scans will conclude when the last subject in the US imaging cohort completes Part A.**

31. To include corrections and clarifications to Table 6 Laboratory Parameters consistent with the amended protocol.

Section 7, Study Assessments, Section 7.5 Safety, Section 7.5.6 Clinical Safety Laboratory Assessments

Table 6 Laboratory 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		
Serum Chemistry		
Sodium	Potassium	Chloride
Bicarbonate	Blood urea nitrogen (BUN)	Creatinine
Glucose	Aspartate transaminase	Alanine transaminase
Alkaline phosphatase	Calcium	Phosphate
Albumin	Total protein	Bilirubin, direct, indirect and total
Fasting lipids		
Total cholesterol	Low density lipoprotein (LDL)	High density lipoprotein (HDL)
Triglycerides		
Serum and urine pregnancy test for premenopausal women only		
Serology for HIV, hepatitis B surface antigen, hepatitis B core antibody and hepatitis C antibody [1]		
Other tests		
Hemoglobin A1c	C-reactive protein (CRP) [2,3]	Erythrocyte sedimentation rate (ESR) [2, 3]
QuantiFERON-TB Gold Test Test ~~(or PPD skin test at sites where QuantiFERON-TB Gold Test is not approved)~~		

4. If hepatitis C antibody positive, a hepatitis C RNA PCR assay should be reflexively performed on ~~the same~~ **a fresh** sample to confirm the result
5. Investigators will remain blinded to the results of the ESR, CRP and fasting lipids **after the start of treatment during Part A of the study** (see Section 6.4). ESR will be analyzed at the local laboratory.
6. Required for the evaluation of efficacy.

32. To update references to include reference for C-SSRS.

Section 11 References

Mundt JC, Greist JH, Gelenberg AJ, Katzelnick DJ, Jefferson JW, Modell JG. Feasibility and validation of a computer-automated Columbia-Suicide Severity

Rating Scale using interactive voice response technology. J Psychiat Res. 2010; 44(16):1224-1228.

33. Update Abbreviations table to include protocol changes.

Section 12 Appendices, Section 12.1 Appendix 1: Abbreviations and Trademarks

CRP	C-reactive Protein
C-SSRS	**Columbia-Suicide Severity Rating Scale**
CTA	Computed Tomography Angiography
CV	Cardiovascular
DBL	**Database lock**
dL	Deciliter

Administrative changes

Updated author list and Table of Contents