NCT03600805

AMENDED CLINICAL TRIAL PROTOCOL NO. 01

COMPOUND: Kevzara®/Sarilumab (SAR153191)

A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of sarilumab in patients with giant cell arteritis

STUDY NUMBER: EFC15068

Version Number:	1	EudraCT: IND Number(s): WHO universal trial number:	2017-002988-18 100632 U1111-1200-2184
Date:	12-Sep-2018	Total number of pages:	150

NAMES AND ADDRESSES OF

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OTHER EMERGENCY TELEPHONE NUMBERS		

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/Countries impacted by amendement	Date, version
Amended Clinical Trial Protocol 01	All	12-Sep-2018, version 1 (electronic 2.0)
Original Protocol	All	09-Feb-2018, version 1 (electronic 4.0)

AMENDMENT PROTOCOL 01 (12-Sep-2018)

This amended protocol (Amendment 01) is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The overall rationale for the changes implemented in the protocol amendment is to address several comments raised by the European Regulatory Authorities during the initial protocol review.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary – Statistical Consideration AND Section 11.1 Determination of sample size	More details on the power calculations were added.	The assumed treatment effects used for the power calculations were added for clarity.
Section 4.1 Benefit and Risk assessment	This sub-section related to benefit and risk assessment was created.	This sub-section of benefit and risk assessment was created to address a specific request from the European Regulatory Authorities and to align it with the current protocol template of the Sponsor.
Section 8.4 Methods of assigning patients to treatment group	More details about the randomization procedure (blocked randomization schedule) were added.	Additional detail was added to this section to provide clarity on the randomization procedure, particularly pertaining to the blocked randomization and stratification process employed in the study.
Section 11.4.2.1 Analysis of primary efficacy endpoint(s)	The non-inferiority test between Sarilumab 200 mg q2w arm and the placebo with 52 week taper arm was removed.	Based on the results from the GiACTA study, the non-inferiority test is deemed as unnecessary and thus removed from the protocol
Section 11.4.2.3 Multiplicity considerations	The hierarchical testing approach including the testing sequence for the secondary endpoints were clarified.	Details on the hierarchical testing sequence for the secondary endpoints were added for clarification to address a specific request from the European Regulatory Authorities.

CLINICAL TRIAL SUMMARY

COMPOUND: Sarilumab	**STUDY No.: EFC15068**
TITLE	A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of sarilumab in patients with giant cell arteritis.
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	Phase 3
STUDY OBJECTIVE(S)	**Primary objective:** • To evaluate the efficacy of sarilumab in patients with giant cell arteritis (GCA) as assessed by the proportion of patients with sustained remission at Week 52 for sarilumab compared to placebo, in combination with a 26-week corticosteroid (CS) tapering course. **Secondary objective(s):** • To demonstrate the efficacy of sarilumab in patients with GCA compared to placebo, in combination with (either 26- or 52-week) CS taper with regards to: - Clinical responses (such as responses based on disease remission rates, time to first disease flare) over time. - Cumulative CS (including prednisone) exposure. • To assess the safety (including immunogenicity) and tolerability of sarilumab in patients with GCA. • To measure sarilumab serum concentrations in patients with GCA. • To assess the effect of sarilumab on sparing glucocorticoid toxicity as measured by glucocorticoid toxicity index (GTI). **Other objectives:** • To assess the effect of sarilumab on physician assessment of disease activity as measured by a visual analogue scale (MD-VAS). • To assess the effect of sarilumab compared with placebo, in combination with a 26-week CS taper as on a variety of patient reported outcome (PRO) concepts including fatigue (FACIT-Fatigue), health status (EuroQol five-dimensional three-level questionnaire [EQ-5D-3L], and Short form-36 [SF-36v2]), physical functioning (health assessment questionnaire disability index [HAQ-DI]), including pain (visual analogue scale) and patient assessment of disease activity (visual analogue scale). • To assess the impact of erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP) levels on remission status. • To characterize the disease activity of GCA patients while on steroid taper or sarilumab treatment in a subset of patients using comprehensive approaches to evaluate circulating immune cell types. • To characterize the disease activity of GCA patients while on steroid taper or sarilumab treatment by evaluating circulating proteins, genetics and gene expression in consenting patients.

STUDY DESIGN	This is a multicenter, randomized, double-blind, placebo-controlled 52-week study with a 24-week post-treatment follow up phase, evaluating the efficacy and safety of sarilumab in patients with GCA. Patients with GCA (new onset or refractory [eg, disease relapse] GCA defined as below) will be randomized to 4 parallel treatment groups with sarilumab 200 mg every 2 weeks (q2w), 150 mg q2w, or placebo q2w plus 26 week prednisone taper, or placebo with standardized prednisone taper of 52 weeks at a ratio of 2:1:1:2 as described below. Randomization will be stratified by the starting dose of prednisone at baseline (<30 mg/day or ≥30 mg/day). • Treatment Group A: sarilumab 200 mg q2w with a 26 week taper of CS. • Treatment Group B: sarilumab 150 mg q2w with a 26 week taper of CS. • Treatment Group C: sarilumab matching placebo q2w with a 26 week taper of CS. • Treatment Group D: sarilumab matching placebo q2w with a 52 week taper of CS. Patients will be dosed with prednisone between 20 to 60 mg/day at the time of randomization (baseline) and initiate taper according to the protocol defined schedule. Patients will have up to 7 weeks to taper down to prednisone dose of 20 mg/day following randomization. If, for example, the patient is randomized on 20 mg prednisone per day, the patient will start the blinded, standardized prednisone taper 1-week after randomization. For other patients randomized on higher prednisone doses, upon reaching prednisone of 20 mg/day, patients will be initiated on a blinded, standardized taper of prednisone of up to 26 weeks or up to 52 weeks from time of randomization. The protocol will aim to enroll at least 30% of new onset patients, therefore, the Sponsor will reserve the possibility to cap enrolment of refractory patients to ≤70% of total patients randomized. For the management of predefined neutropenia, thrombocytopenia and alanine aminotransferase increases, study drug(sarilumab or matching placebo) must be temporarily withheld, and may be reduced to sarilumab 150 mg q2w (for patients randomized to the 200 mg q2w arm only) based on Investigator judgment. The request for dose reduction will be managed via IRT and the sarilumab dose prior to and following the dose reduction will remain blinded to site and Sponsor (for patients in the sarilumab 150 mg or sarilumab matching placebo groups, there will be only a sham dose reduction to maintain the blind). During the course of study, for patients in need of rescue therapy as per Investigator judgment, CS should be the agent of first choice. Patients may continue subcutaneous (SC) administration of sarilumab or matching placebo only if CS is used as rescue therapy. If the patients remain symptomatic despite CS rescue therapy, then other treatment options including nonbiological immunosuppressive drugs may be used and the patient must be discontinued from the study treatment and considered a nonresponder. All patients who prematurely and permanently discontinue study medication will be asked to return to the site for study assessments as per protocol until end of study (EOS) evaluation.

STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** • Diagnosis of GCA classified according to the following criteria: - Age ≥50 years - History of ESR ≥50 mm/hour (or CRP >25 mg/L) - 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) or symptoms of polymyalgia (defined as shoulder and/or hip girdle pain associated with inflammatory stiffness). - Presence of at least one of the following: Temporal artery biopsy revealing features of GCA; Evidence of large-vessel vasculitis by angiography or cross-sectional imaging (angiography, computed tomography angiography [CTA], magnetic resonance angiography [MRA], or positron emission tomography-computed tomography [PET-CT], ultrasound). • New onset active disease or refractory active disease according to the following criteria: - New onset active disease is defined as: Diagnosis within 6 weeks of baseline. - Refractory active disease is defined as: Diagnosis >6 weeks before baseline and previous treatment with ≥40 mg/day prednisone (or equivalent) for at least 2 consecutive weeks at a time. This includes patients who have achieved remission in the past but have a flare in the disease again or patients who have not been able to achieve complete remission since diagnosis of GCA. • At least one of the following symptoms of GCA within 6 weeks of baseline: - Unequivocal cranial symptoms of GCA (such as 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 polymyalgia rheumatica (PMR) (defined as shoulder and/or hip girdle pain associated with inflammatory stiffness). - Other features judged by the Investigator to be consistent with GCA or PMR flares (ie, new or worsened extremity claudication, fever not associated with infection). • Either ESR ≥30 mm/hour or CRP ≥10 mg/L within 6 weeks of baseline. • Receiving or able to receive prednisone 20 to 60 mg/day for the treatment of active GCA. Note: Sites that will consider inclusion of patients in the study using ultrasound as part of screening and diagnostic process for relevant disease status confirmation should only employ this method following completion of certification by the Sponsor (details of the ultrasound certification process are found in the manual).

	Exclusion criteria: • Organ transplantation recipient (except corneas, unless it is within 3 months prior to baseline visit). • Major ischemic event, unrelated to GCA, within 12 weeks of screening. • Prior treatment with any of the following: - Janus kinase (JAK) inhibitor within 4 weeks of baseline. - Alkylating agents including cyclophosphamide within 6 months of baseline. - Tumor necrosis factor (TNF) inhibitors within 2 to 8 weeks of, or less than at least 5 half-lives have elapsed prior to, baseline, whichever is longer. - Abatacept within 8 weeks of baseline. - Anakinra within 1-week of baseline. • Therapeutic failure with biological Interleukin 6/(R) (IL-6/(R) antagonist. • Evidence of serious, uncontrolled concomitant disease (eg, cardiovascular, respiratory, hepatic, renal, endocrine, etc,).
Total expected number of patients	Approximately 360
STUDY TREATMENT(s)	
Investigational medicinal product-1	Sarilumab or placebo.
Formulation:	Single-use prefilled glass syringes of sarilumab 200 mg, sarilumab 150 mg or matching placebo for sarilumab.
Route(s) of administration:	Subcutaneous (SC) route, in abdomen or thigh, or upper arm.
Dose regimen:	Sarilumab 200 mg, sarilumab 150 mg or matching placebo is to be administered q2w.
Investigational medicinal product-2:	Prednisone or placebo
Formulation:	Over-encapsulated tablets/tablets/capsule
Route(s) of administration:	Oral
Dose regimen	During the open-label prednisone period: • Prednisone once a day with dose level from 20 to 60 mg depending on the starting prednisone dose at randomization During the double-blind prednisone period: • Prednisone and/or matching placebo, once a day with dose level as per the prednisone protocol defined tapering regimen.
Noninvestigational medicinal product(s):	The chosen rescue therapy, including CS, as per Investigator judgment.
ENDPOINT(S)	**Primary endpoint:** Proportion of patients achieving sustained remission at Week 52. Sustained remission at Week 52 is defined by having met all of the following parameters: • Achievement of disease remission no later than Week 12. AND

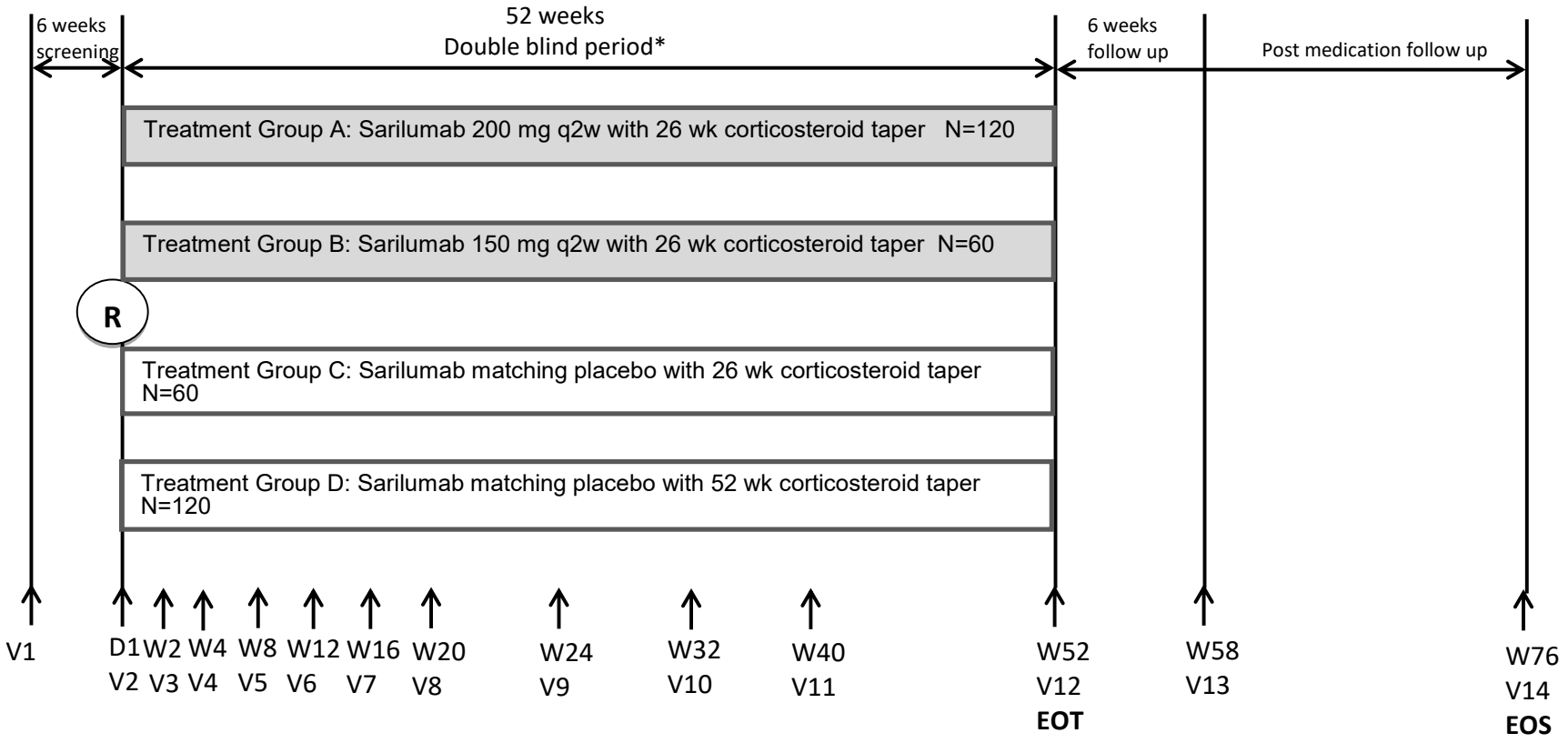
	• Absence of disease flare from Week 12 through Week 52. AND • Normalization of CRP (to <10 mg/L, with an absence of successive elevations to ≥10 mg/L) from Week 12 through Week 52. AND • Successful adherence to the prednisone taper from Week 12 through Week 52. Disease remission is defined as resolution of signs and symptoms of GCA, and normalization of CRP (<10 mg/L). Note: A single CRP elevation (≥10 mg/L) is not considered absence of remission unless CRP remained elevated (≥10 mg/L) at the next study visit. Flare is defined as either 1) recurrence of signs and symptoms attributable to active GCA plus an increase in CS dose due to GCA, or 2) elevation of ESR attributable to active GCA plus an increase in CS dose due to GCA. Increase in CS dose is defined as: • Any dose increase during the protocol defined steroid taper. • Reinitiation of prednisone therapy after the protocol defined taper has been completed. **Secondary endpoint(s):** ***Efficacy:*** • Summary of components of the sustained remission composite measure at Week 52. • Total cumulative CS (including prednisone) dose over 52 weeks. • Proportion of patients achieving disease remission at 2. • Time to first GCA flare. • Glucocorticoid toxicity index (GTI) (total score and domain-specified component scores) ***Safety:*** • Adverse events (AEs), laboratory values (including antidrug antibody [ADA], vital signs. ***Pharmacokinetic:*** • Concentrations of sarilumab in serum. ***Pharmacodynamic:*** • Changes in ESR and CRP over time. • Changes of IL-6 level and soluble IL-6 receptor. • Changes in markers of inflammation and disease activity over time as assessed in circulating immune cell types, circulating proteins and gene expression changes. **Other efficacy endpoints:** • Physician global assessment of disease activity - visual analog scale (MD-VAS).

	• PROs (changes from baseline for the following): - EuroQol 5 dimension questionnaire; 3-level version (EQ-5D-3L) - index score and visual analogue scale score. - Short-form 36-item questionnaire (SF-36v2) - domain scores, and physical and mental component summary scores - Functional assessment of chronic illness therapy fatigue scale (FACIT-fatigue) - total score. - Health Assessment Questionnaire Disability Index (HAQ-DI) - total score, pain score, patient global impression score
ASSESSMENT SCHEDULE	The study will consist of the following visits: • Visit 1 (D -42 - D -1): Screening • Visit 2 (D1): Baseline, randomization, first study drug administration • Visit 2 to 12 (D1-Week 52): on treatment (double-blind phase) • Visit 12 (Week 52): End of Treatment (EOT) visit (last sarilumab or matching placebo administration at Week 50) • Visit 13 (Week 58): 6 weeks post-treatment follow up visit • Visit 14 (Week 76): EOS visit Patient's CS tapering period may vary (maximum of 52 weeks) depending on the dose of daily prednisone at the time of randomization. At screening and baseline visits, a physical examination to assess disease activity and general health will be performed. Patients will be assessed for active or latent tuberculosis (TB) at baseline and during the study. Laboratory tests includes hematology, chemistry, lipids, glucose, insulin, antinuclear antibodies (ANA), glycosylated hemoglobin A1c (HbA1c), urinalysis, human immunodeficiency virus (HIV), Hepatitis B and C, serum and plasma for biomarkers and a 12-lead electrocardiogram (ECG). A serum pregnancy test for women of child bearing potential (WOCBP) will be obtained at screening as well. Blood samples for circulating proteins (serum and plasma) and for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) will be collected from each consenting patient, by signing off the additional research program part (optional) included in the main informed consent forms. Safety assessments are done at each study visit and include AEs, serious adverse events (SAEs) and adverse events of special interest (AESIs) including but not limited to neutropenia, thrombocytopenia, elevations in hepatic enzymes leading to permanent discontinuation and TB, and potential opportunistic infections. A dual assessor approach will be required in order to maintain the blind during the double-blind treatment period with sarilumab, placebo, and prednisone. Efficacy Assessor should be a rheumatologist or other skilled GCA assessor and may be the Principal Investigator; they will be responsible for completing the overall evaluation and management of GCA disease activity. The Safety Assessor should be a physician; they will be responsible for assessing and managing any safety concerns of the patient during the course of the study including access to the patient's laboratory data and AEs, performing assessments related to GTI. The

	Safety Assessor cannot be the Efficacy Assessor. Patients and Investigators must respect the visit schedule per study flow chart. If a visit date is changed, the next visit should take place according to the original schedule. Blood samples in a subset of patients will be collected to evaluate circulating immune cell phenotype.
STATISTICAL CONSIDERATIONS	**Sample size determination:** Based on the results from GiACTA, a trial that evaluated the safety and efficacy of tocilizumab (another IL-6 receptor antagonist similar to sarilumab) in patients with GCA, it is expected that the sustained remission rate at Week 52 (ie, the primary endpoint) will be approximately 14% for Group C (placebo + 26 week taper), approximately 18% for Group D (placebo + 52 week taper), and approximately 54% for sarilumab 200 mg q2w. A slightly lower sustained remission rate of approximately 50% is assumed for sarilumab 150 mg q2w. The proposed sample sizes will provide at least 90% overall power for all the 4 between-group comparisons (between 200 mg q2w and 2 placebo groups, and between 150 mg q2w and 2 placebo groups) on the primary endpoint. All tests will be performed at 0.01 significance level (2-sided). **Analysis population:** The primary efficacy analysis population will be the intent-to-treat (ITT) population, which consists of all randomized patients. All patients will be analyzed according to the treatment to which they are randomized. The safety population will include all randomized patients who have received at least one dose of the study medication. All patients will be analyzed according to the treatment they have actually received. **Primary analysis:** The rate of sustained remission at Week 52 will be analyzed using a Cochran-Mantel-Haenszel test stratified by any randomization strata. A significance level of 0.01 will be used, and the primary comparison will be between the sarilumab 200 mg q2w arm and the placebo arm with 26-week taper. **Analysis of secondary endpoints:** Other binary endpoints will be analyzed using the same approach. The cumulative prednisone dose will be analyzed using a nonparametric van Elteren test stratified by baseline prednisone dose. Time to event analysis will use Kaplan-Meier estimates and a log-rank test.
DURATION OF STUDY PERIOD (per patient)	Total duration of study per patient is expected to be approximately 82 weeks: • Up to 6 weeks screening period. • 52 weeks treatment period (sarilumab or placebo, double-blind phase). • 24 weeks post-treatment follow up period.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



Patients will be randomized to 4 groups with the ratio of 2:1:1:2

*Patients experiencing a disease flare may be rescued with open-label treatment as per Investigator judgment during the study treatment period.

1.2 STUDY FLOW CHART

VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12 (EOT)	V13	V14 (EOS)
DAY	D -42 to D -1	D1	D15 (±3)	D29 (±3)	D57 (±3)	D85 (±3)	D113 (±3)	D141 (±3)	D169 (±3)	D225 (±3)	D281 (±3)	D365 (±3)	D407 (±3)	D532 (±3)
WEEK		Wk 0	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Wk 52	Wk 58	Wk 76
Eligibility														
Written informed consent	X													
Inclusion/exclusion criteria[a]	X[a]	X												
Patient demography	X													
Medical/surgical/smoking/alcohol history	X													
Prior medication history	X													
Family cardiovascular history	X													
Full physical examination	X											X		
Targeted physical examination[b]		X				X			X		X			
Confirm eligibility		X												
Randomization		X												
Call IRT	X	X	X	X	X	X	X	X	X	X	X	X		X
Treatment														
Initial treatment kit assignment (IRT)		X												
IMP administration[c]		X	X	X	X	X	X	X	X[d]	X[d]	X[d]	X		
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense patient diary (for study medications)		X	X	X	X	X	X	X	X	X	X			
Compliance/review patient diary			X	X	X	X	X	X	X	X	X	X		

VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12 (EOT)	V13	V14 (EOS)
DAY	D -42 to D -1	D1	D15 (±3)	D29 (±3)	D57 (±3)	D85 (±3)	D113 (±3)	D141 (±3)	D169 (±3)	D225 (±3)	D281 (±3)	D365 (±3)	D407 (±3)	D532 (±3)
WEEK		Wk 0	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Wk 52	Wk 58	Wk 76
Vital signs														
Temperature, heart rate, blood pressure	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X				X			X		X	X		
Height	X													
Efficacy														
GCA clinical assessments (including disease flare)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PROs[e]		X				X			X			X		
Physician Global Assessment (MD-VAS)		X				X			X			X		
GTI Assessment (excluding Bone Density assessment)		X				X			X		X	X		
Bone density assessment[f]		X										X		
Safety														
AE/SAE recording														
Tuberculosis assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	
QuantiFERON®	X													
Chest X-ray[g]	X													
Laboratory testing														
Hematology[h]	X	X		X		X			X		X	X		
Chemistry[i]	X	X		X		X			X		X	X		
ANA		X										X		

VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12 (EOT)	V13	V14 (EOS)
DAY	D -42 to D -1	D1	D15 (±3)	D29 (±3)	D57 (±3)	D85 (±3)	D113 (±3)	D141 (±3)	D169 (±3)	D225 (±3)	D281 (±3)	D365 (±3)	D407 (±3)	D532 (±3)
WEEK		Wk 0	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Wk 52	Wk 58	Wk 76
Fasting lipids[j, k]/fasting glucose, fasting insulin[j]	X			X		X			X		X	X		
HbA1c	X			X		X			X		X	X		
CRP[l]	X	X	X	X	X	X	X	X	X	X	X	X		
ESR[l]	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis[m]	X													
Virology[n]	X													
Serum pregnancy test[o]	X													
Urine pregnancy test[o]		X		X	X	X	X	X	X	X	X	X		
12-lead ECG	X													
Serum sarilumab[j]		X	X	X		X	X		X[p]			X	X	
Anti-drug antibody[j]		X				X			X			X	X	
Genotyping and biomarkers[j,														
Biomarkers-IL-6 and sIL-6R		X	X			X			X			X		
Blood for circulating immune cell phenotyping[q]		X		X					X					
Future Use of Samples for Circulating proteins (serum/ plasma)[r] (optional)		X	X			X			X			X		

VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12 (EOT)	V13	V14 (EOS)
DAY	D -42 to D -1	D1	D15 (±3)	D29 (±3)	D57 (±3)	D85 (±3)	D113 (±3)	D141 (±3)	D169 (±3)	D225 (±3)	D281 (±3)	D365 (±3)	D407 (±3)	D532 (±3)
WEEK		Wk 0	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Wk 52	Wk 58	Wk 76
DNA[S] (optional)		X												
RNA[S] (optional)		X	X											

AE = Adverse event; ANA = Antinuclear antibodies; CRP = C-reactive protein; D = Day; DNA = Deoxyribonucleic acid; ECG = Electrocardiogram; EOT = End of treatment; EOS = End of study; EQ-5D-3L = EuroQol five-dimensional three-level questionnaire; ESR = Erythrocyte sedimentation rate; FACIT-Fatigue = Functional assessment of chronic illness therapy fatigue scale; GCA = Giant cell arteritis; GTI = Glucocorticoid toxicity index; HAQ-DI = Health assessment questionnaire disability index; HbA1c = Hemoglobin A1c; HBsAg = Hepatitis B surface antigen; HBcore Ab = Hepatitis B core antibodies; HCV = Hepatitis C virus; IL = Interleukin; IMP = Investigational medicinal product; IRT = Interactive response technology; MD-VAS = Physician global assessment of disease activity- visual analog scale; MRI = Magnetic resonance imaging; Pain VAS = Pain visual analog scale; PROs = Patient reported outcomes; Pt-VAS = Patient global assessment of disease activity – visual analog scale; RNA = Ribonucleic acid; SAE = Serious adverse event; SF-36v2 = Short form 36 version 2; TB = Tuberculosis; V = Visit; Wk = Week.

a If ultrasound is being used as a diagnostic tool of GCA, the image needs to be submitted to the central reader for confirmation of eligibility.

b Targeted physical examination: head, eyes, ears, neck and throat, skin, respiratory, cardiovascular, neurologic, lymphatic examinations and abdominal examination.

c Last administration of sarilumab is at Week 50.

d Where the visit interval exceeds 4 weeks, interim shipments of IMP to patients home may be performed using direct to patient (DTP) shipping (according to local regulations and logistics), in order to provide the patient with only 4 weeks IMP at a time in order to minimize compliance errors.

e Patient Reported Outcomes include EQ-5D-3L, FACIT-Fatigue, SF-36v2, HAQ-DI (including Pain VAS and Pt-VAS).

f Bone mineral density assessment must be performed during baseline if not already available within 12 weeks prior to screening visit. A ±2 week time window is allowed at baseline visit and -2 week time window is allowed at EOT visit.

g Posterior-Anterior chest X-ray must be performed during screening if not already available within 12 weeks prior to screening visit.
A standard PA chest X-ray (lateral view is also recommended but not required) is required during the screening period if no chest imaging (X-ray, Computed Tomography [CT], MRI) is available within the previous 12 weeks of V1 that clearly documents the exclusion of TB (or >12 weeks, if appropriate according to local guidelines and requirements for screening of active TB). In countries for which a specific approval procedure for the X-ray is required by a different committee than the local ethics committee/Institutional review board (EC/IRB), a chest MRI between V1 and V2 can be performed.

h Hematology (blood to be drawn before drug administration): Hemoglobin, hematocrit, red blood cell (RBC) count and morphology (if RBC count is abnormal), white blood cell (WBC) differential, platelet count, absolute neutrophil count (ANC).

i Chemistry(blood to be drawn before drug administration): Sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine and creatinine clearance, calcium, phosphate, total protein, albumin, alanine aminotransferase (ALT) (SGPT), aspartate aminotransferase (AST) (SGOT), alkaline phosphatase (ALP), total bilirubin, conjugated bilirubin, unconjugated bilirubin, lactate dehydrogenase (LDH), uric acid.

j Blood to be drawn before drug administration.

k Lipids: Triglycerides (TG), total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol.

l CRP and ESR results will be blinded to Investigator (except screening and baseline). ESR kits will be provided by the central laboratory while the test will be performed locally at the site, results will be blinded to Investigator and staff directly involved in management of study patient, except safety assessor.

m Urinalysis dipstick: specific gravity, pH, glucose, ketones, blood, protein, nitrite, leukocytes, urobilinogen and bilirubin. If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory.

n Human immunodeficiency virus antibodies (a separate local Informed Consent may need to be obtained if applicable); Hepatitis B: HBsAg, total HB core Ab, Hep B Surface Antibody, and Hep B viral DNA (if necessary); Hepatitis C: HCV-antibodies.

o In women of child-bearing potential.

p Additional sample is to be drawn 4-7 days after Wk 24 dosing.

q Immune cell phenotyping may be performed in only a subset of patients as determined by IRT system.

r Future use Samples (for consented patients only).

s Pharmacogenetic Research Informed Consent for collecting and sequencing DNA and RNA samples has to be obtained before any sampling. One DNA (at baseline) and RNA sample (predose) for sequencing sampling time point at baseline and V3 are needed.

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

3 LIST OF ABBREVIATIONS

ADA:	anti-drug antibody
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
BP:	blood pressure
CRFs:	case report forms
CRP:	C-reactive protein
CS:	corticosteroid
DMARDs:	disease modifying anti rheumatic drugs
DNA:	deoxyribonucleic acid
ECG:	electrocardiogram
eCRF:	electronic case report form
EOS:	end of study
EOT:	End of Treatment
EQ-5D-3L:	EuroQol five-dimensional three-level questionnaire
ESR:	Erythrocyte sedimentation rate
FACIT-Fatigue:	functional assessment of chronic illness therapy fatigue scale
GCA:	giant cell arteritis
GTI:	glucocorticoid toxicity index
HAQ-DI:	health assessment questionnaire disability index
HbA1c:	Hemoglobin A1c
HR:	heart rate
IB:	investigator's brochure
ICH:	International Conference on Harmonisation
IEC:	independent ethics committee
Ig:	immunoglobulins
IL-6:	Interleukin 6
IRB:	institutional review board
IRT:	interactive response technology
LDL:	low-density lipoprotein
LFT:	liver function test
mAb:	monoclonal antibody
Max:	maximum
MD-VAS:	physician global assessment of disease activity- visual analog scale
Min:	minimum
NIMP:	noninvestigational medicinal product
PD:	pharmacodynamics
PFS:	prefilled syringe
PK:	pharmacokinetics
PMR:	polymyalgia rheumatica

PRO:	patient reported outcome
q2w:	every 2 Weeks
RA:	rheumatoid arthritis
RNA:	ribonucleic acid
SAA:	serum amyloid A
SAE:	serious adverse event
SC:	subcutaneous
SD:	standard deviation
SF-36v2:	short form 36 version 2
sIL-6R:	soluble IL-6 receptor
TB:	tuberculosis
TBI:	tuberculosis infection
TEAEs:	treatment-emergent AEs
ULN:	upper limits of normal
WOCBP:	woman of child-bearing potential

4 INTRODUCTION AND RATIONALE

Giant cell arteritis (also known as temporal arteritis; GCA) is a chronic, immune-mediated, systemic inflammatory vasculitis that affects medium-sized and large vessels. It is one of the most common types of vasculitis, and usually affects individuals older than 50 years and has a prevalence that ranges from 24 to 280 cases per 100 000 persons in Western countries (1, 2). The vascular involvement can be widespread and variable, including the cranial vascular beds, aorta and primary and secondary branches of the aorta, such as the subclavian and axillary arteries. Clinical manifestations of GCA are indicative of the site of vessel affected, such as headaches, scalp tenderness, jaw claudication and vision loss that are characteristic of cranial vascular involvement while disease involving the subclavian and axillary arteries may manifest as claudication, abnormal pulses and blood pressures (BP), paresthesias, etc in the affected extremity (3). Histologically, all layers of the vessel walls are involved at affected sites, consisting of granulomatous inflammatory infiltrate of activated CD4+ T-cells, macrophages and giant cells. Diagnosis involves a typical constellation of clinical signs/symptoms (eg, headaches, visual disturbances, jaw claudication) and corroborating laboratory abnormalities (eg, elevated acute phase reactants) and radiographic or histological evidence of vasculitis (3, 4, 5).

The precise cause of GCA is unknown. Both the adaptive and innate immune responses have been implicated in the pathogenesis of GCA. It is hypothesized that dysregulation of the innate and adaptive immune response leads to abnormal activation of dendritic cells which attract and activate CD4+ T-cells and macrophages to the vessel wall, which then release proinflammatory cytokines that are responsible for the cascade of inflammatory activities and injuries to the vessels that are characteristics of GCA (4, 5, 6). As a result of the stress and injury, the innate immune system produces the acute-phase systemic response through a cascade of signals where interleukin-6 (IL-6) plays a critical role (7, 8).

Interleukin 6 (IL-6) is a pleiotropic cytokine produced by T-cells, B-cells, macrophages, endothelial cells, and fibroblasts upon different stimuli. The IL-6 pathway is located at the intersection of the innate and adaptive immune systems and, if down-regulated, has the potential to inhibit inflammatory responses. In GCA patients, IL-6 is up-regulated within inflamed arteries and its concentration in the peripheral circulation is elevated compared to healthy controls, serum IL-6 levels mirror disease activity and decline with adequate corticosteroid (CS) treatment. It has been speculated that IL-6R blockade may ameliorate vascular inflammation through several mechanisms. Recent reports from the evaluation of tocilizumab as a therapy for GCA, including a randomized, double-blind, placebo-controlled trial, suggest that blockade of the IL-6 signaling pathway is effective for the treatment of GCA (9, 10, 11).

The current standard of care for GCA, CS therapy, is a suboptimal treatment strategy. Although high dose CSs have generally been effective for the treatment of acute disease and control of inflammation, usually a year or more of coritcosteroid (CS) therapy is required for maintenance of remission or control of disease activity (3, 12, 13, 14). More than 85% of patients suffer from CS-related side effects, which are associated with substantial toxicities, and the elderly population, such as those diagnosed with GCA, are especially at risk for the toxicities associated with long term CS use. In addition, there is a high rate (over 50%) of relapse or flare of the

disease when CS is tapered (13, 15) and persistently active vascular inflammation despite ongoing CS therapy has been demonstrated in animal models and confirmed in patients who lack overt clinical symptoms. Aside from CS, there are limited highly effective treatment options for GCA. Thus, there remains a high unmet medical need for effective treatment that can maintain remission of GCA and spare patients the toxicities of CSs. Tocilizumab, an IL-6R antagonist, has been shown to be effective for the treatment of GCA in open-label treatment and in recent double-blind, placebo-controlled studies (9, 10, 11) and has received recent approval for the treatment of GCA in both the US and Europe.

Sarilumab, a human immunoglobulin (Ig) IgG1 monoclonal antibody (mAb), targets the IL-6R and inhibits IL-6 signaling. In this study, GCA patients will be treated with sarilumab. Sarilumab has been evaluated for the treatment of patients with moderate to severe active rheumatoid arthritis (RA) and has demonstrated superior efficacy compared to placebo when administered on background disease modifying antirheumatic drugs (DMARDs), and superior efficacy compared to another biologic (adalimumab) when administered as monotherapy with an acceptable safety profile consistent with this class of therapy. Sarilumab may be an effective and safe therapy for the treatment of patients with active GCA and sparing patients the toxicities associated with chronic CS therapy. To this end, the current proposed study will evaluate the efficacy and safety of sarilumab in patients with active GCA.

The efficacy and safety of sarilumab have been evaluated in Phase 2 and 3 studies of the RA clinical development program across different segments of the RA populations. Patients with sarilumab treatment showed clinically relevant and significant improvements compared with placebo or active comparator either in combination with methotrexate (MTX) or csDMARDs or as monotherapy, respectively.

In addition to clinical development for RA, sarilumab has also been studied in patients with ankylosing spondylitis and noninfectious uveitis. Overall, the safety observations from these studies were consistent with what has been observed in patients with RA.

The primary dose of sarilumab for this study/indication (ie, 200 mg subcutaneous [SC] every 2 weeks [q2w]) and a second dose (150 mg SC q2w) are selected based largely on the aggregate data from the sarilumab RA clinical development program.

Five different doses of sarilumab were evaluated in a Phase 2 placebo-controlled dose-ranging study in patients with RA, EFC11072 Part A: 100 mg q2w, 150 mg q2w, 100 mg once a week (qw), 200 mg q2w, and 150 mg qw. In this study, the effect on free soluble IL6R-alpha (sIL6Rα) and C-reactive protein (CRP) levels and on efficacy endpoints related to signs and symptoms of RA was apparent at doses of 150 mg q2w or above. A plateau was reached for pharmacodynamics (PD) biomarkers and endpoints at the 200 mg q2w dose, with a further increase in exposure by 2.7-fold (at 150 mg qw) providing, a marginal change in the responses. Therefore, the 200 mg q2w dose delivered sarilumab concentrations near target saturation. In addition, evaluation of the PD effects on RA biological markers of disease activity and inflammation, which are similar to those found in GCA patients, revealed that reduction of CRP and/or serum amyloid A (SAA) levels to a normal range was apparent at sarilumab trough concentrations of 1 mg/L or above. More patients treated with sarilumab 200 mg q2w compared to 150 mg q2w showed trough levels at or exceeding 1 mg/L throughout the dosing interval (86% versus 61%). In addition to the

commonly observed, elevated acute phase reactants, such as erythrocyte sedimentation rate (ESR) and CRP, circulating levels of IL-6 are significantly elevated in GCA patients (40 to 50 pg/mL) compared to healthy controls (16, 17), and these levels are generally higher than those observed in established RA patients, which range from 21 to 36 pg/mL in circulation. Therefore, based on available pharmacokinetic (PK)/PD data from the RA clinical development program and the higher levels of IL-6 in GCA patients, the 200 mg q2w dose is more likely to be the effective dose for the treatment of GCA.

Although both the 200 mg q2w and 150 mg q2w doses have demonstrated robust clinical efficacy in the RA clinical development program with suppression of biological markers of disease and inflammation similar to those found in GCA patients with an acceptable safety profile, the higher dose has a generally more favorable efficacy response (refer Investigator's Brochure [IB] for additional details). Consequently for the treatment of patients with moderate to severe RA, the approved starting dose of sarilumab is 200 mg q2w with the option to decrease to 150 mg q2w for laboratory abnormalities. Therefore, the sarilumab 200 mg q2w dose is selected for evaluation in this study and for the primary comparison while a second dose of sarilumab 150 mg q2w is added to provide additional information on efficacy and safety in GCA patients.

4.1 BENEFIT AND RISK ASSESSMENT

The available aggregate nonclinical and clinical data from the sarilumab development program in RA have demonstrated a potent anti-inflammatory effect and significant clinical benefit for patients with active RA via blockade of the IL-6 signaling pathway, which is also thought to play a key role in the pathogenesis of GCA. Therefore, treatment of GCA patients with sarilumab may lead to clinical benefits as observed in patients with active RA. This likely benefit with sarilumab is further supported by the pivotal GiACTA trial (a phase 3 study which evaluated efficacy and safety of tocilizimab in GCA patients [9]) that resulted in the approval of a similar IL-6 inhibitor, tocilizumab, for the treatment of GCA. Because of the similarity of sarilumab to tocilizumab and a study design that mirrors the successful GiACTA trial, it is expected that the current study will demonstrate a similar efficacy for sarilumab in GCA. Sarilumab is already approved for the treatment of rheumatoid arthritis in multiple countries.

Based on the safety profile of sarilumab available to date and other biological DMARDs, important identified risks include serious infections, neutropenia and hypersensitivity reactions; important potential risks to be considered with sarilumab administration, consistent with this class of therapy, include laboratory abnormalities and the potential clinical consequences, such as thrombocytopenia and the potential risk of bleeding, clinically evident hepatic injury with elevated hepatic transaminases, and lipid abnormalities and potential increased risk of major adverse cardiovascular event (MACE). Other potential important risks include increased risk of malignancy and gastrointestinal perforation. Various risk mitigation strategies are either built into the eligibility criteria (Section 7.1 and Section 7.2) to exclude those with conditions that may jeopardize their safety or into other sections of the protocol (Section 10.4 and Section 10.7) for monitoring and management of certain risks/adverse events (eg, neutropenia, thrombocytopenia, liver transaminase elevation, etc).

Based upon the overall safety and efficacy data of the sarilumab program in RA, the comparability of sarilumab to tocilizumab and the positive GiACTA trial, the benefit/risk assessment favors the study of sarilumab in patients with GCA. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of sarilumab may be found in the Investigator's Brochure.

5 STUDY OBJECTIVES

5.1 PRIMARY

To evaluate the efficacy of sarilumab in patients with GCA as assessed by the proportion of patients with sustained remission at Week 52 for sarilumab compared to placebo, in combination with a 26-week CS tapering course.

5.2 SECONDARY

- To demonstrate the efficacy of sarilumab in patients with GCA compared to placebo, in combination with (either 26 or 52 weeks) CS tapering course with regards to:
  - Clinical responses (such as responses based on disease remission rates, time to first disease flare) over time.
  - Cumulative CS (including prednisone) exposure.
- To assess the safety (including immunogenicity) and tolerability of sarilumab in patients with GCA.
- To measure sarilumab serum concentrations in patients with GCA.
- To assess the effect of sarilumab on sparing glucocorticoid toxicity as measured by glucocorticoid toxicity index (GTI).

5.3 OTHER

- To assess the effect of sarilumab on physician assessment of disease activity as measured by a visual analogue scale (MD-VAS).
- To assess the effect of sarilumab compared with placebo, in combination with a 26-week CS taper as on a variety of patient reported outcome (PRO) concepts including fatigue (FACIT-Fatigue), health status (EuroQol five-dimensional three-level questionnaire [EQ-5D-3L], Short form 36 version 2 [SF-36v2]), physical functioning (health assessment questionnaire disability index [HAQ-DI]), including pain (visual analogue scale) and patient assessment of disease activity (visual analogue scale).
- To assess the impact of ESR/CRP levels on remission status.
- To characterize the disease activity of GCA patients while on steroid taper or sarilumab treatment in a subset of patients using comprehensive approaches to evaluate circulating immune cell types.
- To characterize the disease activity of GCA patients while on steroid taper or sarilumab treatment by evaluating circulating proteins, genetics and gene expression in consenting patients.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This is a multicenter, randomized, double-blind, placebo-controlled 52-week Phase 3 study with a 24-week post-treatment follow up phase, evaluating the efficacy and safety of sarilumab in patients with GCA.

Approximately 360 patients with GCA (new onset or refractory [eg, disease relapse] GCA) who meet the entry criteria will be randomized to 4 parallel treatment groups with sarilumab 200 mg q2w, 150 mg q2w, or placebo q2w plus 26-week prednisone taper, or placebo q2w with 52-week standardized prednisone taper at a ratio of 2:1:1:2 as described below. The protocol will aim to enroll at least 30% of new onset patients, therefore, the Sponsor will reserve the possibility to cap enrolment of refractory patients to ≤70% of total patients randomized. Randomization will be stratified by the starting dose of prednisone at baseline (<30 mg/day or ≥30 mg/day).

- Treatment Group A: sarilumab 200 mg q2w with a 26-week taper of CS.
- Treatment Group B: sarilumab 150 mg q2w with a 26-week taper of CS.
- Treatment Group C: sarilumab matching placebo q2w with a 26-week taper of CS.
- Treatment Group D: sarilumab matching placebo q2w with a 52-week taper of CS.

It is important to optimize CS treatment prior to randomization to minimize the risk of adverse sequelae from GCA. Patients will be dosed with prednisone between 20 to 60 mg/day at the time of randomization (baseline) and initiate taper according to the protocol defined schedule. Patients will be initiated on a standardized taper of prednisone from the time of randomization. The taper will initially be open label; patients will have between 1 to 7 weeks to taper prednisone dose to 20 mg/day following randomization.

The further tapering of prednisone once a dose of 20 mg/day is achieved will be done in a blinded manner. To achieve the appropriate daily dose during this phase, patient will receive a combination of prednisone and/or placebo to prednisone depending on the assigned treatment group and associated taper regimen.

The total tapering period (open label plus double blind prednisone) will be between 46 weeks to 52 weeks depending on the initial prednisone dose at randomization.

At each site visit, the patient's disease will be assessed to determine whether the patient can adhere to the protocol defined prednisone taper schedule.

During the course of study, for patients in need of rescue therapy as per Investigator judgment, CS should be the agent of first choice. Patients may continue SC administration of sarilumab or matching placebo only if CS is used as rescue therapy. If the patients remain symptomatic despite CS rescue therapy, then other treatment options including nonbiological immunosuppressive

drugs may be used and the patient must be discontinued from the study treatment and considered a nonresponder.

If the patient or Investigator decides to discontinue the administration of blinded sarilumab injections, then the patient will be asked to return to the site for study assessments as per protocol until end of study (EOS) evaluation, unless the patient cannot or does not wish to continue the assessments, in which case an early withdrawal visit and safety follow up should be performed. It is recommended that patients complete Visit 13, if possible.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

Total duration of study participation for each patient is up to 82 weeks:

- Up to 6 weeks screening period.
- 52-week treatment period (sarilumab or placebo, double-blind phase).
- 24-weeks post treatment follow up period.

6.2.2 Determination of end of clinical trial (all patients)

The last patient last visit will occur when the last patient has completed the 24-week follow up period (EOS). The end of the clinical trial is defined as the last patient's last visit.

6.3 INTERIM ANALYSIS

No interim analysis is planned.

Primary analysis at Week 52 will be conducted after the final patient has completed the double-blind treatment period and all data have been verified.

Patients will continue into the 24-week posttreatment follow up period with the database lock occurring after the last patient has completed the EOS visit.

6.4 STUDY COMMITTEES

Central review and certification of diagnostic ultrasounds

If ultrasound is used to diagnose GCA and determine patient eligibility, the ultrasound images will be centrally reviewed by an expert rheumatologist (from a group of expert rheumatologists) specialized in the performance and interpretation of diagnostic ultrasounds of the vasculitis in order to confirm the diagnosis. Additionally, the same group of expert rheumatologists will also serve to help certify the sites who wish to have the option of using ultrasound in the diagnosis of GCA for their patients.

6.5 DISCUSSION OF STUDY DESIGN AND CHOICE OF CONTROL GROUPS

EFC15068 has been designed as a 52-week, double-blind, placebo-controlled, randomized, comparator study with a 24-week posttreatment follow up phase, to evaluate the efficacy and safety of sarilumab in patients with GCA. The 52-week study treatment duration reflects the standard duration of corticosterioid therapy required to ensure sustained remission for patients with GCA (hence, the primary endpoint of sustained remission is at Week 52). This duration of treatment is consistent with that in published interventional studies in GCA (11, 18).

Approximately 360 patients who have either newly diagnosed GCA or have refractory active GCA, will be enrolled and randomized into 4 different arms to receive either sarilumab 200 mg q2w with 26-week prednisone taper (Group A) or sarilumab 150 mg q2w (Group B) with 26-week prednisone taper or sarilumab matching placebo with prednisone taper periods of either 26 weeks (Group C) or 52 weeks (Group D) in the ratio of 2:1:1:2.

The 26-week taper is selected to demonstrate that sarilumab can enable patients to taper off CS earlier rather than the usual prolonged taper of 52 weeks with CS alone. The ability to taper off of CS rapidly (26 weeks taper period as opposed to the usual tapering regimen of a year or more) while maintaining disease remission would represent an important clinically meaningful benefit. The 52-week taper mimicks the usual care with CS and serves as a calibrator arm. Therefore, the primary comparison will be between Group A (sarilumab 200 mg q2w) and Group C (placebo sarilumab) where a 26 week taper of CS regimen will be used in both arms. Group B will evaluate a second dose of sarilumab (150 mg q2w) also with a 26 week taper of CS. Group D will evaluate the effect of placebo sarilumab with a 52-week taper of CS that reflects usual care, and will serve as a calibrator for further benefit risk assessment.

The Weeks 12 to 52 period assesses the “sustainability” of the remission that should be achieved by Week 12 as this is the anticipated timepoint where most patients should have achieved remission in usual care with steroids. After completion of the 52-week, double-blind, placebo-controlled treatment period, patients will be followed for another 24 weeks to assess the durability of the treatment response.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Diagnosis of GCA classified according to the following criteria:

- Age ≥50 years.
- History of ESR ≥50 mm/hour (or CRP >25 mg/L).
- 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) or symptoms of polymyalgia (defined as shoulder and/or hip girdle pain associated with inflammatory stiffness).
- Presence of at least one of the following: Temporal artery biopsy revealing features of GCA; Evidence of large-vessel vasculitis by angiography or cross-sectional imaging (angiography, computed tomography angiography [CTA], magnetic resonance angiography [MRA] or positron emission tomography-computed tomography [PET-CT], ultrasound).

Note: For countries where local EC does not approve an angiography, CTA or PET-CT or for which a specific approval procedure for angiography, CTA or PET-CT is required by a different committee than the local EC/IRB, patients may be enrolled using temporal artery biopsy or ultrasound.

Note: Sites that will consider inclusion of patients in the study using ultrasound as part of screening and diagnostic process for relevant disease status confirmation should only employ this method following completion of certification by the sponsor (details of the ultrasound certification process are found in the manual).

I 02. New onset active disease or refractory active disease according to the following criteria:

- New onset active disease is defined as:
  - Diagnosis within 6 weeks of baseline.
- Refractory active disease is defined as:
  - Diagnosis >6 weeks before baseline and previous treatment with ≥40 mg/day prednisone (or equivalent) for at least 2 consecutive weeks at a time. This includes patients who have achieved remission in the past but have a flare in the disease again or patients who have not been able to achieve complete remission since diagnosis of GCA.

I 03. At least one of the following symptoms of GCA within 6 weeks of baseline.

- 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 polymyalgia rheumatica (PMR) (defined as shoulder and/or hip girdle pain associated with inflammatory stiffness).
- Other features judged by the Investigator to be consistent with GCA or PMR flares (ie, new or worsened extremity claudication, fever not associated with infection).

I 04. Either ESR ≥30 mm/hour or CRP ≥10 mg/L within 6 weeks of baseline must be present.

I 05. Receiving or able to receive prednisone 20 to 60 mg/day for the treatment of active GCA.

I 06. Signed written informed consent.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. Organ transplantation recipient (except corneas, unless it is within 3 months prior to baseline visit).

E 02. Major ischemic event, unrelated to GCA, within 12 weeks of screening.

E 03. Any prior use of the following therapies, for the treatment of GCA:

- Janus kinase (JAK) inhibitor (eg, tofacitinib) within 4 weeks of baseline.
- Cell-depletion agents (eg, anti CD20) without evidence of recovery of B cells to baseline level.
- Abatacept within 8 weeks of baseline.
- Anakinra within 1 week of baseline.
- Tumor necrosis factor (TNF) inhibitors within 2 to 8 weeks (etanercept within 2 weeks; infliximab, certolizumab, golimumab, or adalimumab within 8 weeks), or less than at least 5 half-lives have elapsed prior to baseline, whichever is longer.

E 04. Therapeutic failure, including inadequate response or intolerance, or contraindication, to biological IL-6/(R) antagonist (prior experience with IL-6/(R) antagonist that was terminated for reasons unrelated to therapeutic failure at least 3 months before baseline is not exclusionary).

E 05. Use of any alkylating agents including cyclophosphamide (CYC) within 6 months of baseline.

E 06. Use of immunosuppressants, such as hydroxychloroquine (HCQ), cyclosporine (CsA), azathioprine (AZA) or mycophenolate mofetil (MMF) or leflunomide (LEF) within 4 weeks of baseline.(Use of MTX not exceeding 25 mg per week and have been stable for at least 3 months prior to baseline is not exclusionary [see Section 8.8]).

E 07. Concurrent use of systemic CS for conditions other than GCA.

E 08. Use of IV CS at a dose equivalent to 100 mg of methylprednisolone or higher within 8 weeks of baseline for GCA therapy.

E 09. Participation in any clinical research study that evaluated an investigational drug or therapy within 5 half-lives or 60 days of the screening visit, whichever is longer.

E 10. History of alcohol or drug abuse within 5 years prior to the screening visit.

E 11. Patient who withdraws consent during the screening period (following signing of the informed consent form).

E 12. Based on Investigator judgment, conditions/situations such as:

- Patients with short life expectancy
- Patient is the INVESTIGATOR or any subinvestigator, Research Assistant, Pharmacist, Study Coordinator, other staff or relative thereof, directly involved in the conduct of the study, or, as applicable to employee of site/Investigator or Sponsor.
- Uncooperative, or any condition, that could make the patient potentially noncompliant to the study procedures, etc, and individuals who are institutionalized due to regulatory or legal order.

7.2.2 Exclusion criteria related to the current knowledge of Sanofi compound

E 13. Pregnant or breastfeeding woman.

E 14. Woman of childbearing potential (WOCBP) not protected by highly-effective contraceptive method(s) of birth control (as defined in Appendix A), and/or who are unwilling or unable to be tested for pregnancy.

E 15. Exclusion related to tuberculosis (TB):

- Active TB or a history of incompletely treated TB.
- Quantiferon positive patients (no active disease) are excluded from the study unless the following conditions are met:
  - Patients with a history of prior documented completed chemoprophylaxis for latent tuberculosis infection (TBI) (eg, acceptable treatments would be 9 months of isoniazid 300 mg PO daily or equivalent proven regimen per local guidelines) or

treatment of active TBI, has obtained consultation with a specialist to rule out or treat active TBI.

- Patients with no prior history of chemoprophylaxis for latent TBI or treatment for active TBI, have obtained consultation with a specialist to initiate an appropriate regimen of chemoprophylaxis, based on local epidemiology and applicable guidelines and the patient has demonstrated compliance and has tolerated treatment for ≥1 month.
- Consultation with and prior approval from sponsor are required in either of the aforementioned scenarios.

- Clinically significant abnormality consistent with prior/active TB infection based upon chest radiograph with at least posterior-anterior (PA) view (radiograph must be taken within 12 weeks prior to screening visit or during the screening period). Additional lateral view is recommended but not required.
- Suspected extrapulmonary TB infection.
- Patients at high risk of contracting TB, such as close contact with individuals with active or latent TB.
- Patient who received Bacille Calmette Guerin (BCG)-vaccination within 12 months prior to screening.

E 16. Patients with a history of invasive opportunistic infections, including but not limited to histoplasmosis, listeriosis, coccidioidomycosis, candidiasis, Pneumocystis jirovecii, aspergillosis despite resolution or John Cunningham (JC) virus (progressive multifocal leukoencephalopathy [PML]).

E 17. Patients with fever associated with infection (>38ºC), or chronic, persistent, or recurring infection(s) requiring active treatment with antibiotics, antivirals, or antifungals within 4 weeks prior to the screening visit or other frequent recurrent infections deemed unacceptable as per Investigator judgment.

E 18. Patients with uncontrolled diabetes mellitus, defined as Hemoglobin A1c (HbA1c) ≥9% at the screening visit.

E 19. Patients with nonhealed/healing skin ulcers.

E 20. Patients who received any live, attenuated vaccine within 3 months prior to the baseline visit, such as *varicella-zoster* virus, oral polio or measles-mumps-rubella vaccines.

E 21. Patients who had a positive test at screening for hepatitis B surface antigen (HBs-Ag) or total hepatitis B core antibody positive with negative hepatitis B surface antibody (HBs-Ab), or total hepatitis B core antibody positive with positive HBs-Ab and presence of hepatitis B virus (HBV) deoxyribonucleic acid (DNA).

E 22. Patients who are positive for hepatitis C antibodies at the screening visit.

E 23. Patients, who have a positive test at the screening visit or who previously had a positive test, or who are suspected to be positive for human immunodeficiency virus (HIV).

E 24. Patients with a history of recurrent herpes zoster or active herpes zoster.

E 25. Patients with a history of prior articular or prosthetic joint infection.

E 26. Prior or current history of malignancy, including lymphoproliferative diseases, other than adequately-treated carcinoma in-situ of the cervix, nonmetastatic squamous cell or basal cell carcinoma of the skin, within 5 years prior to the baseline visit.

E 27. Prior or current history of other significant concomitant illness(es) that, according to Investigator's judgment, would adversely affect the patient's participation in the study. These include, but are not limited to, cardiovascular (including stage III or IV cardiac failure according to the New York Heart Association classification), renal, neurological (including demyelinating disease), active infectious diseases, endocrinological, gastrointestinal, hepato-biliary, metabolic, pulmonary, non-malignant lymphoproliferative disease or other lymphatic disease(s).

E 28. Any patient who has had surgery within 4 weeks prior to the screening visit or with planned surgery during the course of the study.

E 29. Patients with a history of a systemic hypersensitivity reaction, other than localized injection site reaction, to any biologic drug and known hypersensitivity to any constituent of the sarilumab product.

E 30. Patients with any of the following laboratory abnormalities at the screening visit:

- Hemoglobin <8.5 g/dL.
- White blood cells <3000/mm^3.
- Neutrophils <2000/mm^3.
- Platelet count <150 000 cells/mm^3.
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1.5 x upper limits of normal (ULN), unless this is a manifestation of active GCA in the opinion of the Investigator.
- Bilirubin (total) >ULN, unless documented Gilbert's disease diagnosed by genetic testing.
- Presence of severe uncontrolled hypercholesterolemia (>350 mg/dL, 9.1 mmol/L) or hypertriglyceridemia (>500 mg/dL, 5.6 mmol/L).
- Patients with a calculated creatinine clearance <30 mL/minute (using Cockroft-Gault formula).

Note: Laboratory parameters may be repeated during the screening period if judged to be spurious or due to technical error in order to determine eligibility.

E 31. Patients with a history of inflammatory bowel disease or severe diverticulitis or previous gastrointestinal perforation.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

Details of IMPs are provided in Table 1.

There are 2 IMPs to be administered in this study:

- Sarilumab or sarilumab matching placebo
- Prednisone or prednisone matching placebo

In order to differentiate these 2 IMPs, sarilumab and sarilumab matching placebo are named as SC IMP, prednisone and prednisone matching placebo are named as oral IMP.

Table 1 - Summary of investigational medicinal products

	Name of IMP	Pharmaceutical forms	Dose of drug per administration	Route and method of administration	Treatment duration
Double blind phase of sarilumab	Sarilumab	Single-use 1.14 mL prefilled glass syringes containing 175 mg/mL (200 mg) & Single-use 1.14 mL prefilled glass syringes containing 131.6 mg/ml (150 mg)	Sarilumab 200 mg & Sarilumab 150 mg	Subcutaneous	Entire 52 week treatment period
Double blind phase of sarilumab	Sarilumab matching placebo	Placebo solution for injection	Matching placebo	Subcutaneous	Entire 52 week treatment period
Open label CS taper phase	Prednisone	5 mg & 20 mg Tablets	Refer to standard CS taper regimen Appendix B	Oral administration	1 to 7 weeks OL CS taper phase, depending on starting dose (refer to Appendix B)
Double blind CS taper phase	Prednisone	1 mg & 5 mg Capsules	Refer to standard CS taper regimen Appendix B	Oral administration	45 weeks DB CS taper phase (refer to Appendix B)

	Name of IMP	Pharmaceutical forms	Dose of drug per administration	Route and method of administration	Treatment duration
Double blind CS taper phase	Prednisone matching placebo	Capsules	Refer to standard CS taper regimen Appendix B	Oral administration	45 weeks DB CS taper phase (refer to Appendix B)
CS = corticosteroid; DB = double blind; IMP = investigational medicinal product; OL = open label.					

8.1.1 Sarilumab or matching placebo:

Additional detail regarding the method of administration

Formulation:

Sarilumab drug product will be provided as single-use 1.14 mL prefilled syringe (PFS) containing 131.6 mg/mL (150 mg), 175 mg/mL (200 mg) of sarilumab or placebo solution for SC injection. No preparation at the clinical site is required.

Route of Administration:

Sarilumab will be administered in non-affected skin subcutaneously in the abdomen or thigh when self-injected or in upper arm (lateral side) when injected by a professional or a non-professional caregiver. It is preferred that SC injection sites be alternated between the 4 quadrants of the abdomen (except the navel or waist area) or the thigh (front and side). Each drug administration requires a single injection.

Patients and/or their non-professional caregivers will be trained to prepare and administer study drug at the baseline visit. This training must be documented in the subject's study file. The study staff should review the patient's self-administration technique at Visit 2 (Week 0). For doses not given at the study site, diaries will be provided to record information pertaining to those injections. If the patient is unable or unwilling to administer study drug, arrangements must be made for a qualified site personnel or a caregiver to administer study drug doses that are not scheduled to be given at the study site.

Dose regimen:

The IMP (sarilumab or matching placebo) should be administered every 14 days as per protocol IMP administration schedule, however an IMP administration time window of ±3 days is permitted in exceptional circumstances (eg. Laboratory test result pending, or an ongoing adverse event (AE) or patient schedule difficulty). For subsequent IMP administrations the initial IMP administration schedule should be followed again (see Table 1).

Note: An interval of ≥11 days between 2 IMP doses must be maintained.

If the study visit is not performed at the site as scheduled, the dose will be administered as described above, either by the patient, qualified site personnel, and/or their caregiver(s).

On days when the patient has a study visit, the IMP will be administered after clinic procedures and blood collection.

Patients will be monitored for at least 30 minutes after each dose of sarilumab, or as per country specific requirements (eg, up to 2 hours) for any signs or symptoms of any medical events. In the case that the injection is administered by caregiver or self injection, patients should be instructed to monitor themselves for any signs or symptoms of any medical events.

The total duration of treatment is 52 weeks.

Dose modification/reduction:

Sarilumab dose 200 mg may be reduced in response to elevated liver transaminases, neutropenia, and/or thrombocytopenia. The request for dose reduction will be managed via interactive response technology (IRT) and the sarilumab dose prior to and following the dose reduction will remain blinded to site and Sponsor (for patients in the sarilumab 150 mg or sarilumab matching placebo groups, the other treatment groups there will be only a sham dose reduction to maintain the blind). Please see Section 10.7.2, Section 10.7.3 and Section 10.7.4 for further details. Once the dose is reduced, no further dose increase is permitted for the remainder of the study treatment period. Between the protocol-scheduled on-site visits, interim visits may be required for IMP dispensing. As an alternative to these visits, sarilumab or matching placebo may be supplied from the site to the patient via a Sponsor-approved courier company where allowed by local regulations and approved by the subject.

Post-trial access to sarilumab will be in compliance with all applicable national and local laws and regulations, including safety reporting obligations.

8.1.2 Prednisone or matching placebo:

Additional detail regarding the method of administration

Patients will be trained in the use of the weekly prednisone blister packs at the baseline visit. This training will include instruction on use of the blister packs in the appropriate order and use of the "spare" row of tablets/capsules in the case of loss of a tablet/capsule during dosing. The training must be documented in the patient's study file.

All patients will receive prednisone (at doses of 60 mg/day or less) and/or matching placebo (double-blind prednisone tapering phase only) following different standardized prednisone-taper regimen for treatment of GCA depending on the assigned treatment group. In the open-label phase all patients will receive prednisone tablets while in the double-blind prednisone tapering phase patients will receive encapsulated prednisone tablets in blinded packaging.

There will be 2 standardized CS-taper regimens defined:

- Up to 26 week taper (Group A, Group B and Group C).

- Up to 52 week taper (Group D).

There will be 2 phases for each prednisone taper regimen:

- Open-label phase (from 1 to 7 weeks): all patients will go through this phase in order to have the prednisone dose tapered down to 20 mg/day. Patients may start at 60 mg/day or any of the incremental dosages: 50 mg/day, 40 mg/day, 35 mg/day, 30 mg/day, 25 mg/day, or 20 mg/day. Patients will follow the tapering schedule as per Appendix B, completing the open-label phase and transitioning to the blinded phase of tapering after 1 to 7 weeks, depending on the prednisone dose at baseline (ie, patients starting on 35 mg/day will transition to the double-blind phase of tapering quicker than patients starting on 50 mg/day).
- Blinded phase (45 weeks): Over encapsulated prednisone and/or matching placebo will be used to maintain blinding of the taper regimen regardless of regimens that the patient is assigned to.

During the prednisone taper blinded phase, patients will be supplied with weekly blister packs which will be numbered and will clearly indicate the number of tablets to be taken per day. It is important that the blister packs be used in the correct order and that 7 days of dosing from each blister be taken by the patient before starting the next blister pack. If a patient visit is scheduled before the patient has used 7 days of a particular weekly blister pack, then this blister pack should be returned to the patient so that the patient can complete the remaining days of dosing with that blister pack before starting the next sequentially numbered blister pack. If doses have been missed, it is not necessary for patients to use the missed capsules before progressing to their next blister packs.

During the blinded taper, the daily encapsulated dose may contain prednisone, placebo, or a combination of the two. The number of capsules to be taken each day will vary but will not be indicative of the dosage of prednisone. The number of capsules to be taken daily may increase or decrease during the tapering schedule but will not exceed 5 capsules per day.

Refer to Appendix B for detailed standardized CS-taper regimen during the double-blind study treatment period.

Where the visit interval exceeds 4 weeks (eg. 8-week or 12-week visit interval), the patient may be provided with only the first 4 weeks of treatment during the visit, and interim visits may be required for IMP dispensing to the patient between the protocol-scheduled on-site visits. This is to ensure that the patient only receives a 4-week supply of prednisone weekly blisters at any time, to minimize potential compliance errors. Alternatively, the prednisone may be sent directly to the patient by the site via a Sponsor-approved courier company where allowed by local regulations and approved by the subject.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

Rescue therapy

At each study visit, an assessment of the patient's GCA disease status should be made. If the patient has no evidence for disease flare and is able to follow the per protocol prednisone taper schedule, the patient will continue with the per protocol prednisone taper of the study as per Appendix B for up to 52 weeks. If the patient experiences a disease flare or cannot adhere to the prednisone tapering schedule, then the patient must stop the per protocol prednisone taper and instead may receive rescue therapy, such as CSs, as per Investigator's clinical judgment. The patient should continue in the double-blind period of the study for the full 52 weeks and should continue to receive blinded SC injections unless contraindicated by safety concerns and complete the remainder of the study assessments.

Once the patients are on rescue therapy at the discretion of Investigators, it is not allowed for them to return to per protocol prednisone taper regimen.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

8.3.1.1 Blinding of IMP

A patient randomization list will be generated by the IRT. The lists of treatment kit numbers will be generated by the Sanofi Clinical Supplies Department. Both the randomization and treatment kit lists will be loaded into the IRT. The treatment kit numbers will be obtained by the Investigator at the time of patient randomization and at subsequent patient scheduled visits via IRT that will be available 24 hours a day.

Blinding of Sarilumab

Based on the double blind study design, the Investigators and patients will be blinded to the allocation of the sarilumab 200 mg group, sarilumab 150 mg group and sarilumab matching placebo groups.

Sarilumab and matching placebo will be provided in matching glass PFS in kits suitable for double blinding. For example, every 4 weeks, the patient will receive 1 sarilumab PFS kit.

In accordance with the double-blind design of the randomized treatment period, Investigators will remain blinded to study treatment and will not have access to the randomization (treatment codes) except under exceptional medical circumstances.

Blinding of prednisone

Based on the double blind study design, the Investigators and patients will be blinded to the allocation of the different standardized protocol defined CS-taper 26-week or 52-week regimens as assigned group.

Prednisone will be provided in weekly blister packs suitable for double blinding as per assigned protocol defined CS-taper regimen.

In accordance with the double-blind design of the randomized treatment period, Investigators will remain blinded to study treatment and will not have access to the randomization (treatment codes) except under exceptional medical circumstances. However, in the case where the Investigator choses to switch the patient to rescue treatment, such as in the case of a flare, the double blind prednisone doses that the patient had been taking prior to rescue will remain blinded.

8.3.1.2 Blinding of non investigational medicinal product

Not applicable.

8.3.2 Randomization code breaking during the study

In case of an AE, the code must only be broken in circumstances when knowledge of the IMP is required for treating the patient.

Code breaking can be performed at any time by using the proper module of the IRT and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator must document the date, time of day, and reason for code breaking.

If the blind is broken by the Investigator, for the above stated purpose, the patient must be withdrawn from treatment and will be asked to follow the instructions on Section 10.4.1 for the visits/assessments to be completed.

Knowledge of certain laboratory data may result in inadvertent unblinding of a patient's treatment. In order to maintain the blind, refer to the dual assessor manual.

At the facilities where the PK measurements, anti-drug antibody (ADA) and selected biomarkers are determined, the samples will be analyzed prior to database lock leading to unblinding of responsible bioanalysts. Bioanalysts are excluded from the clinical trial team.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The treatment kit number lists are generated centrally by Sanofi. The IMPs are packaged in accordance with these lists. Patients will be randomized to one of the treatment groups via an IRT. Both the randomization and treatment kit lists will be loaded into the IRT. A patient will be considered randomized when the first treatment number has been provided by the IRT.

Patients who meet the entry criteria will be randomized to 1 of the 4 treatment groups at the ratio of 2:1:1:2. Randomization will be stratified by baseline dose (which is the starting dose determined by Investigator on the day of randomization) of prednisone (<30 mg/day or ≥30 mg/day).

A blocked randomization schedule with records pre-allocated to each of the strata (baseline prednisone use <30 mg/day or ≥30 mg/day) will be used for this study. The first patient randomized to a stratum will be assigned to the first randomization entry from the randomization schedule pre-allocated to that stratum. Subsequent patients randomized to the same stratum will be assigned to the next available randomization entry from the randomization schedule pre-allocated to that stratum.

At the screening Visit 1 (Day -42 to Day -1), the site coordinator will contact the IRT to obtain a patient number for each patient who gives informed consent. Each patient will be allocated a patient number associated with the center and allocated in chronological order in each site.

At the baseline Visit 2 (Week 0, Day 1), after confirming eligibility of the patient for entry into the treatment period, the site coordinator will contact the IRT in order to receive the first treatment allocation kit numbers. At subsequent visits during the treatment period, the site coordinator will call IRT to obtain the next treatment kit numbers. A confirmation fax/e-mail will be sent to the site after each assignment.

Patients who fail to meet eligibility criteria may be rescreened once. A different patient identification will be issued. There is no requirement for a waiting period between the screen-failure and the rescreening. The IRT report will flag rescreened patients. Patients that are rescreened must sign a new consent form and the Visit 1 procedures must be repeated (chest X-ray taken within 12 weeks of the screening visit need not be repeated). Any previously randomized patient cannot be rescreened.

A randomized patient is defined as a patient who is registered and assigned a randomization number from the IRT.

8.5 INVESTIGATIONAL MEDICINAL PRODUCT PACKAGING AND LABELING

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

The investigational products will be supplied in treatment kit boxes that are labeled in accordance with the local regulatory specifications and requirements and content information, dosing instructions and precautionary statement (“for clinical use only”).

The number of treatment kits allocated to the patient will provide sufficient medication until the next clinic visit. An additional treatment kit, to provide medication to randomized patients in special circumstances, eg, a damaged kit, will be allocated by IRT if a “replacement call” is made to the IRT system.

8.6 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP/noninvestigational medicinal product (NIMP) in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

Control of IMP storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound must be managed according to the rules provided by the Sponsor.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 10.5.7).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for direct to patient [DTP] shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

Measures taken to ensure and document treatment compliance and IMP accountability include:

- Proper recording of treatment kit number or packaging number as required on appropriate electronic case report form (eCRF) page for accounting purposes.
- All medication treatment kits (whether empty or unused) are returned by the patient at each visit when a treatment dispensing is planned.
    - As the used PFS cannot be safely returned to the study site after administration of IMP, the completed patient injection diary (returned to the site at each visit), returned treatment kit boxes and any unused PFS will be used for drug accountability purposes.
    - All blister packs of prednisone treatment (whether empty or unused) are returned by the patient at each visit when a treatment dispensing is planned.

- The study coordinator tracks treatment accountability/compliance, either by diary, or by counting the number of used treatment kits/tablets/capsules and fills in the appropriate page of the patient treatment log.

The monitor in charge of the study then checks the data entered on the IMP administration page by comparing them with the IMP that has been retrieved and the patient treatment log form.

8.7.2 Return and/or destruction of treatments

A detailed treatment log of the destroyed IMP and NIMP (if applicable) will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team. The Investigator will not destroy the used and unused IMP unless the Sponsor provides written authorization.

8.8 LIST OF FORBIDDEN AND PERMITTED CONCOMITANT MEDICATIONS

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s).

The use of any biologics for treatment of GCA during the study is not permitted throughout the study treatment and until 6 weeks following the last SC IMP (sarilumab or matching placebo) administration unless otherwise indicated. If any of these treatments is used, the patient should be discontinued from IMP treatment but the patient will continue to be monitored for safety.

Administration of any live (attenuated) vaccine is contraindicated until 3 months following the last IMP (sarilumab or matching placebo) administration. Treatment with non-biological immunosuppressive drugs (such as alkylating agents, hydroxychloroquine, CsA, MMF, AZA, etc) is not permitted during the course of the study, unless used for the purpose of rescue therapy.

During the course of study, for patients in need of rescue therapy as per Investigator judgment, CS should be the agent of first choice. Patients may continue SC administration of sarilumab or matching placebo only if CS is used as rescue therapy. If the patients remain symptomatic despite CS rescue therapy, then other treatment options including nonbiological immunosuppressive drugs may be used and the patient must be discontinued from the study treatment and considered a nonresponder.

Methotrexate not exceeding 25 mg per week is permitted if the dose has been stable for at least 3 months prior to baseline. The dose should also remain stable (may be reduced or discontinued if for safety reasons, if necessary), but should not be initiated or increased throughout the study treatment duration and until 6 weeks following the last SC IMP (sarilumab or matching placebo) administration.

Treatment with any IMP other than sarilumab and prednisone defined by protocol is not permitted.

8.8.1 Steroids

There will be 2 standardized prednisone-taper regimens: one that extends for up to 26 weeks (Group A, B and C), the other for up to 52 weeks (Group D) (Appendix B). The total duration of prednisone taper in each particular case will depend on the initial dose required by patient as judged by the Investigator at enrollment.

If the patient develops an AE for a condition not related to GCA that requires a CS dose modification (eg, increase, or decrease of current concomitant oral prednisone or equivalent), or the introduction of a new oral or systemic steroid medication, the Sponsor must be notified at the time of the steroid dose modification to verify that the patient can continue to participate in the study. Furthermore, the dosage modification and AE must be recorded on the patient eCRF.

Intranasal, inhaled, ophthalmic or topical CS as per label are permitted, as needed throughout the course of the study.

8.8.2 Nonsteroidal anti-inflammatory drugs and analgesics

As there are limited treatment options for inter current pain, all analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs), are allowed. These analgesics must be interrupted 24 hours prior to efficacy assessment, including physical function and quality of life assessments.

Acetaminophen use should be limited to ≤4 g every 24 hours. Specific attention should be paid to coadministration of hepatotoxic drugs.

8.8.3 Treatment of dyslipidemia

Treatments for dyslipidemia, such as statins, are permitted. Any change and reason for change should be recorded on the patients' eCRF. Doses of medications for dyslipidemia should be stable for at least 6 weeks prior to screening visit. Anti-IL-6 drugs, including sarilumab are known to increase serum total cholesterol and this effect will be closely monitored during the study. If, during the treatment period of this study, patients are found to have significant increase in cholesterol levels, or other lipid abnormalities, then cholesterol lowering therapy with statins, or other treatment(s) for dyslipidemia, per American College of Cardiology (ACC)/American Heart Association (AHA) guideline or European Society of Cardiology (ESC)/the European Atherosclerosis Society (EAS) guidelines or local guidelines, should be initiated or the dose adjusted. A referral to a specialist should be considered when dyslipidemia is difficult to manage, such as patients who have elevated low-density lipoprotein (LDL) in spite of being treated with maximum dose of statins.

8.8.4 Glucocorticoid-induced osteopenia/osteoporosis prevention and treatment

Oral calcium, 25-hydroxy vitamin D supplementation, and/or bisphosphonate therapy (eg, alendronate 70 mg weekly or zolendronate 4 mg annually) for the prevention or treatment of glucocorticoid-induced osteopenia/osteoporosis are permitted, the doses and treatment duration should be according to local practice or clinical guidelines at the discretion of the Investigator.

8.8.5 CYP substrates

Interleukin-6 has been shown to reduce cytochrome (CY)P1A2, CYP2C9, CYP2C19, and CYP3A4 enzyme expression in in vitro studies. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as sarilumab, the formation of cytochrome P450 (CYP450) enzymes could be normalized, and as a result drugs that are metabolized by these CYP450 isoforms may have decreased levels when patients start receiving sarilumab. As a precautionary measure, drugs which are metabolized via these cytochromes and with a narrow therapeutic index should be adjusted if needed: doses should be increased to maintain efficacy after initiation of sarilumab and decreased after sarilumab is stopped. Some examples of CYP450 substrates with a narrow therapeutic index, requiring monitoring of effect are warfarin or monitoring of drug concentration include, but are not limited to, the following: warfarin, CsA, theophylline, digoxin, antiepileptics, such as carbamazepine (Carbatrol®, Tegretol®), divalproex (Depakote®), phenytoin (Dilantin®), or valproic acid (Depakene®); or antiarrhythmics, such as disopyramide (Norpace®), procainamide (Procan®, Pronestyl®), or quinidine (Quinidex®, Quin Release Quin-G®).

8.8.6 Anti-platelet therapy

Treatments with anti-platelet therapy (eg, aspirin or clopidogrel) are permitted, the doses and treatment duration should be according to the local practice at the discretion of the Investigator.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

9.1.1 Primary efficacy endpoint

Proportion of patients achieving sustained remission at Week 52. Sustained remission at Week 52 is defined by having met all of the following parameters:

- Achievement of disease remission not later than Week 12.

  AND

- Absence of disease flare from Week 12 through Week 52.

  AND

- Normalization of CRP (to <10 mg/L, with an absence of successive elevations to ≥10 mg/L) from Week 12 through Week 52, and

  AND

- Successful adherence to the prednisone taper from Week 12 through Week 52.

Disease remission is defined as resolution of signs and symptoms of GCA, and normalization of CRP (<10 mg/L).

Note: A single CRP elevation (≥10 mg/L) is not considered absence of remission unless CRP remained elevated (≥10 mg/L) at the next study visit.

Signs and symptoms of disease

Evaluation of clinical signs and symptoms by the Efficacy Assessor at every study visit according to the schedule of assessment will include the following:

- Symptoms of PMR as indicated by the Efficacy Assessor (morning stiffness and/or pain, in the shoulder and/or hip girdles)
- Cranial symptoms.
  - Localized headache.
  - Temporal artery or scalp tenderness.
  - Visual signs or symptoms such as acute or subacute vision loss due to arteritic anterior ischemic optic neuropathy (A-AION), transient blurry vision (generally monocular or at least affecting 1 eye at a time, but potentially affecting both eyes), diplopia.
  - Jaw or mouth pain, tongue claudication.

- Constitutional syndrome, including but not limited to fever, malaise, unintentional weight loss, night sweat, asthenia, fatigue, loss of appetite.
- New or worsened extremity claudication, bruits and asymmetrical pulses.
- Other features judged by the Investigator to be consistent with a GCA or PMR flare.

Flare is defined as either 1) recurrence of signs and symptoms attributable to active GCA plus an increase in CS dose due to GCA, or 2) elevation of ESR attributable to active GCA plus an increase in CS dose due to GCA. Increase in CS dose is defined as:

- Any dose increase during the protocol defined steroid taper.
- Reinitiation of prednisone therapy after the protocol defined taper has been completed.

Blinding of CRP and ESR assessment results

Investigators, including Efficacy Assessors, and patients will remain blinded to CRP and ESR results (except screening and baseline). Safety Assessors will also be blinded on post baseline CRP but will have access to ESR results.

ESR kits will be provided by the central laboratory while the test will be performed locally at site, results (the distance in millimeters (mm) that red blood cells has descended in 1 hour) will be blinded to Investigators including Efficacy Assessors and staff directly involved in efficacy assessment of study patients.

9.2 SECONDARY ENDPOINTS

9.2.1 Secondary efficacy endpoints

9.2.1.1 Components of the sustained remission composite measure at Week 52

- Proportion of patients who achieved disease remission by Week 12.
- Proportion of patients who have no disease flare from Week 12 through Week 52.
- Proportion of patients who have normalization of CRP (to <10 mg/L, with an absence of successive elevations to ≥10 mg/L) from Week 12 through Week 52.
- Proportion of patients who successfully adhere to the prednisone taper from Week 12 through Week 52.

9.2.1.2 Total cumulative corticosteroid (including prednisone) dose over 52 weeks

The total cumulative CS dose (including prednisone) over the 52-week period for each group will be analyzed.

9.2.1.3 Time to first GCA flare

The duration to first GCA flare from clinical remission up to 52 weeks for each group will be analyzed.

9.2.1.4 Glucocorticoid toxicity index and components

Glucocorticoid toxicity index (GTI) is a composite scale designed to assess glucocorticoid related morbidity and potential steroid-sparing effect of treatment alternatives. The Composite GTI and Specific List constitute the overall GTI. The composite GTI consists of nine domains and 31 items that assess the potential side effects of glucocorticoid, and include evaluation of body mass index (BMI), glucose tolerance, blood pressure, lipids, bone density, steroid myopathy, skin toxicity, neuropsychiatric toxicity and infection. These are the potential CS toxicities that are likely to occur during the course of a CS treatment and may vary depending on the extent of CS exposure, and that are weighted and scored (see Appendix C).

The domains of the Composite GTI will be assessed at V2 (baseline), V6 (Week 12), V9 (Week 24), V11 (Week 40) and V12 (Week 52) (except bone density which will be assessed at baseline and Week 52 only).

- Bone mineral density assessment will be performed at V2 (baseline) and V12 (Week 52) using Dual-Energy X-ray Absorptiometry (DXA) scan, The scan can be performed within ±2 weeks of baseline visit and -2 weeks of EOT visit, needs to include the lumbosacral and femoral neck regions. However, the baseline visit DXA scan is not required if there is one available within 12 weeks of baseline that includes the assessment of the lumbosacral and femoral neck regions. In order to minimize variability, the same machine should be used each time to obtain the scan and the machine should be well calibrated according to the recommendations of the machine's manual.

GC toxicity or the changes in GC toxicity (comparison with baseline data) for domains will be scored (score range from -36 to 439) based on the information from clinical laboratory assessments, vital sign assessments, concomitant medications and clinical assessments. The composite GTI can be reported as both a total score and domain-specific scores, in order to account for scenarios when improvements in certain domains compensate for worsening in others.

The Specific List consists of 11 domains and 23 items that are not weighted, and captures other CS related toxicities not found in the composite GTI (see Appendix C). Information related to the domains/items of the Specific List will be collected when available, but no prespecified assessments related to the domains in the Specific List (see Appendix D), unless for cause (19) are required within the conduct of this study protocol.

9.2.2 Safety endpoints

9.2.2.1 Adverse events

Refer to Section 10.5 to Section 10.7 for details.

9.2.2.2 Laboratory safety variables

The clinical laboratory data consist of blood analysis (including hematology, clinical chemistry) and urinalysis. Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

The following laboratory tests are performed, at designated visits specified the study flow charts (Section 1.2):

- Hematology: hemoglobin, hematocrit, red blood cell count and morphology (if red blood cell count is abnormal), white blood cell count, white blood cell differential, absolute neutrophil count and platelet count.
- Full chemistry profiles: blood urea nitrogen, calcium, chloride, bicarbonate, phosphate, creatinine and creatinine clearance, lactate dehydrogenase, sodium, potassium, total protein, uric acid, and albumin, alkaline phosphatase, ALT, AST, total bilirubin, conjugated bilirubin, and unconjugated bilirubin.
- ANA will be checked at baseline and End of Treatment (EOT) visits.
- Fasting lipids: total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides.
- Fasting glucose, fasting insulin and HbA1c.
- For women of child-bearing potential: serum pregnancy test beta-human chorionic gonadotropin (β-hCG) at screening (V1) only and urine pregnancy tests for the remainder of the study.
- QuantiFERON® -TB Gold evaluation (screening visit only).
- Human immunodeficiency virus-1/HIV-2 antibody testing (screening visit only).
- Hepatitis B and C serology (screening visit, or in case of liver injury): Hepatitis B: Hepatitis B surface antigen (HBsAg), total HB core Antibody, Hepatitis B surface Antibody, and Hepatitis B viral DNA (if necessary); Hepatitis C: HCV-antibodies.
- Urine analysis including specific gravity, pH, glucose, ketones, blood, protein, nitrite, leukocytes, urobilinogen, and bilirubin (by dipstick) at screening visit only. If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory.

Anti-drug antibody (see Section 9.4.2).

Specimens are submitted for analysis as per the instructions of the central laboratory.

9.2.2.3 Chest X-ray

A standard PA chest X-ray (lateral view is also recommended but not required) is required during the screening period if no chest imaging (X-ray, CT, MRI) is available within the previous 12 weeks of V1 that clearly documents the exclusion of TB (or >12 weeks, if appropriate according to local guidelines and requirements for screening of active TB). In countries for which a specific

approval procedure for the X-ray is required by a different committee than the local EC/IRB, a chest MRI between V1 and V2 can be performed. A radiologist or pulmonologist interpretation (signed and dated) should note the absence of calcified granulomas and/or pleural scaring and/or any findings consistent with TB. The information must be documented in the patient's chart and in the eCRF at the screening visit. In case of any symptom suggestive of TB at any time during the course of the study, a chest X-ray should be performed and conclusion recorded (see Section 10.7).

9.2.2.4 Vital signs

Vital signs include temperature, BP, and heart rate (HR). They will be collected at every site visit prior to IMP administration. Weight will be collected at the screening Visit 1 (Day -42 to Day -1), Visit 2 (Week 0), Visit 6 (Week 12), Visit 9 (Week 24), Visit 11 (Week 40) and Visit 12 (Week 52). Weight should be taken with the patient wearing undergarments or very light clothing and no shoes and with an empty bladder. The same scale is recommended to be used throughout the study. Height will be collected at Visit 1 during screening only.

Body temperature

Body temperature must be collected using the same method for a given patient. Any fever (body temperature ≥38°C) associated with infection should be recorded as an AE and the Investigator should perform all investigations necessary to rule out infection.

Blood pressure

Blood pressure must be measured, using the same method consistently. Blood pressure is determined at each study visit using the same well-calibrated apparatus. The same arm should be used to measure BP throughout the study. The blood pressure should also be obtained with the patient in the same position (recumbent preferred) each time.

9.2.2.5 Physical examination

A complete physical examination will be performed at the screening Visit 1 (Day -42 to Day -1) and Visit 12 (Week 52) or early termination visit, and a targeted physical examination will be performed at baseline visit (Visit 2), Visit 6 (Week 12), Visit 9 (Week 24) and Visit 11(Week 40). Any clinically significant abnormalities should be reported in the patient eCRF as medical history if observed at Visit 1 or reported as an AE if observed during subsequent visits.

9.2.2.6 Electrocardiogram variables

A standard 12-lead electrocardiogram (ECG) will be performed at the screening Visit 1 only (Day -42 to Day -1). It will be used to determine if there is any clinically significant finding that would preclude the patient from participating in the study safely per protocol.

9.3 OTHER EFFICACY ENDPOINTS

9.3.1 Clinical outcome assessments

9.3.1.1 Patient-reported outcomes

Patients will be asked to complete the PRO questionnaires described below at baseline, Week 12, Week 24 and Week 52. Translations of the PRO questionnaires, where not already available, will follow industry best practices (20).

9.3.1.1.1 The functional assessment of chronic illness therapy fatigue scale (FACIT-fatigue)

The functional assessment of chronic illness therapy fatigue scale (FACIT-Fatigue) is a generic PRO instrument which includes 13 items to measure fatigue. Each item is rated by patients on a 0 to 4 scale (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much). Scores are summarized to give a total score between 0 and 52. The recall period is the last 7 days (21) (see Appendix E).

9.3.1.1.2 EQ-5D-3L

The EQ-5D-3L is a generic PRO instrument which measures health status. There are two components to the EQ-5D; a health utility index score derived from 5 items addressing mobility, self-care, usual activities, pain/discomfort, and anxiety/depression "today", and a current ("right now") general health status score derived from a single 0-100 Visual Analog Scale (VAS) (see Appendix F). The items contributing to the EQ-5D-3L health utility index score each have the same 3-point response scale (1 = no problem, 2 = moderate problems, 3 = severe problems). The VAS is anchored with 'Best imaginable health state' and 'Worst imaginable health state' (22).

9.3.1.1.3 SF-36v2

The SF-36v2 is a short-form generic, 36-item PRO instrument that evaluates 8 multi-item dimensions of health: physical functioning (PF; 10 items), social functioning (SF; 2 items), role limitations due to physical problems (RP; 4 items), role limitations due to emotional problems (RE; 3 items), mental health (MH; 5 items), energy/vitality (VT; 4 items), bodily pain (BP; 2 items), and general health perception (GH; 5 items). For each dimension, item scores are coded, summed, and transformed on to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state). Two standardized summary scores can also be calculated from the SF-36v2; the physical component summary (PCS) and the mental health component summary (MCS) on a scale from 0-100 (23, 24) (see Appendix G).

9.3.1.1.4 HAQ-DI

The HAQ-DI was developed to assess physical functional status in adults with arthritis, but is now commonly used among many rheumatologic conditions. It contains 25 items: 20 4-point Likert-scale questions assessing 8 physical dimensions of activities of daily living (dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and errands and chores),

13 additional questions assessing use of assistive devices, and 8 additional questions assessing help received from another. The recall period is the last week. To calculate the HAQ-DI Score, there are 3 steps:

- Sum the 8 category scores by using the highest sub-category score from each category.
- Adjust for use of aids/devices and/or help from another person when indicated.
- Divide the summed category scores by the number of categories answered (must be a minimum of 6) to obtain a HAQ-DI score of 0-3 (3=worst functioning).

In addition to the above, the HAQ-DI has 2 additional questions, measured on 0 - 100 scales:

- How much pain have you had IN THE PAST WEEK?
- Please rate how well you are doing on a scale of 0 to 100 (0 represents "very well" and 100 represents "very poor" health).

These questions, measuring pain and global assessment respectively, are independently scored (see Appendix H).

9.3.1.2 Clinician-reported outcomes

9.3.1.2.1 Physician global assessment of disease activity- Visual Analog Scale [MD-VAS]

The efficacy assessor will be requested to rate the patient's disease activity on an anchored 100 mm horizontal VAS where 0 is considered the best disease activity and 100 the worst (see Appendix I).

9.4 PHARMACODYNAMICS

9.4.1 Pharmacodynamic variables

- Changes in ESR and CRP over time from baseline through Week 52.
- Changes of IL-6 level and soluble IL-6 receptor (sIL-6R) over time from baseline through Week 52.
- Changes in markers of inflammation and disease activity over time as assessed in circulating immune cell types, circulating proteins, and gene expression changes as follows (refer to Appendix J).
  - Markers of inflammation will be assessed in a subset of patient population during the study at V2 (baseline), V4 (Week 4), V9 (Week 24) as measured by immune cells phenotyping. In total 120 patients will be selected via IRT for this analysis, please refer to Lab Manual for detail.
    - 40 patients each in Group A and Group D
    - 20 patients each in Group B and Group C

- Disease activity assessment of GCA patients will be assessed via evaluation of circulating proteins and gene expression.

Serum and plasma samples will be collected at V2 (baseline), V3 (Week 2), V6 (Week12), V9 (Week 24), V12 (Week 52 EOT) for circulating protein measurements (a separate "Future Use of Samples" informed consent needs to be obtained) (refer to Section 9.5).

Deoxyribonucleic acid (DNA) samples will be collected at V2 (baseline), ribonucleic acid (RNA) samples will be collected at V2 (baseline) and/or V3 (Week 2) (refer to Section 1.2) for gene expression measurement (a separate "pharmacogenetics informed consent needs to be obtained", refer to Section 9.4.3).

9.4.2 Pharmacokinetics and antidrug antibodies

9.4.2.1 Sampling time

Predose blood samples at each study visit will be collected for determination of serum functional sarilumab, and serum ADA as designated on the randomized treatment period study flow chart Section 1.2). The date of collection should be recorded in the patient eCRF.

Note: Sarilumab concentrations (functional) in serum, and antidrug antibodies results are blinded to both Investigator and Sponsor.

If a serious adverse event (SAE) occurs in a patient, blood samples should be collected for determination of sarilumab concentration (functional), and ADA assessment at or near the onset and completion of the occurrence of the event, if possible. The exact date and time of sample collection and last dose must be recorded on the label and the unscheduled PK page in the eCRF should be filled in.

9.4.2.2 Sample handling procedure

Special procedures for collection, storage and shipping of serum are described in separate operational manuals.

9.4.2.3 Bioanalytical method

Serum samples will be assayed using validated methods as described in Table 2.

Table 2 - Summary of bioanalytical methods for functional sarilumab and antidrug antibody

Bioanalysis	Functional sarilumab	Antidrug antibody
Matrix	Serum	Serum
Analytical Technique	ELISA	Electrochemiluminescence
Site of Bioanalysis	Regeneron	Regeneron

ELISA = . Enzyme-linked immunosorbent assay

9.4.2.4 Pharmacokinetics parameters

Predose serum sarilumab concentrations at Week 0, sarilumab trough levels at Weeks 2, 4, 12, 16, 24, 52 and Week 58.

In addition, postdose sample will be taken 4 to 7 days after the Week 24/V9.

9.4.3 Pharmacogenetic assessment

9.4.3.1 Optional stored DNA and RNA samples

Pharmacogenetic testing is optional and voluntary. Written informed consent must be obtained before sampling.

For those patients who provided written consent to the collection of the optional pharmacogenetic samples, blood samples for exploratory genetic analysis of DNA and RNA will be collected at the study visit as specified in the study flow chart (Section 1.2), and these samples will be stored for future analysis. Specific procedures for collection, storage, and shipping of pharmacogenetic samples will be provided in a lab manual (refer Appendix K for the detailed information).

The blood DNA sample, and the DNA that is extracted, will be assigned a second number, a Genetic ID (de-identification code) that is different from the patient ID. This “double coding” is performed to separate a patient’s medical information and DNA data.

The clinical study data (coded by patient ID) will be stored in the clinical data management system (CDMS), which is a distinct database in a separate environment from the database containing the pharmacogenetic data (coded by Genetic ID). The key linking patient ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and pharmacogenetic data, for the purpose of data analysis, will be possible only by using this key, which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality.

The aliquots of DNA and RNA sent to the bioanalytical laboratories for specific genetic testing will be destroyed after completion of that specific analysis and issuance of the related analytical data (see Appendix K).

9.5 FUTURE USE OF SAMPLES

Not all of the samples collected during this study may be required for the tests planned in this clinical trial. For patient(s) who have consented to it, the samples that are archived, unused or left over after planned testing may be used for other research purposes (any genetic analysis subject to additional consent per Section 9.4.3.1). For subjects who have consented to it, archival blood sample(s) will be collected at the visits specified in the study flow chart (see Section 1.2). Additional details will be provided in the laboratory manual (refer Appendix J for the detailed information).

9.5.1 Serum and plasma for future biomarker analysis (circulating proteins)

Prior to sampling, informed consent agreeing to participate in this additional research program needs to be obtained as this is optional and voluntary. Once obtained, both serum and plasma will be collected at Visit 2 (baseline), Visit 3 (Week 2), Visit 6 (Week 12), Visit 9 (Week 24) and Visit 12 (Week 52).

These samples will remain labelled with the same identifiers used during the study (ie, patient ID). They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting subject confidentiality and personal data (see Section 14.3 and Section 14.5).

9.6 APPROPRIATENESS OF MEASUREMENTS

The goals of a new therapy for GCA are to reduce the cumulative dose of prednisone and thereby reduce the toxicity associated with prednisone while maintaining disease remission. To this end, the primary endpoint is a composite that includes, firstly, a requirement to achieve disease remission by Week 12 of study treatment to ensure that patients are having rapid, adequate control of disease activity. It also includes the ability to adhere to the predefined prednisone taper that represents a substantial reduction in prednisone exposure compared to usual care. Lastly it assesses the durability of treatment response (maintenance of remission) over an extended period of time compared to current usual prednisone treatment, which is important for a chronic disease, such as GCA. The secondary endpoints evaluate specific components of the primary endpoint and thereby provide additional evaluation of total CS use and disease activity to further assess the efficacy of sarilumab as a steroid-sparing treatment option in the target patient population.

The safety assessments are performed in accordance to the known profile of sarilumab and will further inform the safety profile of sarilumab when administered to GCA patients. The patient and clinician reported outcomes will further evaluate the potential clinical benefits of sarilumab in the treatment of GCA. The PK and PD assessments will provide additional information related to the exposure of sarilumab and biological effect of sarilumab in GCA patients.

10 STUDY PROCEDURES

10.1 INDEPENDENT EFFICACY AND SAFETY ASSESSORS

A dual assessor approach will be required during this study in order to maintain the blind during the double-blind treatment period with sarilumab, placebo, and prednisone. The precise definitions of the efficacy and safety assessors' roles and responsibilities are specified in the Dual Assessor Guidance Document supplied to sites. An overview of those definitions is provided below.

Efficacy Assessor

The Efficacy Assessor will be responsible for completing the overall evaluation and management of GCA disease activity including the following:

- Assessment of clinical signs and symptoms of GCA (without access to ESR and any central laboratory data including CRP).
- Assessment of adherence to the protocol defined prednisone taper regimen.
- Management of rescue medication which is led by Investigator per protocol.

The Efficacy Assessor should not have access to central laboratory results obtained per protocol. If knowledge of the ESR is absolutely required in making a medical decision related to disease activity, the Efficacy Assessor may request the last available value obtained per protocol from the Safety Assessor or obtain a local laboratory value for ESR. Otherwise it is strongly recommended for the Efficacy Assessor not to have access to any laboratory data. Additionally, if necessary for the management of any safety concern for a particular patient that cannot wait to be addressed by the Safety Assessor, the Efficacy Assessor may arrange for local laboratory assessments to be performed and will have access to the results of these assessments.

To ensure consistency of assessments, it is encouraged that efficacy evaluations throughout the study be conducted by the same Efficacy Assessor for all study visits for a given patient, whenever possible.

It is mandatory that assessments by the Efficacy Assessor be completed before assessments by the Safety Assessor.

The Efficacy Assessor may permanently discontinue oral IMP (prednisone as per taper regimen) and initiate rescue therapy in order to properly manage disease activity, if necessary. In such a scenario, the SC IMP (sarilumab or matching placebo) may continue per protocol unless nonbiological immunosuppressive drugs are used and a safety concern is raised by the Safety Assessor.

Safety Assessor

The Safety Assessor will be responsible for assessing and managing any safety concerns of the patient during the course of the study. The specific responsibilities include:

- Eliciting and recording of any clinical and/or laboratory AEs.
- Management of any clinical and/or laboratory AEs.
- Review of all laboratory data (except CRP after baseline).
- Perform the assessments related to GTI.

The Safety Assessor may temporarily (or permanently) discontinue IMP (SC and/or oral) during the management of an AE and only the Safety Assessor may reinitiate the IMP upon his/her discretion. If the IMP is permanently discontinued, both Efficacy and Safety Assessors should be informed in order to make subsequent medical management decisions.

10.2 VISIT SCHEDULE

It is preferred that all study visits that require fasting blood samples to take place in the morning. The study visits occur on the planned dates (relative to randomization date), as scheduled. The visit schedule should be adhered to within the ±3 day visit window. In general, PRO assessments should be completed at the study site as part of the visit (per study flow chart Section 1.2) but prior to any meaningful communication with a health care professional or any other study procedures, unless noted otherwise in the suggested order of the study procedures for each individual visit described below:

- Consent
- Eligibility
- Randomization
- PRO questionnaires
- GCA assessments
- Other clinical assessments and AE reporting
- Blood sampling
- IRT call to obtain resupply treatment
- Dose administration

10.2.1 Visit 1: Screening from Day -42 to Day -1

The following activities will be performed:

- An explanation of the purpose, procedures, potential risks, and benefits of this study will be provided to the patient.

- Informed consent signature and date will be collected.
- If required locally, the locally provided consent for the required HIV screening test will be collected.
- Call IRT to assign patient number and register screening visit.
- Patient demography will be recorded.
- Medical/surgical/smoking/alcohol history.
- Review of prior and concomitant medication history.
- Family cardiovascular history.
- Full physical examination.
- GCA clinical assessments (including disease flare).
- Measure vital signs (including systolic and diastolic BP [mmHg], HR [beats per minute], body temperature [°C], and height [cm]).
- Body weight [kg].
- Perform blood sampling (fasting) for the following tests:
  - Hematology, chemistry.
  - Fasting lipids, fasting glucose and fating insulin.
  - HbA1c.
  - CRP and ESR.
  - Virology.
  - Serum β-hCG pregnancy test (for WOCBP).
- Tuberculosis assessment including Quantiferon gold testing.
- Urinalysis (dipstick)
- 12-lead ECG.
- Perform chest X-ray if not performed at least 12 weeks prior to screening visit date.
- Confirmation of eligibility by the Investigator.
- Schedule a Visit 2 (D1, Week 0) within a maximum of 42 days from Visit 1.

Note: if the ultrasound is being used as a diagnostic tool for GCA to satisfy the Inclusion Criteria I01, the image needs to be submitted to the central reader for confirmation of eligibility.

10.2.2 Double blind period (52 weeks)

10.2.2.1 Visit 2/Baseline visit (Day 1, Week 0)

- Review of concomitant medication.
- Confirm eligibility by review of Inclusion/Exclusion Criteria.

  If the patient meets all the inclusion criteria and does not meet any exclusion criteria, please conduct the following procedures in the recommended order, if possible:
- Call IRT to randomize the patient and obtain the initial treatment kit assignments.
- If the patient has been selected to complete the immunophenotyping blood sampling, the system will provide this information during the call.
- Administer PRO questionnaires (EQ-5D, FACIT-Fatigue, SF-36v2, HAQ-DI) and VAS.

  Note: PRO questionnaires should be completed prior to any significant interaction with the study team and prior to any physical examination or sampling.
- Measure vital signs (including systolic and diastolic BP [mmHg], and HR [beats per minute], body temperature [°C]).
- Body weight (kg).
- GCA clinical assessments (including disease flare).
- Complete physician global assessment (MD-VAS).
- Inquire about AEs/SAEs.
- Tuberculosis assessment.
- Targeted physical examination (including head, eyes, ears, neck and throat, skin, respiratory, cardiovascular, neurologic, lymphatic examinations and abdominal examination).
- GTI Assessment.
- Bone density assessment by DXA (dual-energy x-ray absorptiometry) (±2 week time window is allowed at baseline visit).

Note: Bone density assessment is not required if already available within 12 weeks prior to screening visit.

- Perform blood sampling (prior to administration of IMP) for the following tests:
  - Hematology and chemistry.
  - ANA.
  - CRP and ESR.
  - Serum sarilumab and ADA.
  - Biomarkers IL-6, sIL-6R.

- Serum and plasma sampling for circulating protein (for consented patients only).
- Sample for DNA and RNA for those patients who have consented to pharmacogenetics.
- Sample for circulating immune cell phenotyping for patients identified to perform this test.

- Perform urine pregnancy test (for WOCBP).
- Dispense patient diary to record injections performed at home (date, time, injection location, and local reaction or any medical events pertaining to the injection).
- IMP training. Provide instructions on preparation and self-injection of the prefilled syringes and the use of the weekly blister packs of prednisone. Document this training in the patients study file. Note: If the patient is unable or unwilling to perform the SC injections themselves, arrangements must be made for qualified site personnel and/or caregiver to administer SC study drug every 2 weeks for doses that are not scheduled to be given at the study site.
- Dispense and administer IMP. Patients will be monitored for at least 30 minutes or up to 2 hours as per country specific requirements after first dose of IMP for any signs or symptoms of a hypersensitivity reaction.
- Schedule an appointment for the next visit.

10.2.2.2 Visit 3 (Day 15 ±3, Week 2)

- Review of concomitant medication.
- Dispense new patient diary and review last visit patient diary.
- Measure vital signs (including systolic and diastolic BP [mmHg], HR [beats per minute], and body temperature [°C]).
- GCA clinical assessments (including disease flare).
- Inquire about AEs/SAEs.
- Tuberculosis assessment.
- Perform blood sampling (prior to administration of IMP) for the following tests:
  - CRP and ESR.
  - Serum sarilumab.
  - Biomarkers IL-6, sIL-6R.
  - Serum and plasma sampling for circulating protein (for consented patients only).
  - Sample for RNA for those patients who have consented to pharmacogenetics.
- Administration of IMP. Patients will be monitored for at least 30 minutes or up to 2 hours as per country specific requirements after first dose of IMP for any signs or symptoms of a hypersensitivity reaction.

- Call IRT to register visit and obtain next treatment kit assignments.
- Schedule an appointment for the next visit.

10.2.2.3 Visit 4-11 (Day 29 ±3, Week 4 to Day 281±3, Week 40)

- Administer PRO questionnaires (EQ-5D, FACIT-Fatigue, SF-36v2, HAQ-DI) (**Applicable only at Visits 6 and 9**; at these visits PRO questionnaires should be completed prior to any significant interaction with the study team and prior to any physical examination or sampling).
- Review of concomitant medication.
- Dispense new patient diary and review last visit patient diary.
- Measure vital signs (including systolic and diastolic BP [mmHg], HR [beats per minute], and body temperature [°C]). (**Applicable only at Visits 6, 9 and 11**).
- Measure body weight (Kg) (**Applicable only at Visits 6, 9 and 11**).
- GCA clinical assessments (including disease flare).
- Complete physician global assessment (MD-VAS) at Visits 6 and 9.
- Inquire about AEs/SAEs.
- Tuberculosis assessment.
- Targeted physical examination (including head, eyes, ears, neck and throat, skin, respiratory, cardiovascular, neurologic, lymphatic examinations and abdominal examination) (**Applicable only at Visits 6, 9, and 11**).
- GTI Assessment (**Applicable only at Visits 6, 9 and 11**).
- Perform blood sampling (prior to administration of IMP) for the following tests:
  - CRP and ESR.
- Perform blood sampling (fasting, prior to administration of IMP) for the following tests: **(Applicable only at Visits 4, 6, 9 and 11)**
  - Hematology and chemistry.
  - Fasting lipids, fasting glucose and fasting insulin.
  - HbA1c.
- Perform blood sampling (prior to administration of IMP) for the following tests: **(Applicable only at Visits 4, 6, 7 and 9)**
  - Serum sarilumab.
  - **Note**: Additional sample is to be drawn 4-7 days after **Visit 9** dosing. May be performed at the patient's home, if compatible with local organization.
  - Sample for circulating immune cell phenotyping for patients identified to perform this test. **(Applicable only at Visits 4 and 9).**

- Perform blood sampling (prior to administration of IMP) for the following tests: **(Applicable only at Visits 6 and 9)**
  - Antidrug antibody.
  - Biomarkers IL-6, sIL-6R.
  - Serum and plasma sampling for circulating protein (for consented patients only).
- Perform urine pregnancy test (for WOCBP).
- Call IRT to register visit and obtain next treatment kit assignments.
- Administration of IMP. Patients will be monitored for at least 30 minutes or up to 2 hours as per country specific requirements after first dose of IMP for any signs or symptoms of a hypersensitivity reaction.
  - Where the visit interval will exceed 4 weeks (**Applicable only at Visits 9, 10 and 11**), interim shipments of IMP to patients home may be performed using DTP shipping (according to local regulations and logistics), in order to provide the patient with only 4 weeks IMP at a time in order to minimize compliance errors.
- Schedule an appointment for the next planned visit.

10.2.2.4 Visit 12/End of Treatment (Day 365 ±3, Week 52)

- Call IRT to register visit.
- Administer PRO questionnaires (EQ-5D, FACIT-Fatigue, SF-36v2, HAQ-DI).

  Note: PRO questionnaires should be completed prior to any significant interaction with the study team and prior to any physical examination or sampling.
- Review of concomitant medication.
- Review last visit patient diary.
- Measure vital signs (including systolic and diastolic BP [mmHg], and HR [beats per minute], body temperature [°C]).
- Body weight (kg).
- GCA clinical assessments (including disease flare).
- Complete physician global assessment (MD-VAS).
- Inquire about AEs/SAEs.
- Tuberculosis assessment.
- Full physical examination.
- GTI Assessment.
- Bone density assessment by DXA (-2 week time window is allowed).

- Perform blood sampling (fasting) for the following tests:
  - Hematology and chemistry.
  - ANA.
  - Fasting lipids, fasting glucose and fasting insulin.
  - HbA1c.
  - CRP and ESR.
  - Serum sarilumab and ADA.
  - Biomarkers IL-6, sIL-6R.
  - Serum and plasma sampling for circulating protein (for consented patients only).
- Perform urine pregnancy test (for WOCBP).
- Schedule an appointment for Visit 13.

10.2.3 Post-treatment follow up period (24 weeks)

10.2.3.1 Visit 13 (Day 407 ±3, Week 58)

- Review of concomitant medication.
- Measure vital signs (including systolic and diastolic BP [mmHg], HR [beats per minute], and body temperature [°C]).
- GCA clinical assessments (including disease flare).
- Inquire about AEs/SAEs.
- Tuberculosis assessment.
- Perform blood sampling for the following tests:
- Serum sarilumab and ADA.

10.2.3.2 Visit 14/End of study (Day 532 ±3, Week 76)

- Call IRT to register visit.
- Review of concomitant medication.
- Measure vital signs (including systolic and diastolic BP [mmHg], HR [beats per minute], and body temperature [°C]).
- GCA clinical assessments (including disease flare).
- Inquire about AEs/SAEs.

10.3 DEFINITION OF SOURCE DATA

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are original documents, data and records such as hospital records, clinic and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, etc.

The following data collected in the case report forms (CRFs) will be source data:

- SF-36v2
- FACIT-F
- EQ-5D-3L and associated VAS
- HAQ-DI and associated VAS

Additional data that are considered to be source data are:

- Chest X-ray or signed documented X-ray and reports.
- Patient home dosing diaries.
- ECG tracings and reports.
- Diagnostic imaging or biopsy reports for inclusion.
- Central lab reports.
- Local lab reports and ESR results.
- Bone density assessment results by DXA.
- Diagnostic results from other healthcare professionals, if appropriate, for GCA and GTI assessments.

10.4 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation must be fully documented in the eCRF. In any case, the patient should remain in the study as long as possible.

In case of permanent sarilumab discontinuation, the patient will also withdraw from prednisone tapering.

10.4.1 Temporary treatment discontinuation with investigational medicinal product

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Reinitiation of treatment with the IMP will be done under close and appropriate clinical/and

or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2).

For all temporary treatment discontinuations, duration must be recorded by the Investigator in the appropriate pages of the eCRF.

Temporary IMP (sarilumab or matching placebo) treatment discontinuation decided by the Investigator corresponds to ≥1 dose not administered to the patient.

A temporary discontinuation of IMP (sarilumab or matching placebo) that is >31 consecutive days will be considered permanent.

For all confirmed temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

The following is a list of criteria for temporary discontinuation (refer to Section 10.7 for details):

- Increase in ALT level to ≥3 x ULN to ≤5 x ULN and bilirubin ≤2 x ULN. The IMP (sarilumab or matching placebo) can be resumed only after the ALT has returned to a value <3 x ULN and all requirements for resumption of study drug administration are met based on Investigator judgment. The IMP (sarilumab or matching placebo) may be resumed at the same dose or at the lower dose of 150 mg q2w in such cases, if the patient is randomized to the sarilumab 200 mg q2w dose group (see Section 10.7.2 and Appendix L)
- Decrease in neutrophil count to a level ≥500/mm^3 to <1000/mm^3 without signs of infection. The IMP (sarilumab or matching placebo) can be resumed only after the neutrophils have returned to a value ≥1000/ mm^3 and all requirements for resumption of study drug administration are met based on Investigator judgment. The IMP (sarilumab or matching placebo) may be resumed at the same dose or at the lower dose of 150 mg q2w in such cases, if the patient is randomized to the sarilumab 200 mg q2w dose group (see Section 10.7.3 and Appendix L).
- Decrease in platelet count to a level of ≥50 000 cells/mm^3 to <100 000 cells/mm^3 without spontaneous bleeding. The IMP can be resumed only after the platelet count is ≥100 000/mm^3 and all requirements for resumption of study drug administration are met based on Investigator judgment. The IMP may be resumed at the same dose or at the lower dose of 150 mg q2w in such cases if the patient is randomized to the sarilumab 200 mg q2w dose group (See Section 10.7.4 and Appendix L).
- Intercurrent infections requiring oral or parenteral treatment with antibacterial, antiviral and/or antifungal agents.

10.4.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator not to reexpose the patient to the IMP at any time during the study, or from the patient not to be reexposed to the IMP whatever the reason.

10.4.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reason(s) for treatment discontinuation and this should be documented in the eCRF.

Investigational medicinal products will be permanently discontinued in case of the following events (refer to Section 10.7 for details):

- Opportunistic infections (as assessed by the Investigator) including, but not limited to, active TB.
  - The initial diagnosis of TB may be made either on symptoms or on a chest radiograph suggestive of active TB. Patients should be referred to appropriate medical specialists and whenever possible, culture confirmation of disease should be obtained and recorded in the eCRF.
  - Culture positive for nonTB mycobacteria.
- The patient is at risk through close contact with a person with active TB and the patient refuses to undergo TB evaluation.
- Symptoms of systemic hypersensitivity or anaphylactic reactions.
- Severe neurologic disease such as demyelinating disease or PML.
- Significant laboratory abnormalities:
  - ALT >5 x ULN or ALT >3 x ULN with concomitant total bilirubin >2 x ULN (unless patient with documented Gilbert's Syndrome).
  - neutrophil count <500/mm^3, or neutrophil count <1000/mm^3 with evidence of infection.
  - platelet count <50 000/mm^3, or platelet count <100 000/mm^3 with evidence of bleeding.
- Acute renal failure (refer Section 10.7.8).
- Pregnancy in female participant.
- Use of any biologic DMARDs other than IMP.
- Any AEs, per Investigator's judgment, that may jeopardize the patient's safety.

Any abnormal laboratory value will be immediately rechecked for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient.

10.4.4 Handling of patients after permanent treatment discontinuation

Every effort should be made to maintain patients in the study after permanent study treatment discontinuation. Patients should be followed up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed up as specified in this protocol, whichever comes last. The scientific value of the complete collection of data will be explained to patients, and site personnel will receive training regarding strategies for patient retention, and access to tools to assist with this during the study.

If a patient prematurely and permanently discontinues study treatment, a premature EOT visit (see Section 10.4.2) should be scheduled at the time of treatment discontinuation, if possible. If not possible, the EOT should be scheduled as soon as possible after treatment discontinuation. The IRT should be notified of EOT. Of note, during this premature EOT visit, the bone density test does not need to be performed if it has been less than 6 months since the bone density test from the baseline visit.

Following the premature EOT visit, the remaining visits will be performed as scheduled. All efforts should be made to follow the patients for safety at least 6 weeks after the last dose of SC IMP and for primary endpoint, key secondary endpoints a through the remainder of the study visits up to Week 52 after premature EOT.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the CRF when considered as confirmed. Details recording the specific reasons for discontinuation should be collected.

10.4.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Discontinuation of study treatment should be distinguished from withdrawal of consent for follow up visits and from withdrawal of consent for nonpatient contact follow up, eg, medical records check. Patients will be told that they are free to withdraw from the study at any time without any adverse effect on their care. However, if they no longer wish to take the IMP, they will be encouraged to remain in the study and attend the remaining visits. The value of critical study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Should the patient or the patient's representatives withdraw from the study without a preferred written withdrawal of consent, the site should clearly document and sign the reason for the patient's reason for withdrawal of consent, if known.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the CRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.

For patients who withdraw from the study, unless the patient withdraws consent for follow up, the Investigator should make the best effort to recontact the patient (eg, contact patient's family or private physician, review available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

Patients who have withdrawn from the study cannot be rerandomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.5 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.5.1 Definitions of adverse events

10.5.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.5.1.2 Serious adverse event

A SAE is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or

  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient 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.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event

  Medical and scientific judgment should be exercised in deciding whether expedited 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 patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

  Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
  - Development of drug dependence or drug abuse
  - ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
  - Suicide attempt or any event suggestive of suicidality
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
  - Bullous cutaneous eruptions
  - Cancers diagnosed during the study or aggravated during the study
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study

10.5.1.3 Adverse event of special interest

An AE of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

The following listed events are considered as AESI:

- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP; Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.5.1.2).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - An attempt to follow up of the pregnancy in a female participant or in a female partner of a male participant is made until the outcome has been determined (see Appendix A).
- Symptomatic overdose (serious or nonserious) with SC IMP.
- An overdose (accidental or intentional) with the SC IMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the intended dose during an interval of <11 days (for sarilumab or matching placebo).

  Of note, both symptomatic and asymptomatic overdoses have to be reported on a specific AE page. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.

- Increase in alanine transaminase (ALT) ≥3 x ULN (see the "Increase in ALT" flow diagram in Appendix L).Clinically significant infections including:
  - Confirmed diagnosis of opportunistic infections based on the Investigator's assessment with appropriate diagnostic workups and consultations. For any infection from the list of potential opportunistic infections provided in Appendix M, for reporting purpose, even if it is not confirmed to be an opportunistic infection based on the Investigator's assessment, it should still be reported as AESI.
  - Active/latent TB or initiation of medications for suspected TB.
  - Note: Parasitic infections are not considered opportunistic infections. Fungal infections are not considered opportunistic infections, unless they are systemic and/or extensive muco-cutaneous cases.
  - Infection requiring prolonged medication (>14 days). These are infections which require treatment (continuous or intermittent) for >14 days, with antibiotics, antifungals, or antivirals (exclude when medications are only administered topically).
  - Infections requiring any parenteral antibiotics, parenteral antifungals, or parenteral antiviral agents.
- The following laboratory abnormalities:
  - ALT increase leading to permanent discontinuation.
  - ANC decrease leading to permanent discontinuation.
  - Thrombocytopenia leading to permanent discontinuation.

10.5.2 Serious adverse events waived from expedited regulatory reporting to regulatory authorities

Not applicable.

10.5.3 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the eCRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional

investigations may be requested by the monitoring team up to as noticed by the Sponsor. At the prespecified study end-date, patients who experience an ongoing SAE or an AESI should be followed until resolution, stabilization, or death and related data will be collected.

- When treatment is prematurely discontinued, the patient's observations will continue until the End of Study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI

10.5.4 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator or any designees must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the eCRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the eCRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the eCRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the eCRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.5.5 Guidelines for reporting adverse events of special interest

For AESIs and SAEs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.5.4, even if not fulfilling a seriousness criterion, using the screens in the eCRF. Instructions for AE reporting are summarized in Section 10.5.3.

10.5.6 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix L.

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia (also refer to Section 10.7.3)
- Thrombocytopenia (also refer to Section 10.7.4)
- Increase in ALT (also refer to Section 10.7.2)
- Increase in serum creatinine

10.5.7 Guidelines for reporting product complaints (IMP)

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

10.6 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, independent ethics committee (IECs)/institutional review boards (IRBs) as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

In this study, some AEs are considered related to the underlying condition (eg, progression of disease) and thus will not be considered unexpected.

For the IMP, any other AE not listed as an expected event in the IB for sarilumab or defined in this protocol or local label summary of product characteristics(SmPC)/package insert for prednisone will be considered unexpected.

For safety, the Sponsor will report to the Health Authorities of any SUSAR and reasonably associated with the use of the SC IMP (sarilumab or matching placebo) according to either the judgment of the Investigator and/or the Sponsor.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.7 SAFETY INSTRUCTIONS

10.7.1 Infections

Biologics including TNF antagonists and tocilizumab (another IL-6 receptor antagonist similar to sarilumab) have been associated with an increased risk of infection, including black box warnings for serious infections leading to hospitalization or death. In sarilumab studies, the most commonly reported Treatment-emergent AEs (TEAEs) were infections (mostly nonserious upper respiratory and urinary tract infections), clinically significant infections including life threatening sepsis, have been reported, some notably associated with minor trauma. As a precautionary measure, Investigators should carefully follow any signs of infection with particular care to identify potential infective complications in immune-suppressed individuals where superficial skin wounds or abrasions may lead to serious infections including necrotizing fasciitis and/or sepsis.

Any infection should be reported by the Investigator as an AE and a corresponding eCRF form should be filled in. If possible, culture should be performed to identify the type of infection. The type of infection should be listed in the eCRF from. Treatment with antibiotics if any should be recorded including the route of administration.

Clinically significant infections including opportunistic infections are AESI and should be reported accordingly (see Section 10.5.1.3). Infections requiring prolonged treatment (>14 days) or anti-TB medication are considered AESI with immediate notification. Systemic opportunistic infections should be reported as SAE. The IMP must be withheld in case of suspicion of a clinically significant infection and a complete diagnosis work-up should be performed including but not limited to cultures for bacterial infections, fungi and/or mycobacteria, histopathological or cytological evaluation, antigen detection and serum antibody titers.

- Tuberculosis assessment: sarilumab is a biologic treatment that may induce immunosuppression, increasing the risk of reactivation of latent TB. A special warning of the increased risk of TB is included in the label of TNF inhibitors and tocilizumab. As a precautionary measure, patients at risk for TB will be excluded from the study. For inclusion, patient with a past history of TB could be included only if there is a documented confirmation medically validated by the Investigator that the patient was adequately treated and does not meet any of the TB-related exclusion criteria.
    - A clinical examination and history will be performed at every visit to assess any signs and symptoms of TB or contact with a patient with active TB.

- A QuantiFERON TB Gold test will be performed at screening and can be repeated at any time during the course of the studies in case of suspicion of TB. A repeat chest X-ray should be performed in all patients with suspected TB.
- In case of suspicion of TB, the Investigator must refer the patient to a specialist for a complete examination. The IMP should be discontinued until TB is ruled out.

- Chest X-ray: A standard PA chest X-ray (lateral view is also recommended but not required) is required during the screening period if no chest imaging (X-Ray, CT, MRI) is available within the previous 12 weeks of V1 that clearly documents the exclusion of TB (or >12 weeks, if appropriate according to local guidelines and requirements for screening of active TB). In countries for which a specific approval procedure for the x-ray is required by a different committee than the local EC/IRB, a chest MRI between V1 and V2 can be performed. A radiologist or pulmonologist interpretation (signed and dated) should note the absence of calcified granulomas and/or pleural scaring and/or any findings consistent with TB. The information must be documented in the patient's chart and in the eCRF at the screening visit. In case of any symptom suggestive of TB at any time during the course of the study, a chest X-ray should be performed and conclusion recorded.
- Repeat chest radiographs should be performed as indicated by local treatment guidelines or practice for monitoring while on immunosuppressive/immunomodulatory therapy. If such guidelines are not available/applicable, routine chest X-rays should be performed when clinically necessary.
- QuantiFERON TB Gold test will be performed at screening. This is an in vitro TB test that measures a memory T-cell mediated response (production of interferon γ) in TB-infected patients. This test is unaffected by Bacillus Calmette-Guerin vaccination or nontuberculous mycobacteria. The test received regulatory and policy approvals in the US, Japan, EU, Canada. Blood samples will be incubated within 16 hours of blood collection and sent to the central laboratory for analysis the day after collection or as soon as possible. In case of suspicion of TB, those patients will be referred to a specialist for follow up.

10.7.2 Liver function tests

Please refer to Section 10.5.1.3 for liver function test (LFT) abnormalities to be reported as AESI with immediate notification.

The Sponsor relies on the Investigator's, particularly Safety Assessor's judgment and safety Assessor for adapting concomitant medication in case of LFT abnormalities.

In the present protocol, in order to closely follow LFT, assessment of ALT, AST, alkaline phosphatase, and bilirubin (total, conjugated) are performed per specifications on the study flow charts (see Section 1.2).

- The IMP (sarilumab or matching placebo) should be permanently discontinued in case of confirmed ALT >5 x ULN or in case of confirmed ALT >3 x ULN and concomitant total bilirubin >2 x ULN (unless the patient has documented Gilbert's disease). A complete

serological and ultrasonography work-up should be conducted in case of ALT >5 x ULN or ALT >3 x ULN and concomitant total bilirubin >2 x ULN (see Appendix K).

- If ALT is ≥3 x ULN and ≤5 x ULN and bilirubin is ≤2 x ULN, administration of IMP must be temporarily interrupted, and LFT must be repeated within 48 hours from the study Investigator's awareness for confirmation of transaminase levels. If the elevated ALT level is confirmed but stays below the 5 x ULN thresholds, then LFTs must be repeated according to the provided guideline and at a minimum of every 7 days until conditions for resumption of IMP administration are met (see Appendix K).
- The IMP may then be restarted at the Investigator's discretion after conditions for resumption of IMP administration are met (ALT <3 x ULN). Safety assessor will either resume the patient at the initial dose or perform blinded dose reduction request through IRT (dose of sarilumab may be reduced to 150 mg if patient was randomized to the 200 mg group).

10.7.3 Neutrophils

Refer to Section 10.5.1.3 criteria for reporting neutropenia as AESI with immediate notification.

- Absolute neutrophil count (ANC) >1000/mm^3 current dosage of sarilumab can be maintained.

In case of a decrease in neutrophil count to a level ≥500/mm^3 and <1000/mm^3:

- The IMP (sarilumab or matching placebo) must be temporarily discontinued, the patient must be assessed for evidence of infection and CBC blood test repeated within 48 hours from the study Investigator's awareness of neutrophil count ≥500/mm^3 and <1000/mm^3.
- Discontinuation of IMP is maintained until the neutrophil count returns to ≥1000/mm^3.
- After the patient meets all requirements for resumption of IMP administration, including neutrophil count ≥1000/mm^3, then IMP administration may resume based on Investigator's clinical judgment. Safety assessor will either resume the patient at the initial dose or perform blinded dose reduction request through IRT (dose of sarilumab may be reduced to 150 mg if patient was randomized to the 200 mg group).

IMP must be permanently discontinued in case of a decrease in neutrophil count <1000/mm^3 and signs of infection or neutrophil count <500/mm^3.

- The patient must be assessed for evidence of infection and CBC blood test repeated within 48 hours from the study Investigator's awareness of neutrophil count <1000/mm^3 with signs of infection or neutrophil count <500/mm^3.
- It is recommended to admit the patient to the hospital in case of neutrophil count <1000/mm^3 with suspicion of infection or neutrophil count <500/mm^3.
- The neutrophil count <500/mm^3 persisting for more than 5 days are reported as an SAE.

10.7.4 Platelets

Refer to Section 10.5.1.3 for criteria for reporting thrombocytopenia as AESI.

A level ≥50 000/mm^3 and <100 000/mm^3:

- The IMP must be temporarily discontinued, the patient must be assessed for evidence of spontaneous bleeding, and CBC blood test repeated within 48 hours from the study Investigator's awareness of platelet count ≥50 000/mm^3 and <100 000/mm^3.
- Discontinuation of IMP is maintained until the platelet count returns to ≥100 000/mm^3.
- After the patient meets all requirements for resumption of IMP administration, including platelet count ≥100 000/mm^3, then IMP administration may resume based on Investigator's clinical judgment. Safety assessor will either resume the patient at the initial dose or perform blinded dose reduction request through IRT (dose may be reduced to 150 mg if patient was randomized to the 200 mg group).

The IMP must be permanently discontinued if platelet count is <50 000/mm^3 or if <100 000/mm^3 with spontaneous bleeding (see Section 10.4.2).

10.7.5 Systemic hypersensitivity reactions/anaphylaxis

Severe systemic hypersensitivity reactions (in rare cases, fatal anaphylaxis) have been reported with biologics, including tocilizumab. Rare, severe, nonfatal, systemic hypersensitivity reactions have been observed with sarilumab. The patient should be monitored for 30 minutes after the IMP injection when given at the study site. Also patient should be advised, when IMP is administered at home, to self-monitor for potential signs and symptoms that may suggest a hypersensitive reaction for 30 minutes after administration. Any problems should be documented in the patient's Home Dosing Diary or in the medical notes and reported as AE. In case of systemic hypersensitivity reaction, the IMP should be discontinued and those events meeting seriousness criteria (eg, hospitalization, life threatening, etc; see Section 10.5.1.2) should be reported as SAEs. Appendix N defines clinical criteria for diagnosing anaphylaxis. If clinical criteria for anaphylaxis are met, appropriate treatment should be administered immediately and the event should be reported as a SAE.

10.7.6 Diverticulitis and gastrointestinal perforation

The Investigator should pay particular attention to gastrointestinal symptoms such as, but not limited to, abdominal pain, hemorrhage, or unexplained change in bowel habits with fever to assure that the diagnosis is not missed and that the conditions are managed appropriately to avoid the complication of perforation. If necessary, the patient should be referred to a specialist.

Corticosteroid use or prior history of diverticulitis is known to increase the risk of gastrointestinal perforations. The Investigator should be aware of this potential risk and monitor any sign of diverticulitis.

Gastro-intestinal perforation must be reported as SAE (see Section 10.5.4). Confirmed diverticulitis or gastrointestinal ulceration should be reported as AEs.

10.7.7 Management of dyslipidemia

Patients treated with tocilizumab have been observed to have increased elevations of all lipid parameters, including LDL cholesterol. A similar finding has been observed for sarilumab. The potential cardiovascular effect of the lipid elevations, including LDL levels with antiIL-6R antagonists is unknown.

Patients who are found to have dyslipidemia during the course of the study should be treated according to the American College of Cardiology (ACC)/American Heart Association (AHA) guideline or European Society of Cardiology (ESC)/the European Atherosclerosis Society (EAS) guidelines or applicable local guideline.

10.7.8 Acute renal failure

Sarilumab is not known to be associated with a clinically significant effect on renal function.

10.8 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size calculations are based on the primary efficacy variable of sustained remission at Week 52. Assuming the treatment effect of sarilumab compared to placebo will be similar to what was observed from GiACTA, a trial that evaluated the safety and efficacy of tocilizumab (another IL-6 receptor antagonist similar to sarilumab) in patients with GCA (9), it is expected that the sustained remission rate at Week 52 will be approximately 14% for Group C (placebo + 26 week taper), approximately 18% for Group D (placebo + 52 week taper), and approximately 54% for Group A (sarilumab 200 mg q2w +26 week taper). A slightly lower sustained remission rate of approximately 50% is assumed for Group B (sarilumab 150 mg q2w + 26 week taper). The details of the power calculations are summarized in the table below, where the proposed sample sizes will provide at least 90% overall power for all the 4 between-group comparisons at 0.01 level.

Table 3 - Sample size determination

Treatment	Estimate of the sustained remission rate	Sample size		Comparison	Power
Group A	54%	120		Group A vs. Group C	99%
Group B	50%	60		Group A vs. Group D	99%
Group C	14%	60		Group B vs. Group C	96%
Group D	18%	120		Group B vs. Group D	96%
				Overall	>90%

Treatment Group A: sarilumab 200 mg q2w with a 26 week taper of CS.
Treatment Group B: sarilumab 150 mg q2w with a 26 week taper of CS.
Treatment Group C: sarilumab matching placebo q2w with a 26 week taper of CS.
Treatment Group D: sarilumab matching placebo q2w with a 52 week taper of CS.
Power was calculated based on a 2-sided alpha level of 0.01 using the Chi-square test for each comparison.

The sample size has also been selected to ensure adequate power for sensitivity analyses excluding acute phase reactants from the primary endpoint definition (9).

Calculations were made using nQuery Advisor 7.0.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who signed informed consent.

Randomized patients consist of all patients, with signed informed consent, with a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used or not. These patients form the randomized population.

Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

11.3.1.1 Intent–to-treat population

Intent-to-treat (ITT) population: all randomized patients analyzed according to the treatment group allocated by randomization. All efficacy analyses will use this population.

11.3.2 Safety population

Safety population: all randomized patients who have received at least one dose or part of a dose of the study medication (IMP) analyzed according to the treatment they have actually received.

In addition:

- Nonrandomized but treated patients will not be part of the safety population, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- For patients receiving more than 1 study treatment during the trial, the treatment group allocation for as-treated analysis will the treatment for which the patient received the majority of doses.

11.3.3 Pharmacokinetic analysis population

The PK population will consist of all patients in the safety population with at least 1 postdose, nonmissing serum sarilumab concentration.

11.3.4 Antidrug antibody (ADA) population

The ADA population will consist of all patients in the safety population with at least one nonmissing ADA result in the ADA assay following the first dose of the study medication.

11.4 STATISTICAL METHODS

Analysis of the randomization DB phase is described below. The posttreatment follow up phase will be presented separately without formal statistical testing, and details of the follow up phase will be provided in the SAP.

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received within the safety population.

11.4.1.1 Extent of investigational medicinal product exposure

Duration of IMP (sarilumab) exposure is defined as: last double-blind dose date - first double-blind dose date +14 days, regardless of unplanned intermittent discontinuations.

Duration of exposure to the double-blind IMP will be summarized for each treatment group descriptively as a quantitative variable (N, Mean, standard deviation [SD], Median, minimum [Min], and maximum [Max]).

In addition, the number and percentage of patients randomized and exposed to the double-blind IMP will be presented by specific time periods for each treatment group.

11.4.1.2 Compliance

Treatment compliance to the double-blind IMP is defined as the actual amount of injections received compared to the scheduled amount of injections during the double-blind treatment period. It is calculated according to the following formula:

100 x total number of injections administered/(nominal number of injections for the duration of double-blind exposure).

A given administration will be considered noncompliant if the patient did not take the planned dose of injection as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Treatment compliance, above-planned and under-planned dosing percentages will be summarized descriptively (N, Mean, SD, Median, Min, and Max). The percentage of patients with compliance is <80% will be summarized. In addition, number and percentage of patients with at least 1 above-planned dosing administration will be given, as well as the number and percentage of patients with 0, (0, 20%), and >20% under-planned dosing administrations.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint(s)

The primary endpoint is the proportion of patients achieving sustained remission at Week 52 compared between the sarilumab 200 mg q2w arm and the placebo arm with 26-week taper and analyzed in the ITT population. The primary endpoint will be summarized as counts and proportions in each treatment group and analyzed using a Cochran-Mantel-Haenszel (CMH) test, stratified by baseline prednisone dose. Patients who do not achieve remission, receive rescue treatment with open label prednisone (or equivalent), withdraw from the study before Week 52, or have missing data that prevents assessment of the primary endpoint will be considered as nonresponders. Successful adherence to the prednisone taper may include the use of any excess prednisone (beyond the per protocol CS tapering regimen) with a cumulative dose of ≤100 mg (or equivalent), such as those employed to manage AE not related to GCA. The significance level for all tests will be 0.01 (2-sided).

Secondary comparisons will be made between the sarilumab 200 mg q2w arm and the placebo arm with 52 week taper using the CMH test as described previously.

Sensitivity analyses will be performed based on a revised remission definition excluding acute phase reactants.

11.4.2.2 Analyses of secondary efficacy endpoints

Other binary endpoints will be analyzed as described for the primary endpoint.

The cumulative prednisone dose will be analyzed using a nonparametric van Elteren test stratified by baseline prednisone dose and the mean and median dose will be summarized.

Time events will be analyzed by Kaplan-Meier method. Treatment groups will be compared with the use of Cox proportional hazards models, with adjustment for the baseline prednisone dose. Data censoring will be used for patients who withdraw from the study.

The GTI assessment (total score and domain-specific scores) will be analyzed with a mixed model repeated measures (MMRM) approach. The model, including treatment, visit, treatment-by-visit interaction, baseline prednisone dose (<30 mg/day or ≥30 mg/day) as fixed effects and baseline score as a covariate, will be used to test the difference of least-square means (LS means) between treatment groups. Descriptive statistics including number of subjects, mean, standard error and LS means will be provided. In addition, difference in LS means, the corresponding 99% CI and the p-value will be provided.

11.4.2.3 Multiplicity considerations

In order to maintain an overall type I error of 0.01 a hierarchical testing approach will be used.

The testing sequence for the primary endpoint will be:

- Comparison of 200 mg versus placebo with 26 week taper for primary endpoint.
- Comparison of 200 mg versus placebo with 52 week taper for primary endpoint.
- Comparison of 150 mg versus placebo with 26 week taper for primary endpoint.
- Comparison of 150 mg versus placebo with 52 week taper for primary endpoint.

Since sarilumab 200 mg q2w is the primary dose for the study while sarilumab 150 mg q2w is added to provide additional information on efficacy and safety in GCA patients, the comparisons on the secondary endpoints will be focusing on the 200 mg q2w only.

After significance is established at a 0.01 level for all 4 comparisons on the primary endpoint as listed above, the following secondary endpoints will be tested sequentially as below:

- Total cumulative corticosteroid dose
- Time to first flare after remission

For each secondary endpoint, the comparison between 200 mg versus placebo + 26 week taper will be performed first; if significance is achieved at a 0.01 level, then the comparison between 200 mg versus placebo + 52 week taper will be performed.

Nominal p-values will be provided for the comparisons of all other secondary endpoints.

11.4.3 Analyses of safety data

The summary of safety results will be presented by treatment group. Incidence rates and exposure adjusted event summaries will be provided for categorical safety summaries.

All safety analyses will be performed on the safety population using the following common rules:

The baseline value is defined generally as the last available value before randomization.

- The observation period to be used for the safety population is the TEAE period. The TEAE period is defined as the time from first dose of randomized study treatment to the last dose date of IMP + 60 days.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group.
- The analysis of the safety variables will be essentially descriptive and no hypothesis testing is planned.

The following definitions will be applied to laboratory parameters, vital signs and ECG.

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined

criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG.

- PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

11.4.3.1 Analysis of adverse event data

Treatment-emergent AEs, treatment-emergent SAEs, TEAEs leading to treatment discontinuation and treatment-emergent AESIs will be summarized for each treatment group based on MedDRA coding of verbatim terms reported by Investigators.

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment period. The denominator for computation of percentages is the safety population within each treatment group.

Treatment-emergent AESI, by AESI category and PT, will show number (%) of patients overall, sorted by decreasing incidence of PT within each AESI category. The AESIs include, but are not limited to, the following categories and details of the MedDRA coding will be provided in the statistical analysis plan: Neutropenia, thrombocytopenia, infections, hepatic disorders, diverticulitis/GI ulcerations/GI perforations, elevation in lipids, systemic allergic reactions, malignancy, autoimmune or drug-induced lupus like syndrome and demyelinating disorders.

Death: The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) summarized on the safety population by treatment received
- Death in nonrandomized patients or randomized and not treated patients
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC, HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

11.4.3.2 Analysis of laboratory data

The summary statistics (including number, mean, median, SD, minimum and maximum) of all laboratory variables will be calculated for each visit or study assessment (baseline, each post-baseline time point, endpoint) by treatment group. Listings will be provided with flags indicating the out of range values as well as the PCSA values.

The incidence of PCSA at any time will be summarized by treatment group for each laboratory parameter. Shift tables showing changes with respect to the baseline status will be provided.

11.4.3.2.1 Neutropenia

The incidence of neutropenia by maximal grade (lowest neutrophils value reported) during the TEAE period will be summarized. The 4 grades are defined as below:

- Grade 1: ≥1.5 Giga/L - LLN
- Grade 2: ≥1.0 - 1.5 Giga/L
- Grade 3: ≥0.5 - 1.0 Giga/L
- Grade 4: <0.5 Gigal/L

For patients with Grade 3 or 4 neutropenia, a listing with the individual neutropenia counts, and selected laboratory tests at each visit (including unscheduled visits for retest) will be provided. In addition, the neutrophil counts at each scheduled visit during the study will be plotted by treatment groups.

11.4.3.2.2 Assessment of potential drug-induced liver injury

The LFT, namely ALT, AST, alkaline phosphatase and total bilirubin, are used to assess possible drug induced liver toxicity. The proportion of patients with PCSA values at any post-baseline visit by baseline status will be displayed by treatment group for each parameter. The proportion of patients with PCSA values at any post-baseline visit will also be displayed by duration of exposure for each treatment group.

Time to onset of the initial ALT elevation (>3x ULN), time to onset of the initial AST elevation (>3x ULN), time to onset of the initial total bilirubin elevation (>2x ULN), and time to first observation of ALT >3ULN or Total Bilirubin >2 ULN (whichever comes first) will be analyzed using Kaplan-Meier estimates, using the midpoint of the time interval between the first assessment showing the elevation and the previous assessment, presented by treatment group. A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented. Note that the ALT and Total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3xULN for ALT and a horizontal line corresponding to 2x ULN for total bilirubin.

Summarize the normalization by parameter (to ≤1 ULN or return to baseline) of elevated LFT by categories of elevation (1-<3x, 3x, 5x, 10x, 20x ULN for ALT and AST, 1.5 x ULN for Alkaline phosphatase, and 1.5x and 2x ULN for total bilirubin), with following categories of normalization: never normalized, normalized after IMP discontinuation. Note that a patient will be counted only under the maximum elevation category. 1 - 3, 3 - 5, 5 - 10, 10 - 20, >20.

The incidence of liver-related AEs will be summarized by treatment group. The selection of preferred terms will be based on standardized MedDRA query (SMQ) Hepatic disorder. Time to liver-related treatment discontinuation and time to liver death may also be provided based on hepatic disorder SMQ.

11.4.3.3 Analysis of the vital signs data

The summary statistics (including number, mean, median, SD, minimum and maximum) of all vital signs variables will be calculated for each visit or study assessment (baseline, each post-baseline time point, endpoint) by treatment group.

The incidence of PCSA at any time will be summarized by treatment group for each vital signs variable. Shift tables showing changes with respect to the baseline status will be provided. Listings will be provided with flags indicating the out of range values as well as the PCSA values.

11.4.3.4 Analysis of antidrug antibody data

Antidrug (sarilumab) antibody (ADA) variables include status (positive or negative) and titer as follows:

- Total number of patients negative in ADA assay at all time
- Total number of patients with preexisting immunoreactivity - defined as either an ADA positive response in the assay at baseline with all post-baseline ADA results negative, or a positive response at baseline with all post-baseline ADA titer <4-fold over baseline titer level
- Total number of patients with treatment-emergent ADA response in ADA assay - defined as a positive response in the ADA assay post-first dose, when baseline results are negative, or missing:
- Total number of patients with treatment-boosted ADA response in ADA assay - defined as a positive ADA assay response at baseline with any post-baseline ADA titer ≥4-fold over baseline titer level.
- Titer value category
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)

Antidrug antibody positive samples will be further characterized for the presence of neutralizing antibody (NAb) response:

- Total number of patients positive in the NAb assay at the time points analyzed.

These ADA variables will be summarized using descriptive statistics by treatment group. Drug concentration data will be examined and the influence of ADAs on individual concentration-time profiles will be evaluated. Assessment of the potential impact of ADA on safety and efficacy may be provided.

11.4.4 Analyses of pharmacokinetic and pharmacodynamic variables

Serum concentrations of functional sarilumab will be summarized using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV%), minimum, median, and maximum by visit.

IL-6 and sIL-6R will be summarized using arithmetic and geometric means, SD, SEM, CV%, minimum, median, and maximum by visit.

11.4.5 Analyses of patient reported outcomes

Change from baseline in patient reported endpoints at Weeks 12, 24, and 52 will be analyzed with a mixed model repeated measures approach as appropriate (all data is continuous):

- SF-36v2 physical component summary score
- SF-36v2 mental component summary score
- Each SF-36v2 domain (n= 8)
- The EQ-5D-3L single index utility score
- The EQ-5D-3L VAS score
- The FACIT-Fatigue total score
- The HAQ-DI standardized score
- The HAQ-DI pain score
- The HAQ-DI global assessment score

The model, including treatment, visit, treatment-by-visit interaction, baseline prednisone dose (<30 mg/day or ≥ 30mg/day) as fixed effects and baseline score as a covariate, will be used to test the difference of least-square means (LS means) between treatment groups in each variable. Descriptive statistics including number of subjects, mean, standard error and LS means will be provided. In addition, difference in LS means, the corresponding 99% CI and the p-value will be provided.

11.5 INTERIM ANALYSIS

No interim analysis is planned,

Primary analysis at Week 52 will be conducted after the final patient has completed the double blind treatment period and all data have been cleaned.

Patients will continue into the 24-week posttreatment follow up period with the database lock occurring after the last patient has completed the EOS Visit.

Planned database lock date

The first data snapshot will occur approximately 4 weeks after last patient last visit for Week 52 (primary analysis). The database lock will occur approximately 4 weeks after the last patient has completed the EOS Visit (Week 76).

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and Subinvestigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, in particular the Declaration of Helsinki as amended in 1996 for clinical trials with medicinal products in the EU, and the International Conference on Harmonisation (ICH) guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient’s participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative (as specified for Germany: only in cases where the patient can be consented but cannot sign his or her name), and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

If informed consent is obtained under special circumstances (emergency, etc), the method should be specified following the ICH requirements.

Prior to collection of blood for pharmacogenetics and blood for biomarker of circulating protein analysis, the ICF of optional participating in the additional research program (written) should be completed by the patient or by the subject’s legally acceptable representative, and by the person who conducted the informed consent discussion.

The ICF, including the optional for participating in the additional research program, used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the health authorities (competent regulatory authority) and the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, ICF, IB with any addenda or labeling documents [summary of product characteristics, package insert] Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

The IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the IB or labeling information will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the eCRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All subinvestigators shall be appointed and listed in a timely manner. The subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the eCRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the eCRF entries against the source documents, except for the preidentified source data directly recorded in the eCRF. The informed consent form will include a statement by which the patient allows the Sponsor’s duly authorized

personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the eCRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All eCRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the eCRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the eCRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the eCRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor trial master file.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the CV describing the experience, qualification and training of each Investigator and subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years (or longer if required by local regulation) after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the CRFs, the IB and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the subinvestigators of the confidential nature of the clinical trial.

The Investigator and the subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database, shall be treated in compliance with all applicable laws and regulations.
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.
- Subject race or ethnicity will be collected in this study because these data are required by several regulatory authorities.

Analyses of subject genetic data will be conducted as described in the protocol as this is needed for pharmacogenetics analyses required for the purposes of the study or by regulatory authorities.

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/risk ratio, efficacy, and safety of the product(s). They may be further processed if they have been anonymized.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements.

The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, good clinical practice, and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio.
- Patient enrollment is unsatisfactory.
- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.
- Noncompliance of the Investigator or subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP.

- The total number of patients are included earlier than expected.

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor’s written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway, or planned within 12 months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes to the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be recollected if necessary.

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17 APPENDICES

Appendix A Contraceptive guidance and collection of pregnancy information

DEFINITIONS

Nonreproductive potential

1. Premenopausal female with 1 of the following:

   NOTE: Documentation can come from the review of subject's medical records, medical examination, or medical history interview.

   - Documented hysterectomy.
   - Documented bilateral salpingectomy.
   - Documented bilateral oophorectomy.

2. Postmenopausal

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH)/estradiol level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH/estradiol measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Reproductive potential (WOCBP)

A woman is considered of reproductive potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

CONTRACEPTIVE GUIDANCE

Women of Child bearing potential should avoid pregnancy and should use the highly effective contraceptive methods detailed below through the course of the entire study (until the End of the Study Visit) or until 12 weeks after the last dose of sarilumab or matching placebo if the patient early withdraw from the study.

Female subjects:

Highly Effective Contraceptive Methods That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation - oral - intravaginal - transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation - oral - injectable - implantable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device
• Intrauterine hormone-releasing system
• Bilateral tubal occlusion
• Vasectomized partner
• Sexual abstinence *if* this is *the preferred and usual lifestyle of the* subject

Male subjects **with partners** of reproductive potential **who become pregnant**

- The Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor.
- Generally, follow up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female subjects **who become pregnant**

- The Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow up information on participant and neonate, which will be forwarded to the Sponsor. 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.

For UK and Germany Only:

Acceptable forms of effective contraception include:

- Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation;
- Established use of oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation;
- Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS);
- Bilateral tubal occlusion;
- Male sterilization (provided that the partner is the sole sexual partner of the woman of childbearing potential study participant and that the sterilized partner has received medical assessment of the surgical success.);
- True abstinence: When this is in line with the preferred and usual lifestyle of the subject.

  (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

For Denmark Only:

Acceptable methods of contraception include:

- Intra-uterine devices (IUD);

Hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release).

Appendix B Standardized corticosteroid-taper regimen during study treatment period

Week	Daily prednisone dose 26 week taper regimen (mg/Day)						
0 (Day 1)	60[a,b]	50[a,b]	40[ab]	35[a,b]	30[a,b]	25[a,b]	20[a,b]
1	50[a]	40[a]	35[a]	30[a]	25[a]	20[a]	15
2	40[a]	35[a]	30[a]	25[a]	20[a]	15	13
3	35[a]	30[a]	25[a]	20[a]	15	13	12
4	30[a]	25[a]	20[a]	15	13	12	10
5	25[a]	20[a]	15	13	12	10	9
6	20[a]	15	13	12	10	9	8
7	15	13	12	10	9	8	7
8	13	12	10	9	8	7	6
9	12	10	9	8	7	6	6
10	10	9	8	7	6	6	5
11	9	8	7	6	6	5	5
12	8	7	6	6	5	5	4
13	7	6	6	5	5	4	4
14	6	6	5	5	4	4	3
15	6	5	5	4	4	3	3
16	5	5	4	4	3	3	2
17	5	4	4	3	3	2	2
18	4	4	3	3	2	2	1
19	4	3	3	2	2	1	1
20	3	3	2	2	1	1	PS placebo

21	3	2	2	1	1	PS placebo	PS placebo
22	2	2	1	1	PS placebo	PS placebo	PS placebo
23	2	1	1	PS placebo	PS placebo	PS placebo	PS placebo
24	1	1	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
25	1	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
26	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
27	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
28	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
29	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
30	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
31	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
32	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
33	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
34	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
35	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
36	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
37	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
38	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
39	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
40	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
41	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
42	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
43	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
44	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo

45	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo
46	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	**No PS dosing**
47	PS placebo	PS placebo	PS placebo	PS placebo	PS placebo	**No PS dosing**	**No PS dosing**
48	PS placebo	PS placebo	PS placebo	PS placebo	**No PS dosing**	**No PS dosing**	**No PS dosing**
49	PS placebo	PS placebo	PS placebo	**No PS dosing**	**No PS dosing**	**No PS dosing**	**No PS dosing**
50	PS placebo	PS placebo	**No PS dosing**	**No PS dosing**	**No PS dosing**	**No PS dosing**	**No PS dosing**
51	PS placebo	**No PS dosing**	**No PS dosing**	**No PS dosing**	**No PS dosing**	**No PS dosing**	**No PS dosing**

a prednisone will be provided as open label.

b Prednisone Starting dose

Week	Daily prednisone dose 52 week taper regimen (mg/Day)						
0 (Day 1)	60[a,b]	50[a,b]	40[a,b]	35[a,b]	30[ab]	25[ab]	20[ab]
1	50[a]	40[a]	35[a]	30[a]	25[a]	20[a]	17
2	40[a]	35[a]	30[a]	25[a]	20[a]	17	17
3	35[a]	30[a]	25[a]	20[a]	17	17	15
4	30[a]	25[a]	20[a]	17	17	15	15
5	25[a]	20[a]	17	17	15	15	12
6	20[a]	17	17	15	15	12	10
7	17	17	15	15	12	10	10
8	17	15	15	12	10	10	10
9	15	15	12	10	10	10	10
10	15	12	10	10	10	10	9
11	12	10	10	10	10	9	9
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13	10	10	10	9	9	9	9
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19	9	8	8	8	8	7	7
20	8	8	8	8	7	7	7
21	8	8	8	7	7	7	7

22	8	8	7	7	7	7	6
23	8	7	7	7	7	6	6
24	7	7	7	7	6	6	6
25	7	7	7	6	6	6	6
26	7	7	6	6	6	6	5
27	7	6	6	6	6	5	5
28	6	6	6	6	5	5	5
29	6	6	6	5	5	5	5
30	6	6	5	5	5	5	4
31	6	5	5	5	5	4	4
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33	5	5	5	4	4	4	4
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39	4	3	3	3	3	2	2
40	3	3	3	3	2	2	2
41	3	3	3	2	2	2	2
42	3	3	2	2	2	2	1
43	3	2	2	2	2	1	1
44	2	2	2	2	1	1	1
45	2	2	2	1	1	1	1

46	2	2	1	1	1	1	No PS dosing
47	2	1	1	1	1	No PS dosing	No PS dosing
48	1	1	1	1	No PS dosing	No PS dosing	No PS dosing
49	1	1	1	No PS dosing	No PS dosing	No PS dosing	No PS dosing
50	1	1	No PS dosing	No PS dosing	No PS dosing	No PS dosing	No PS dosing
51	1	No PS dosing	No PS dosing	No PS dosing	No PS dosing	No PS dosing	No PS dosing

a prednisone will be provided as open label medication.

b Prednisone Starting dose.

Appendix C Composite Glucocorticoid Toxicity Index

1. Body Mass Index (BMI) (compared to baseline)

a. Improvement in the direction of the normal range by more than 2 BMI units [normal range = 18.5-24.9 kg/m^2]
b. No significant change (BMI remains within +/- 2 BMI units compared with baseline)
OR BMI remains within the normal range
c. Moderate increase in BMI (increase by more than 2 but less that 5 BMI units, to above the upper limit of normal BMI [24.9 kg/m^2])
d. Major increase in BMI (increase by at least 5 but less than 8 BMI units above normal BMI [24.9 kg/m^2])

2. Glucose Tolerance (compared to baseline)

a. Improvement in glucose tolerance:
- HbA1c declined >10% from baseline without medication increase
OR
- Decrease in diabetic medication without an increase in HbA1c of >10% or HbA1c < 5.7%

b. No significant change in glucose tolerance:
- HbA1c within 10% of baseline or HbA1c < 5.7% AND no change in medication
OR
- HbA1c increased to > 10% of baseline with a decrease in medication
OR
- HbA1c decreased by > 10% of baseline with an increase in medication

c. Worsening of glucose tolerance or medication status:
- HbA1c > 5.7% and increased to >10% of baseline without a change in medication
OR
- Increase in diabetic medication with < 10% increase in HbA1c

d. Worsening of glucose tolerance despite increased treatment:
- HbA1c > 5.7% AND increased to >10% of baseline AND an increase in diabetic medication

3. Blood Pressure (BP) (compared to baseline)

a. Improvement in BP:
- Decrease in BP of >10% of baseline without medication increase, unless baseline systolic BP ≤ 120 and diastolic BP ≤ 85
OR
- Decrease in medication without an increase in BP of >10%, unless baseline systolic BP ≤ 120 and diastolic BP ≤ 85

b. No significant change in BP:
- BP within 10% of baseline or systolic BP ≤ 120 and diastolic BP ≤ 85 AND no change in medication
OR
- Increase in either systolic or diastolic BP >10% with a decrease in medication
OR
- Improvement in systolic or diastolic BP of > 10% with an increase in medication

c. Worsening of hypertension:

1

- Increase in BP of >10% such that the systolic BP exceeds 120 mmHg or the diastolic BP exceeds 85 mmHg without a change in medication
  OR
- An increase in anti-hypertensive medication accompanied by stability or no significant change in both the systolic and diastolic BP

d. Worsening of hypertension despite treatment:
- Increase in BP of >10% such that the systolic BP exceeds 120 mmHg or the diastolic BP exceeds 85 mmHg AND an increase in medication

4. Lipid metabolism (low-density lipoprotein [LDL] compared to baseline)

a. Improvement in lipids:
- Decrease in LDL concentration >10% of baseline toward the target range without medication increase
  OR
- Decrease in medication without an increase in LDL of >10% or LDL remains within target range

b. No significant change in LDL:
- LDL within 10% of baseline or within the target range for patient AND no change in medication
  OR
- Increase in LDL > 10% with a decrease in medication
  OR
- Improvement in LDL of > 10% with an increase in medication

c. Worsening of LDL or medication status:
- Increase in LDL of >10% to above target range without a change in medication
  OR
- Increase in medication with <10% change in LDL

d. Worsening of LDL despite treatment:
- Increase in LDL of >10% AND an increase in medication

5. Bone Mineral Density (compared to baseline)

a. Improvement – increase in BMD by >3%
b. No significant change (BMD between -3% and +3%
c. Deterioration - decrease in BMD (BMD decrease by ->3%)

% refers to total BMD in gms/cm^2

6. Glucocorticoid-induced myopathy

a. No steroid myopathy
b. Mild steroid myopathy (weakness WITHOUT functional limitation)
c. Moderate steroid myopathy (weakness WITH functional limitation)

See Steroid Myopathy definitions, below

7. Skin

a. No skin toxicity
b. Mild skin toxicity
c. Moderate skin toxicity

See Skin definitions, below
8. Neuropsychiatric toxicity a. No neuropsychiatric symptoms b. Mild neuropsychiatric symptoms c. Moderate neuropsychiatric symptoms **See Neuropsychiatry definitions, below**
9. Infection (since last assessment) a. No significant infection b. Specific infections < Grade 3 (oral or vaginal candidiasis, uncomplicated zoster) c. Grade 3 or complicated herpes zoster **See Infection definitions, below**

3

Glucocorticoid-induced Myopathy Definitions

Glucocorticoid-induced myopathy is defined as mild symmetrical weakness of the proximal muscles and/or neck flexors associated with steroid therapy, and NOT due to any other apparent cause. Muscle enzymes are typically within normal limits.

Mild and moderate severity of myopathy are defined by a muscle strength of 4 on the standard Medical Research Council rating scale.

A 4 means weaker than normal but greater than antigravity strength against resistance.

"Mild" is mild weakness (Grade 4) that does NOT functionally limit the patient.

"Moderate" is mild weakness (Grade 4) that does impose functional limitations on the patient enough to interfere with normal daily activities.

Note that a person may have muscle weakness consistent with glucocorticoid-induced myopathy that detectable on physical examination but might not be aware of it or have any corresponding functional limitation - this would be classified as mild.

Severe glucocorticoid-induced myopathy (defined as weakness of Grade 3 or less, which means no more than antigravity strength and unable to overcome any resistance or any degree weaker) is included in the Specific List. People who are severely weak may have difficulty rising from a chair without assistance or other major functional limitations but the formal categorization for severe should be based the degree of weakness on strength testing.

Severity of Glucocorticoid Toxicity in the Skin

Manifestations to be considered:

- Acneiform rash
- Easy Bruising
- Hirsutism
- Atrophy/striae
- Erosions/tears/ulcerations

Skin 6b. Mild	Skin 6c. Moderate	Severe (Specific Domain)
Acneiform rash (Grades 1-2)	Acneiform rash (Grade 3)	Acneiform rash (Grade 4)
Easy bruising (Grade 1)	Easy bruising (Grade 2)	
Hirsutism (Grade 1)	Hirsutism (Grade 2)	
Atrophy/Striae (Grade 1)	Atrophy/Striae (Grade 2)	Atrophy/Striae (Grade 3)
Erosions/Tears/Ulcerations (Grade 1)	Erosions/Tears/Ulcerations (Grade 2)	Erosions/Tears/Ulcerations (Grade 3)

Skin Definitions (from National Cancer Institute Common Terminology Criteria for Adverse Events):

Acneiform rash
- Grade 1 - Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness
- Grade 2 – Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; OR associated with psychosocial impact; OR limiting instrumental ADL
- Grade 3 - Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; OR limiting self care ADL; OR associated with local superinfection with oral antibiotics indicated
- Grade 4 - Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; OR life- threatening consequences

Easy bruising
- Grade 1 – Localized or in a dependent area
- Grade 2 - Generalized

Hirsutism - In women, increase in length, thickness or density of hair in a male distribution
- Grade 1 - Hirsutism that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair
- Grade 2 - Hirsutism that requires daily shaving or consistent destructive means of hair removal to camouflage; OR associated with psychosocial impact

Atrophy / Striae
- Grade 1 - Covering <10% BSA; OR associated with telangiectasias or changes in skin color
- Grade 2 – Covering 10 - 30% BSA; OR associated with striae or adnexal structure loss
- Grade 3 - Covering >30% BSA; OR associated with ulceration

Erosions / Tears / Ulcerations
- Grade 1 – Combined area of ulcers <1 cm; OR nonblanchable erythema of intact skin associated with warmth or erythema
- Grade 2 – Combined area of ulcers 1 - 2 cm; OR partial thickness skin loss involving skin or subcutaneous fat
- Grade 3 – Combined area of ulcers >2 cm; OR full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia

Severity of Neuropsychiatric Glucocorticoid Toxicity

Manifestations to be considered:

- Insomnia
- Mania
- Cognitive Impairment
- Depression

7b. Mild	7c. Moderate	Severe (Specific Domain)
Insomnia – (Grade 1)	Insomnia – (Grade 2)	
Mania (Grade 1)	Mania (Grade 2)	Mania (Grade 3)
Cognitive impairment (Grade 1)	Cognitive impairment (Grade 2)	Cognitive impairment (Grade 3)
Depression (Grade 1)	Depression (Grade 2)	Depression (Grade 3)

Definitions of severity within the Neuropsychiatric Domain

Insomnia - Dissatisfaction with sleep quality and difficulty initiating or maintaining sleep or early morning awakening
- Grade 1: not associated with functional impairment
- Grade 2: associated with functional impairment

Mania
- Grade 1: Slightly or occasionally elevated or irritable mood and 0-1 mild or occasional additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.
- Grade 2: Frequent or moderately elevated or irritable mood and 2-3 mild additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.
- Grade 3: Severe or constantly elevated or irritable mood and 4 or more additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.

Cognitive impairment
- Grade 1: Minor cognitive complaints, no objective findings on mental status examination (i.e., not apparent to the examiner) that were not present before initiating steroids
- Grade 2: New moderate cognitive deficits that were not present before initiating steroids
- Grade 3: Frank delirium

Depression
- Grade 1: Feeling slightly down or depressed and 0-2 mild or occasional addition symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite.
- Grade 2: Frequent or moderate feelings of being down or depression and/or 3-4 symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite.
- Grade 3: Severe constant feeling of being down or depression and/or 5 or more symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite and/or suicidal thoughts.

Infection Definitions

No significant infection = No specific infections or serious infections, grade 3 or greater

Specific Infections – Oral or vaginal candidiasis or zoster infections without post-herpetic neuralgia or eye involvement

Grade 3 – Intravenous antibiotic, antifungal, or antiviral intervention or hospitalization indicated OR radiologic or operative intervention indicated OR herpes zoster complicated by post-herpetic neuralgia or eye involvement

Grade 4 or 5 - Life-threatening consequences; urgent intervention indicated OR death from infection (included in the Specific List)

References

Medical Research Council of the United Kingdom. Guide to Examination of the Peripheral Nervous System: Memorandum No 45. Palo Alto, Calif: Pedragon House; 1978.

National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 NCI, NIH, DHHS. May 29, 2009 NIH publication # 09-7473.

Appendix D Specific list for Glucocorticoid Toxicity Index

	At Baseline or Before	New Since Baseline
Body Mass Index - An absolute increase in BMI of more than 8 units (and >24.9 kg/m^2)		
Blood Pressure - Hypertensive emergency (see definition, below) - PRES (Posterior reversible encephalopathy syndrome) (see definition, below)		
Endocrine - Symptomatic adrenal insufficiency		
Bone Health - Osteonecrosis of one joint - Osteonecrosis of more than one joint - Bone mineral density decrease > 6% - Insufficiency fracture - Insufficiency fracture in more than one bone		
Muscle & Tendon - Severe glucocorticoid myopathy (see definition) - Tendon rupture - More than one tendon rupture		
Eye - Central serous retinopathy - New-onset or worsened elevation of intra-ocular pressure requiring treatment or change in treatment - Posterior subcapsular cataracts (or history of same)		

Infection - Grade 4 infection (see definition, below) - Grade 5 infection (death from infection)		
Glucose Tolerance - Diabetic nephropathy - Diabetic neuropathy - Diabetic retinopathy		
Gastrointestinal Tract - Gastrointestinal perforation (occurring in the absence of regular nonsteroidal anti-inflammatory drug use) - Peptic ulcer disease confirmed by endoscopy (excluding *H. pylori*)		
Skin - Severe skin toxicity (see definition, below)		
Neuropsychiatric - Psychosis, defined as hallucinations, delusions, or disorganized thought processes (occurring in the absence of mania, delirium, or depression) - Glucocorticoid-induced violence toward self or others		
Other glucocorticoid toxicities Please specify: _____ _____		

DEFINITIONS:

Hypertensive emergency: The blood pressure has reached levels that are damaging organs. Hypertensive emergencies generally occur at blood pressure levels exceeding 180 mmHg systolic OR 120 mmHg diastolic, but can occur at even lower levels in patients whose blood pressure have not been elevated before. Complications can include: stroke, loss of consciousness, memory loss, myocardial infarction, hypertensive retinopathy or nephropathy, aortic dissection, angina, pulmonary edema.

Posterior reversible leukoencephalopathy syndrome (PRES): A clinical radiological entity. Clinical features may include headaches, altered mental status, seizures, and visual loss, depending on the affected neuroanatomy. Characteristic Magnetic Resonance Imaging (MRI) findings include vasogenic edema involving the white matter that predominantly affects the posterior occipital and parietal lobes of the brain, although other brain regions may also be affected. Confirmation by MRI is required as is exclusion of other potential causes (including hypertensive emergency).

Severe glucocorticoid myopathy: Grade 3 or worse myopathic weakness or respiratory myopathic weakness attributable to glucocorticoid myopathy.

Central serous retinopathy: a fluid detachment of macula layers from their supporting tissue. Requires formal ophthalmology examination, typically accompanied by optical coherence tomography and/or fluorescein angiography for diagnostic confirmation.

Grade 4 infection: Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis).

Diabetic nephropathy: Macroalbuminuria; i.e., a urinary albumin excretion > 300 mg in a 24-hour collection or a urinary protein: creatinine ratio > 300mg/g.

Diabetic neuropathy: Any of four types of peripheral neuropathy occurring in the setting of diabetes mellitus, namely: 1) a distal sensory polyneuropathy; 2) autonomic neuropathy (hypoglycemia unawareness, bladder or bowel problems, erectile dysfunction, and other autonomic nervous system issues); 3) diabetic amyotrophy (muscle infarction); or 4) mononeuritis (e.g., foot drop attributed to diabetic neuropathy).

Diabetic retinopathy: Any form of retinopathy associated with diabetes mellitus, including both non-proliferative and proliferative forms of diabetic retinopathy as well as diabetic macular edema. These complications must be confirmed by an ophthalmologist.

Severe skin toxicity: Any of the three following manifestations:
Grade 4 acneiform lesions - Papules and/or pustules covering any % body suraface area (BSA), which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated or life- threatening consequences
Grade 3 striae - Covering >30% BSA or associated with ulceration
Grade 3 ulcers - Combined area of ulcers >2 cm or full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia

References

National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 NCI, NIH, DHHS. May 29, 2009 NIH publication # 09-7473.

Medical Research Council of the United Kingdom. Guide to Examination of the Peripheral Nervous System: Memorandum No 45. Palo Alto, Calif: Pedragon House; 1978.

American Heart Association. Hypertensive Crisis. Accessed http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/AboutHighBloodPressure/Hypertensive-Crisis_UCM_301782_Article.jsp#.V0NnSzv2ZaQ. 5/1/2015.

Appendix E FACIT Fatigue Scale (Version 4) (Paper Version)*

English (Universal)
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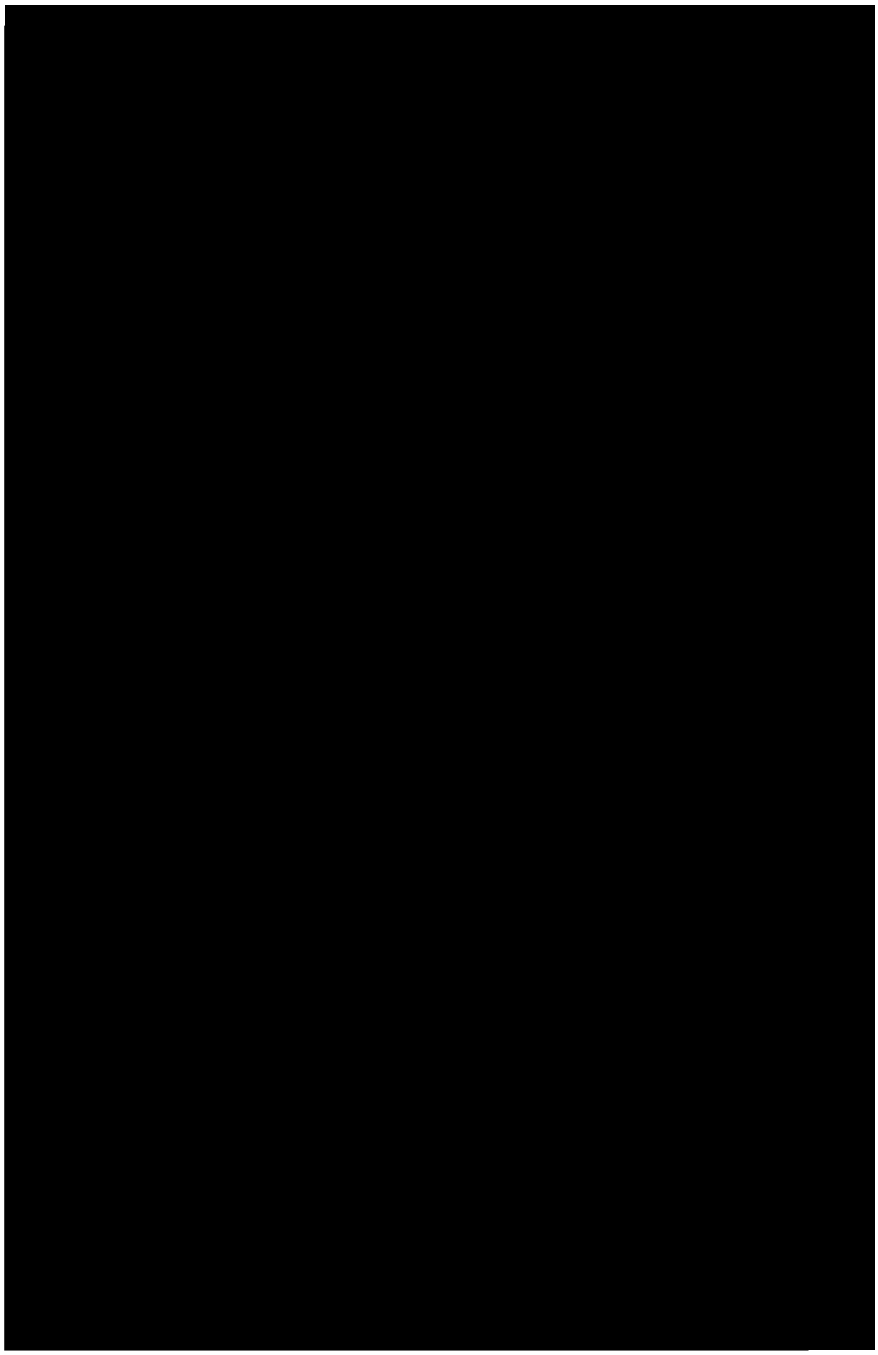
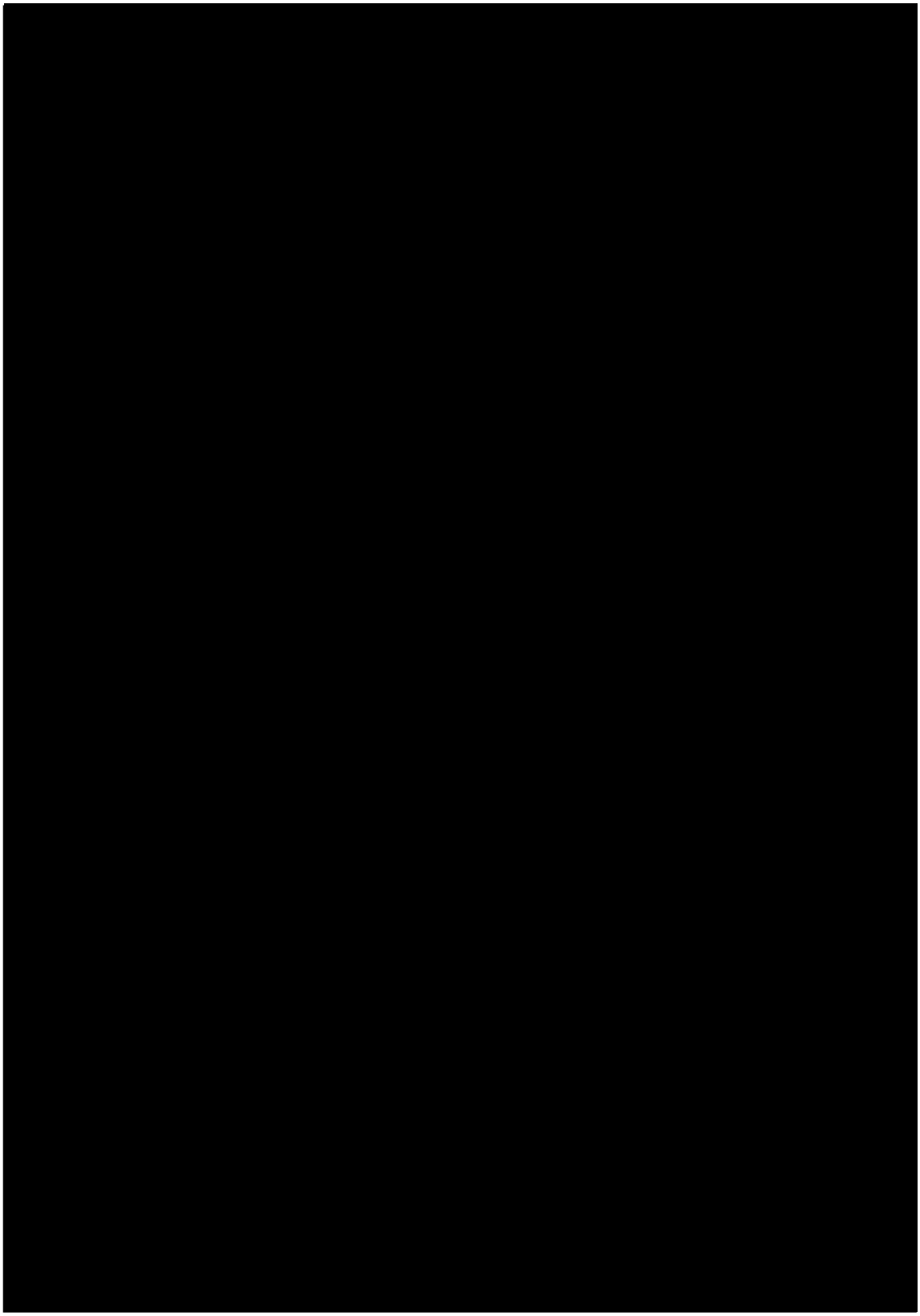
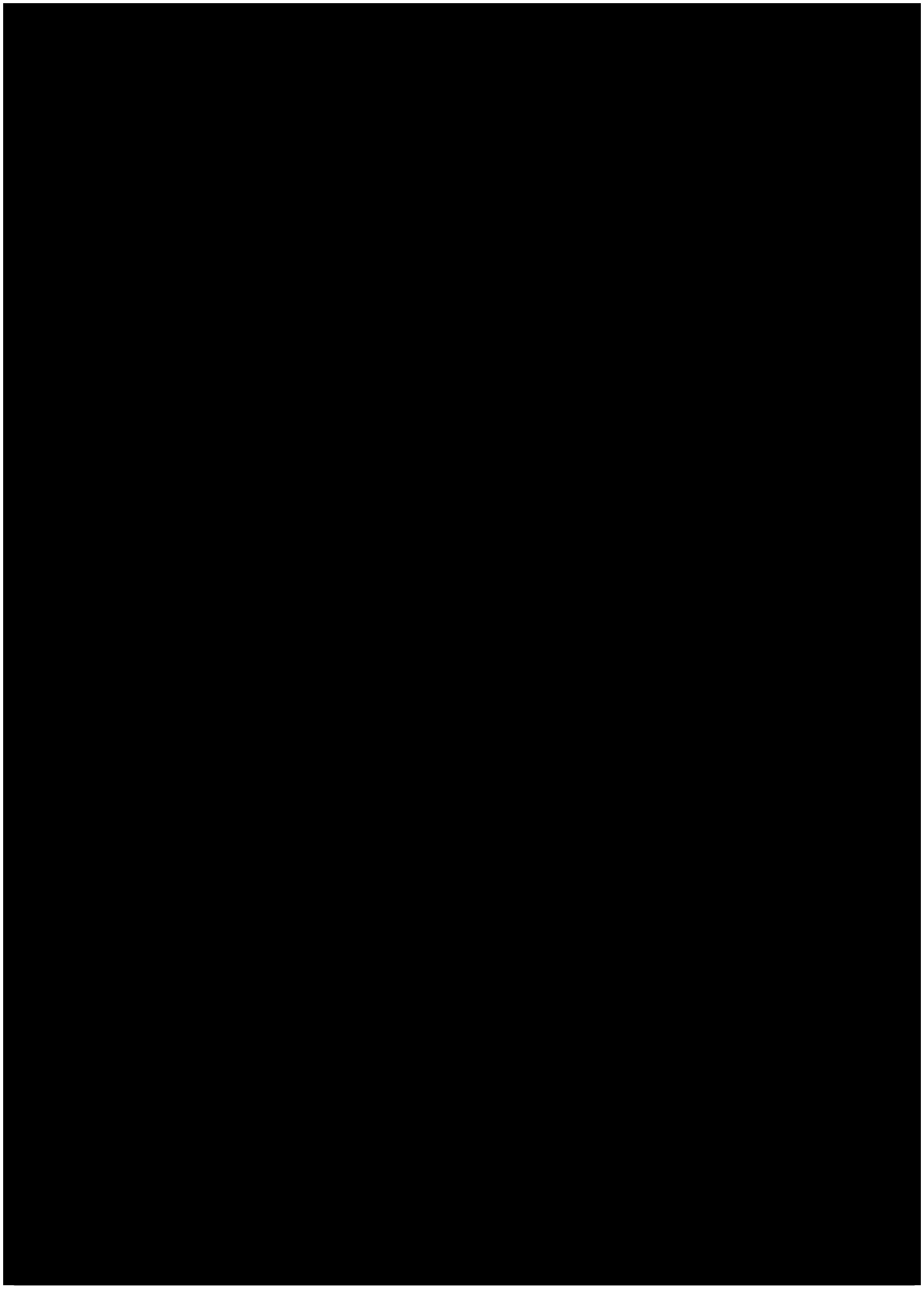
Page 1 of 1

*This version will be adapted for use in the electronic format.

Appendix F EuroQol Questionnaire (EQ-5D-3L) (Paper Version)*

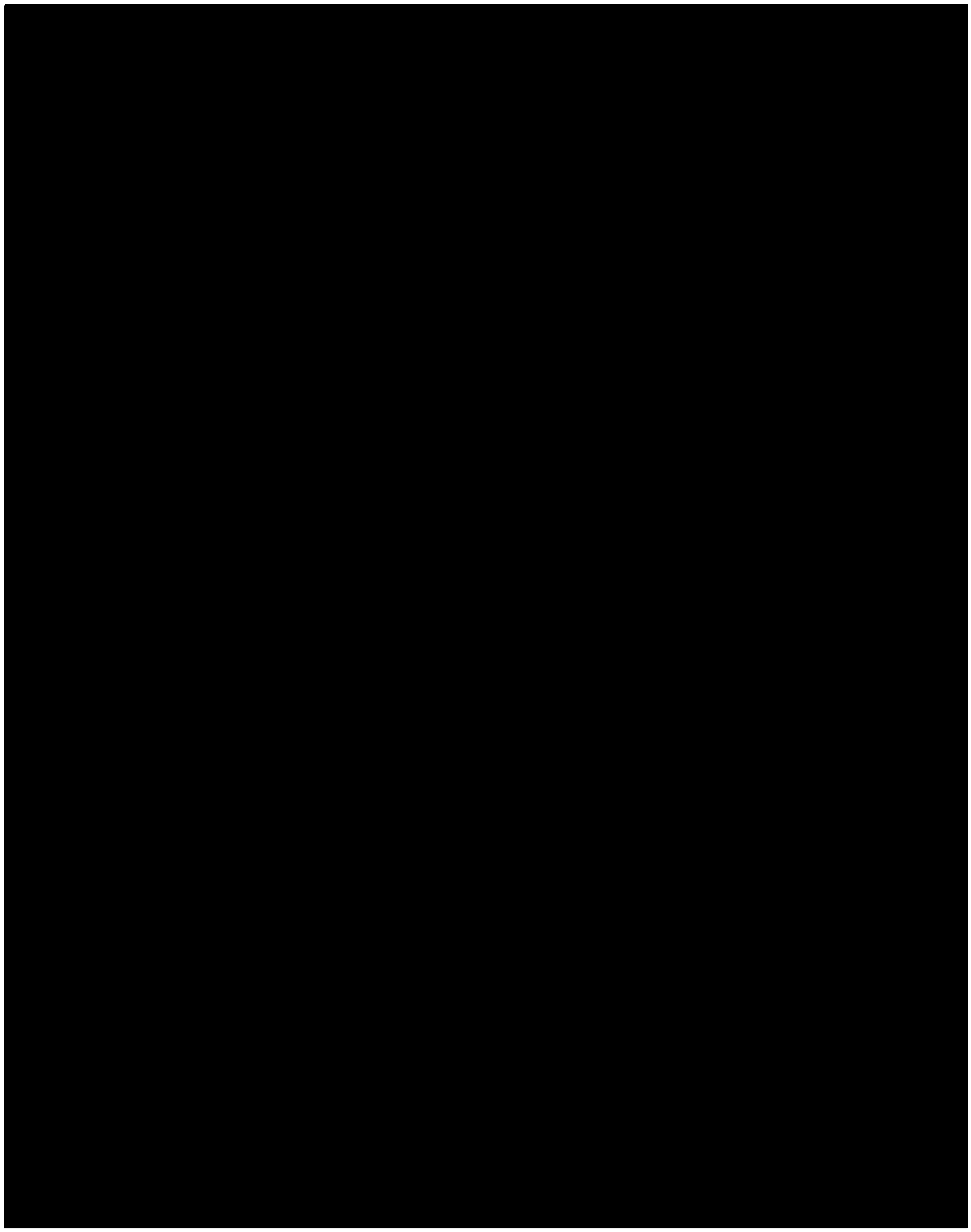


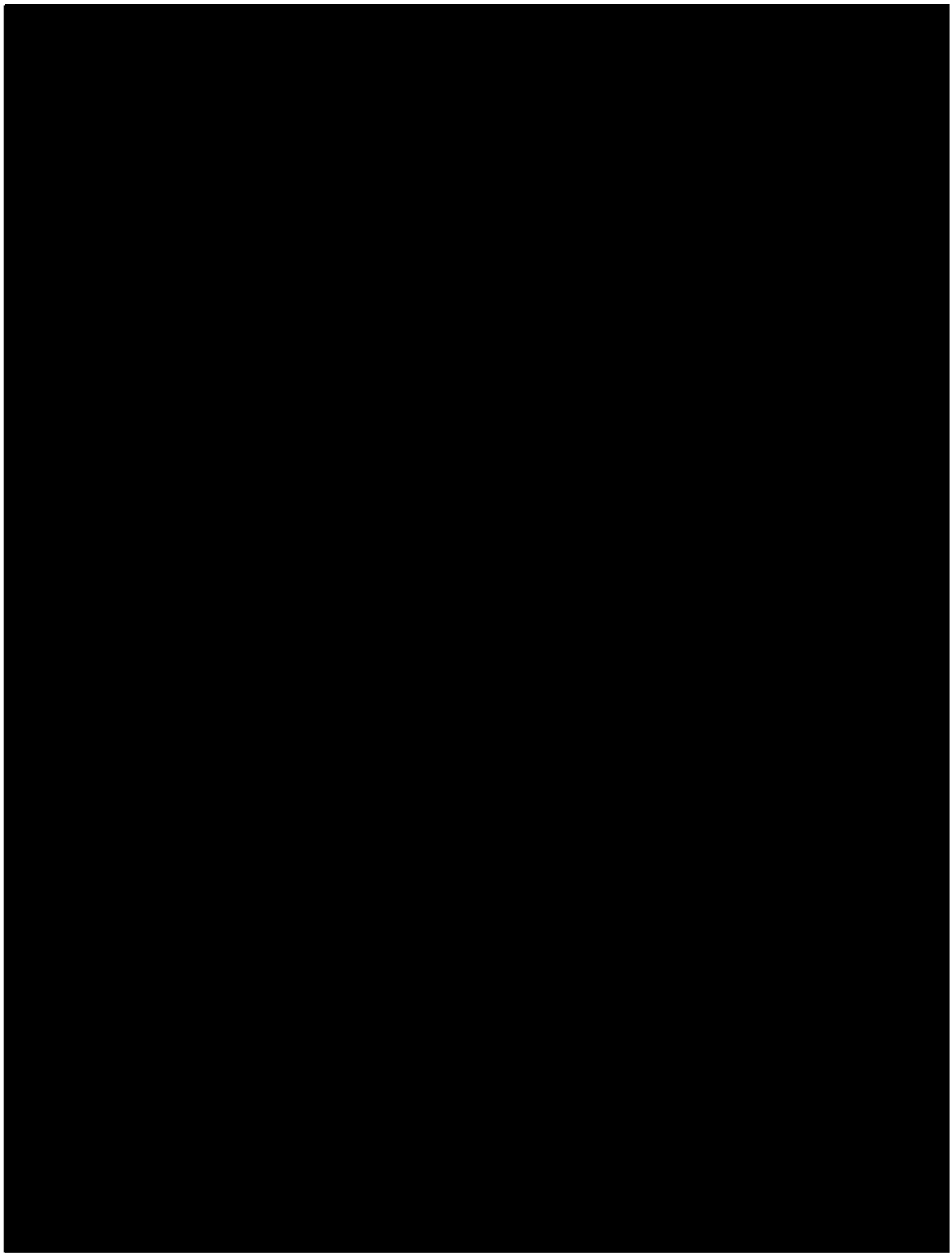


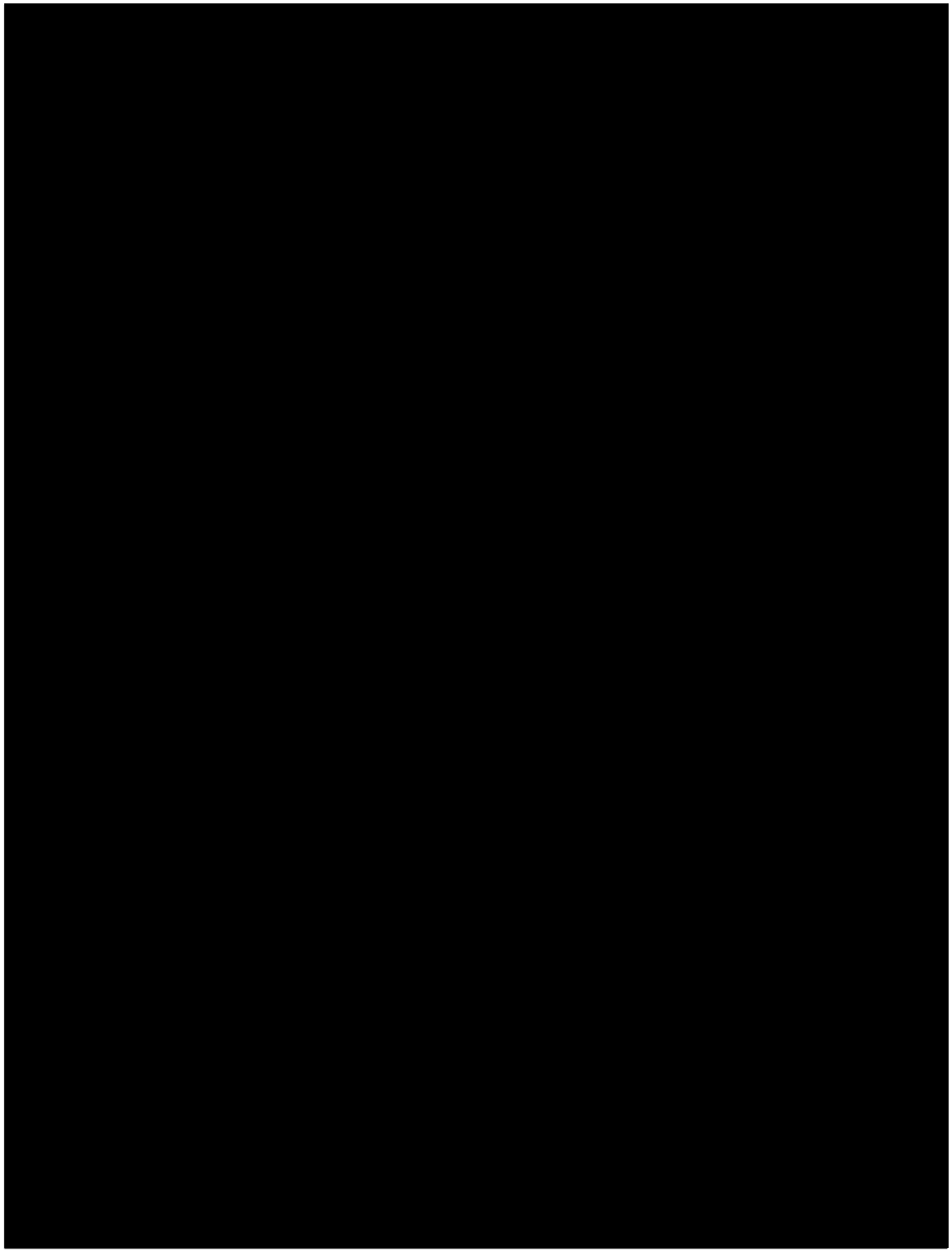


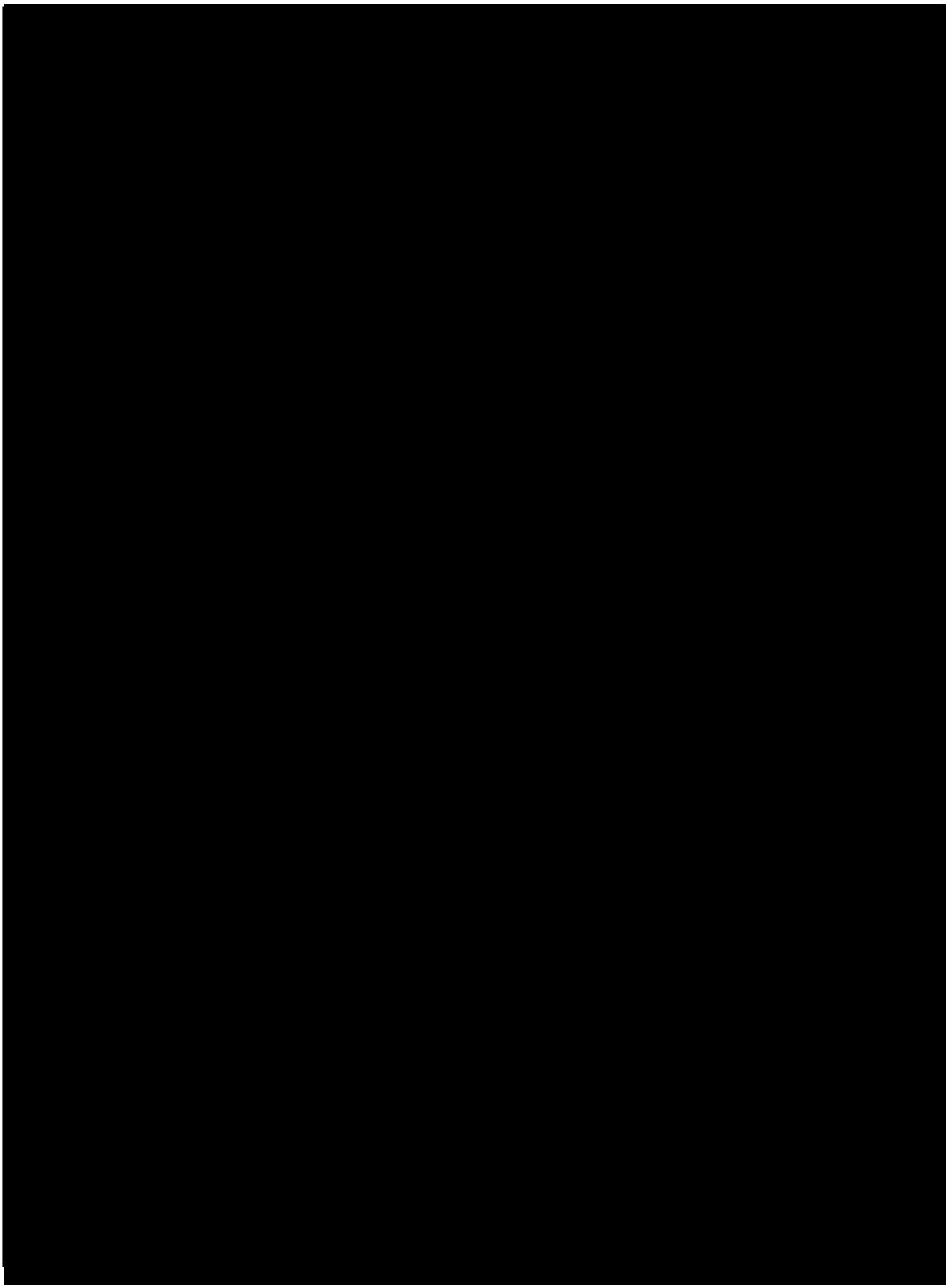
- *This version will be adapted for use in the electronic format.

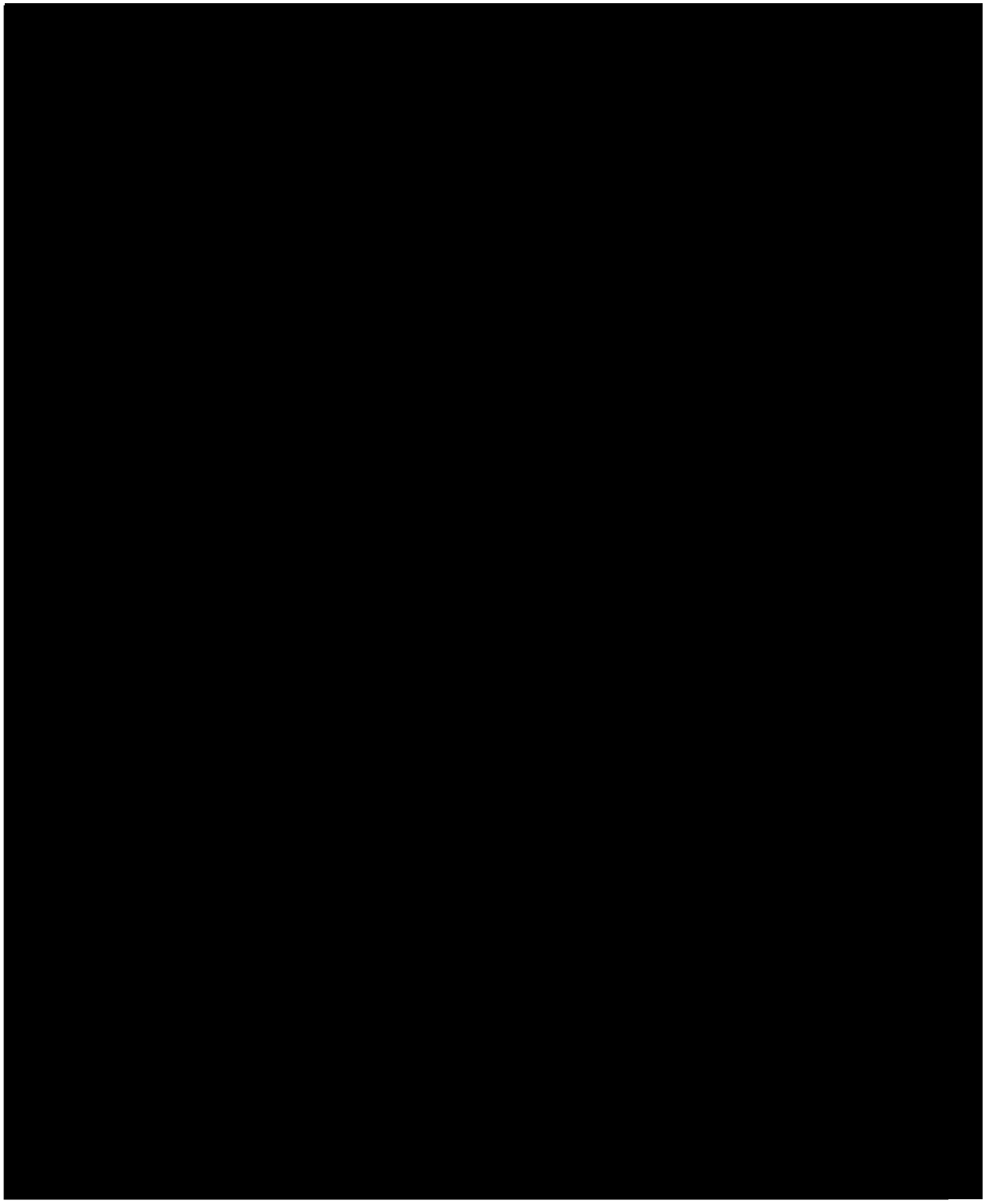
Appendix G SF-36 (Version 2) (Paper Version)*

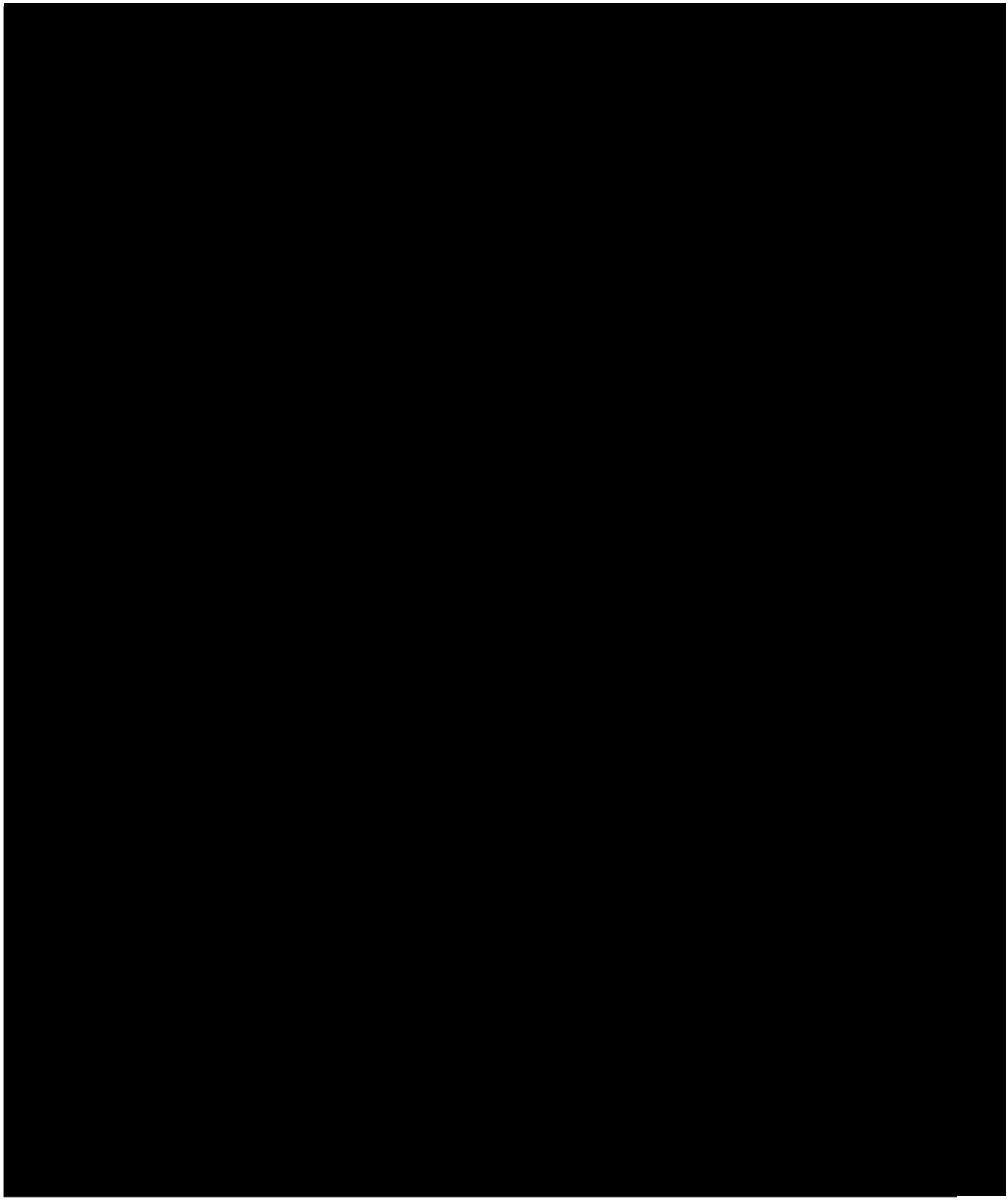






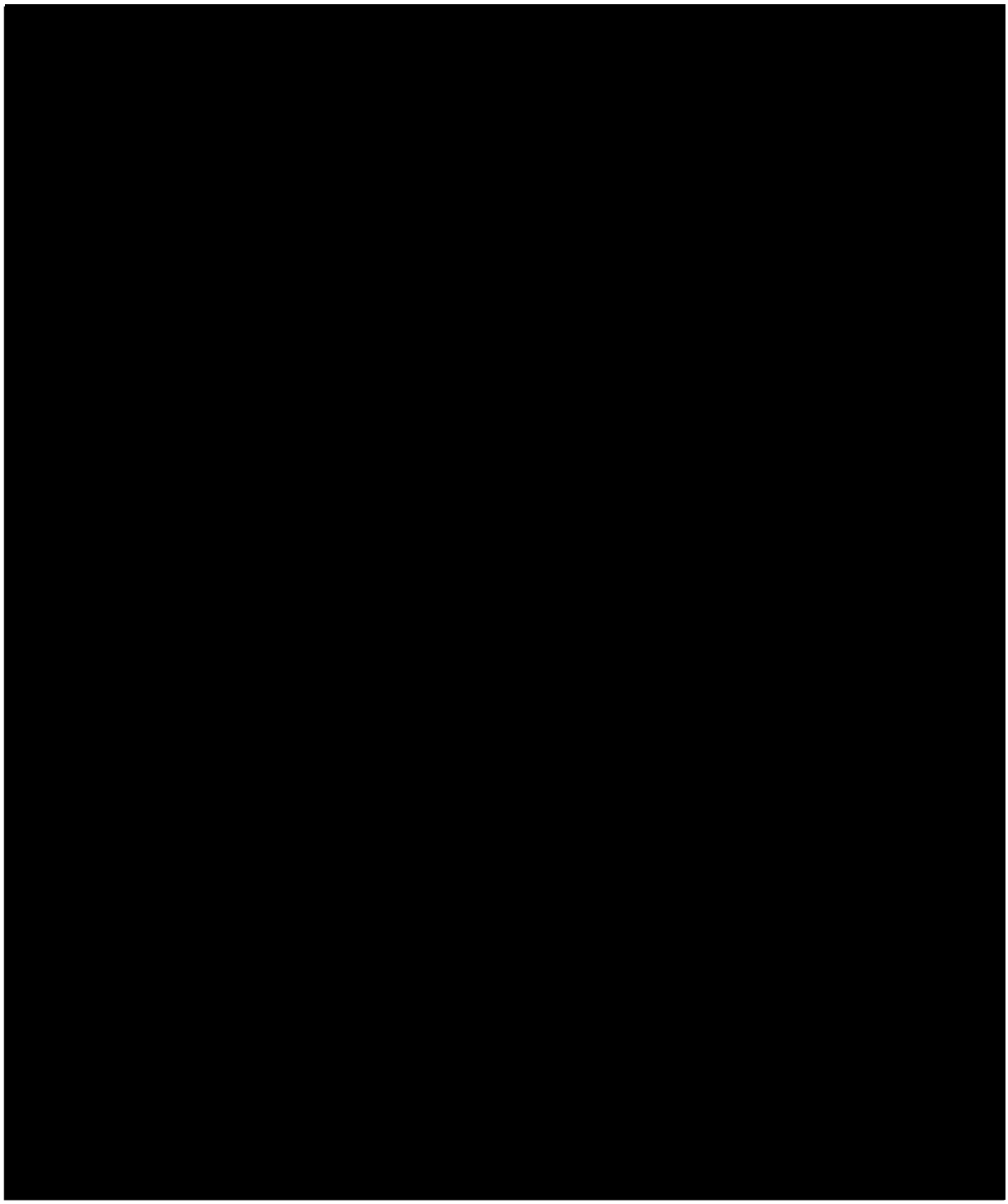






*This version will be adapted for use in the electronic format.

Appendix H Health Assessment Questionnaire (HAQ-DI) (Paper Version)*



HAQ – United States/English
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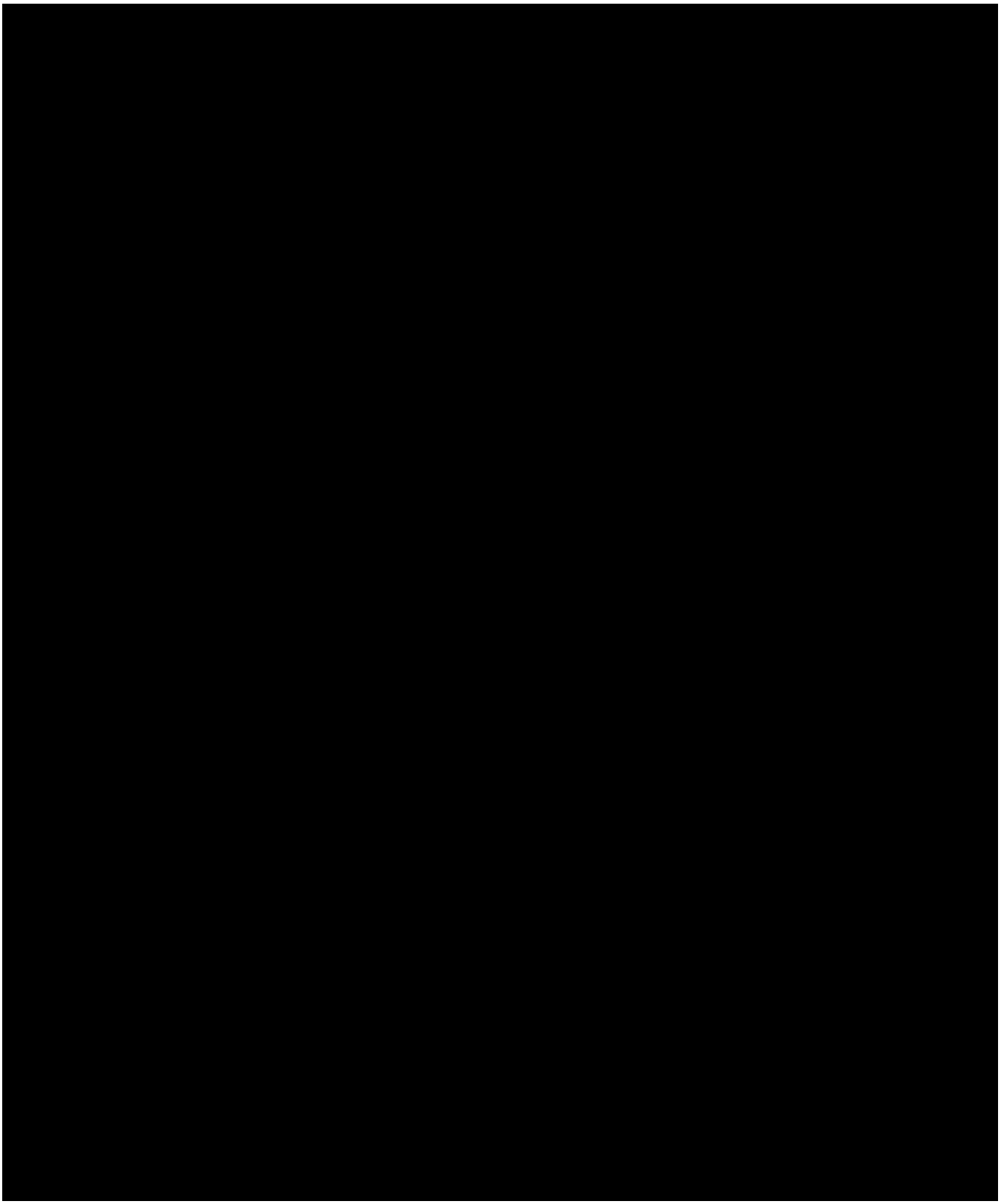
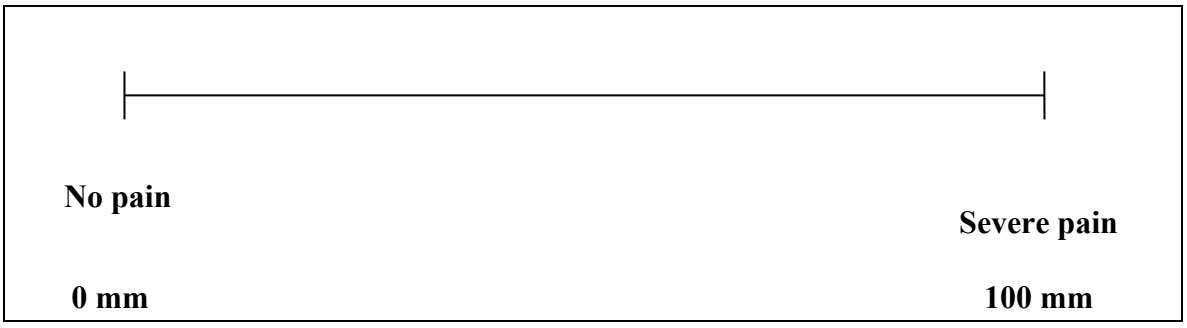


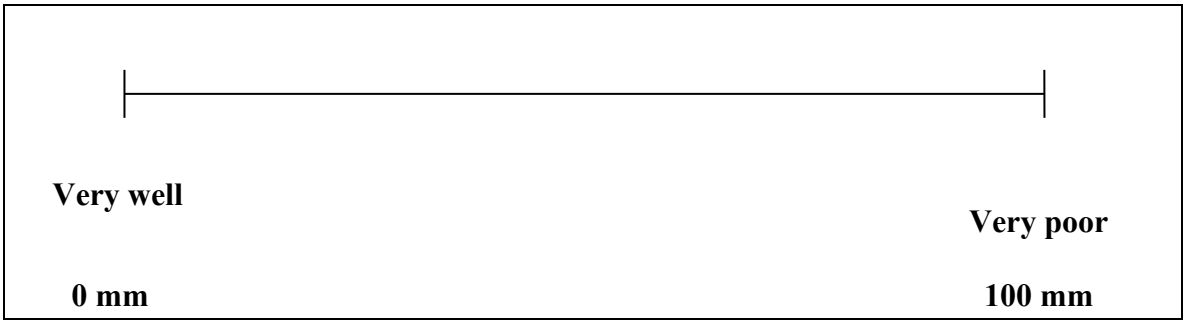
Your PAIN: How much pain have you had IN THE PAST WEEK:

Place a vertical (I) mark on the line to indicate the pain



Your HEALTH: Please rate how well you are doing on a scale of 0 to 100 (0 represents "very well" and 100 represents "very poor" health)

Please place a vertical mark (I) on the line below to indicate how well you are doing.

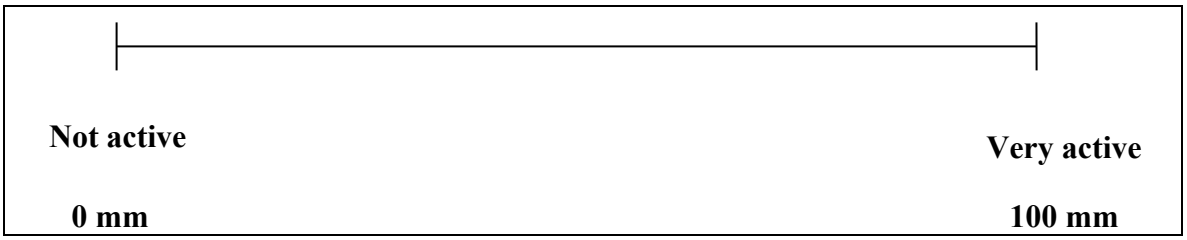


*This version will be adapted for use in the electronic format.

Appendix I Physician's Global Assessment of Disease Activity (Paper Version)*

PHYSICIAN'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY

Place a vertical mark on the line for how you would assess your patient's current disease activity



*This version will be adapted for use in the electronic format.

Appendix J GCA Biomarker Objectives

The objectives of the Precision Medicine Plan are to characterize the disease activity of GCA patients while on steroid taper or sarilumab treatment. Both treatment arms will be exposed to anti-inflammatory agents so evaluation of baseline inflammation and changes over time will be evaluated using comprehensive approaches to evaluating circulating immune cell types, circulating proteins and evaluation of gene expression changes.

Whole blood for immunophenotyping of circulating immune cells

The contribution of the innate and adaptive immune systems to GCA disease activity and treatment response are not well understood. In order to better characterize alterations of the innate and adaptive immune system predose and after steroid taper or sarilumab treatment, whole blood collections at predose at V2, V4 and V9 are proposed to characterize T cell subsets that are purported to be dysregulated in patients and that may not be controlled by steroids CD4 (Treg, Th1, Th17), CD8 (cytotoxic lymphocytes) [1-5] or cells that produce or are activated by IL6 signaling (monocytes [6], B cells [8] respectively). In total 120 patients will be selected via IRT for this analysis, please refer to Lab Manual in detail

- 40 patients each in Group A and Group D
- 20 patients each in Group B and Group C

Optional Future Biomarker Serum and Plasma for circulating protein analysis

The purpose of banking serum and plasma is to analyze proteins at baseline and after treatment that may be associated with disease progression, severity and treatment response to anti IL-6R therapy. Although acute phase reactants have been well described in GCA patients, proteins that associate with overlapping PMR symptoms of morning stiffness and shoulder and hip pain have not been explored in the other studies. Proteins that may be explored but not limited to the following: proteins involved in the IL6 signaling pathway (IL-6, soluble IL-6R, fibrinogen, serum amyloid A etc), synovitis and bursitis (adhesion and proteases [9,10]), cytokines involved in TH1/Th17 pathway and the HPA axis (cortisol) .

Optional Pharmacogenetics analysis for DNA and RNA

DNA will be collected at a single visit to analyze the sequence to determine if there are genetic variants that predict disease flare, remission or response to anti-IL-6R therapy. RNA will be collected predose at V2 and then predose at V3 2 weeks after the first study drug administration to determine if anti-IL6R therapy changes gene expression patterns in circulating blood cells compared to steroid taper + placebo. DNA and RNA samples for the genomics sub-study will be double-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Sub-study samples will be stored for up to 15 years after the final date of the database lock and may be used for research purposes. The purpose of the genomic analyses is to identify genomic associations with clinical or biomarker response, other clinical outcome measures and possible AEs. In addition, associations between genomic variants and prognosis or progression of as well

as related diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug or and related diseases. Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, and transcriptome sequencing may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period.

References:

1. Deng et al 2010

2. Visvanathan et al, 2011

3. Corbera-Bellata 2015

3. Samson et al., journal of autoimmunity 2016

4. Samson et al. 2012;

5. Miyabe et al. Annu Review Rheum. 2017

6. Van Sleen et al, Nature Scie Rep 2017 7:6553

7. Nadkarni et al Circ Cell. 2014

8. Alegria et al, Rheumatology 2016

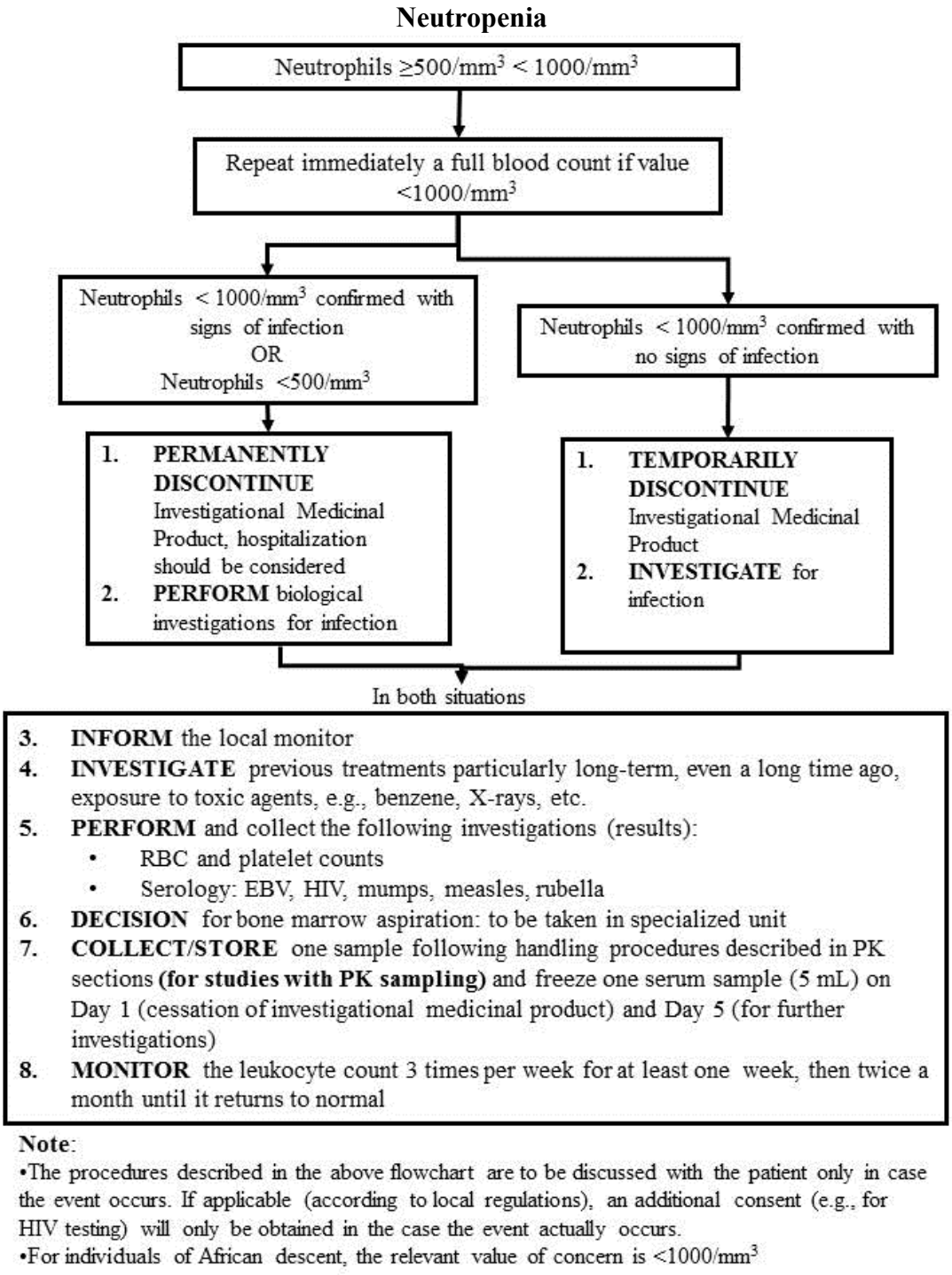
9. Ribbens 2002 ARD 61:161

10. Kim 2013 J Bone Joint Surg Am. 20;95(4):e181-8

Appendix K Procedure for collection, handling, storage, and shipment of SAR153191 specimens for pharmacogenetic samples

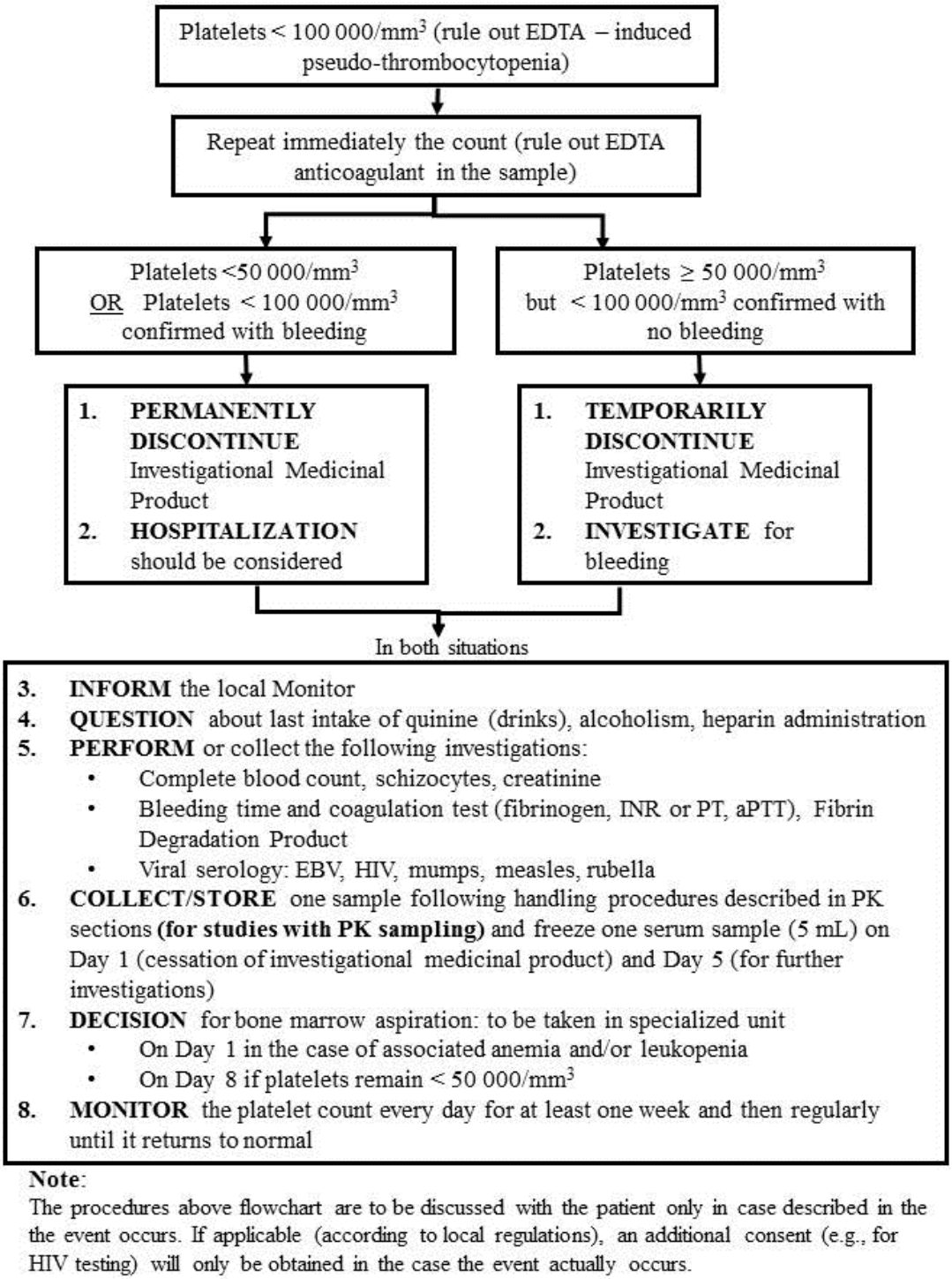
Detailed information regarding collection, handling, storage, shipments of pharmacogenetics samples will be provided as separate lab manual.

Appendix L General guidance for the follow up of laboratory abnormalities by Sanofi



Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.5.3 is met.

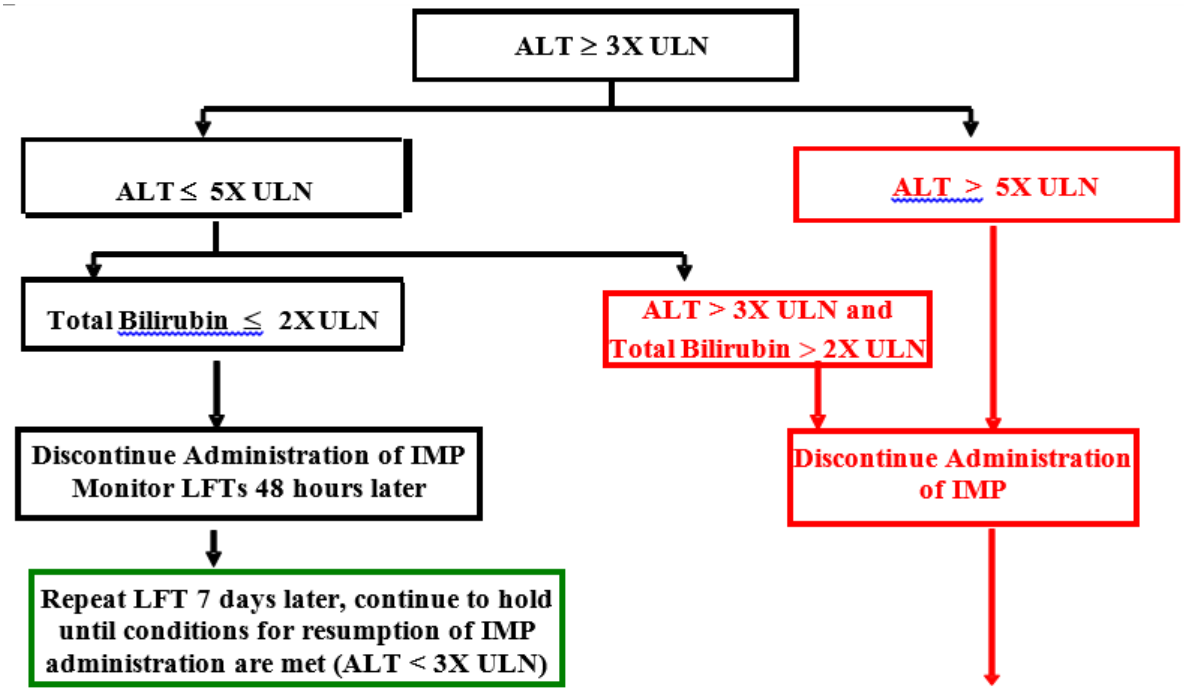
THROMBOCYTOPENIA



Note:
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.5.3 is met.

Increase in ALT

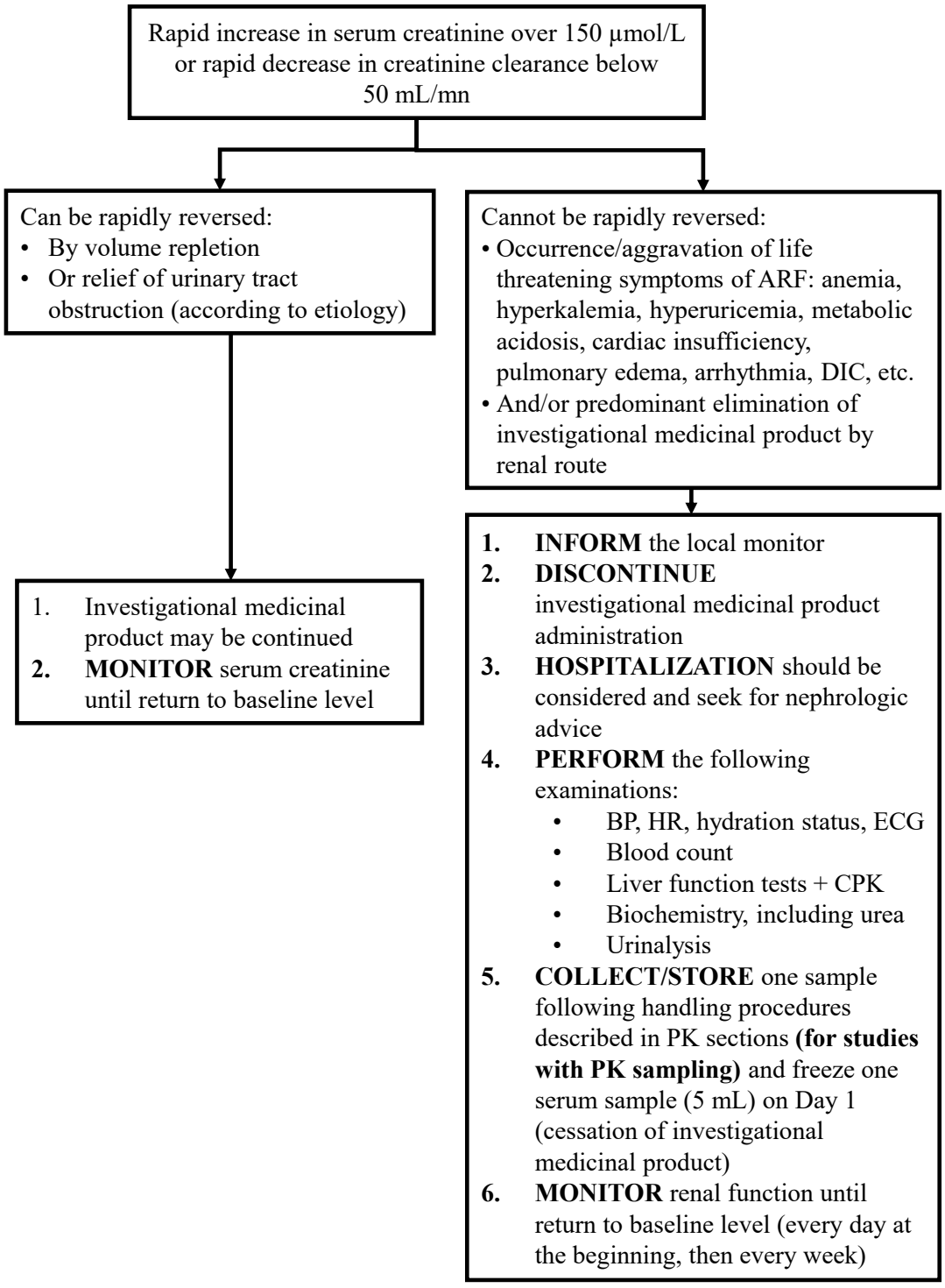


In **ANY CASE**, **FOLLOW** the instructions #1 to #8 listed in the box below.

1. **INFORM** the medical monitor/CRA
2. **COMPLETE** the specific form for "Liver Injury"
3. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
4. **PERFORM** the following tests:
   -LFTs: AST, ALT, alkaline phosphatase, total and conjugated bilirubin, and prothrombin time /INR
   -CPK, serum creatinine, complete blood count
   -Anti-HAV IgM, anti-HBc IgM, anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   -Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
   -Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   -Hepatobiliary ultrasonography (can be completed by other imaging investigations if needed)
5. **CONSIDER** consulting with hepatologist
6. **CONSIDER** patient hospitalization if INR >2 (or PT <50%) and/or central nervous system disturbances suggesting hepatic encephalopathy
7. **MONITOR** LFTs
   -If investigational medicinal product is discontinued due to ALT increases *as closely as possible* to **every 48 hours** until stabilization, then every 2 weeks until return to normal (<2 x ULN) or baseline for at least 3 months, whichever comes last
8. **FREEZE** serum (5 mL x 2)
9. **In case of SUSPICION of GILBERT Syndrome**, a DNA diagnostic test could be proposed

Note: in addition, as soon as a seriousness criterion is met, the event should be notified within 24 hours to the monitoring team

INCREASE IN SERUM CREATININE



Increase in serum creatinine is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.5.3 is met.

Appendix M List of opportunistic infections

- Aspergillosis
- Blastomyces dermatitidis (endemic in the south-eastern and south-central Unites States, along Mississippi and Ohio rivers)
- Systemic candidiasis and extensive cutaneous cases
- Coccidioides immitis (endemic Southwestern US and Central and South America)
- Cryptococcus infection
- Cytomegalovirus infection
- Herpes simplex (severe/disseminated)
- Herpes zoster infection
- Histoplasmosis (pulmonary or disseminated; most common tropical areas Tennessee-Ohio-Mississippi river basins)
- Listeriosis
- Malaria (developing world)
- Infection with mycobacterium avium and other non-TB mycobacteria
- Pneumocystis Carinii pneumonia (PCP)

This list is indicative and not exhaustive

Appendix N Definition of Anaphylaxis

"Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death."

(Adapted from *Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA , Branum A, et al. 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 2006;117:391-7)*

Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Appendix O Country-specific Requirements

Not applicable.

Appendix P Protocol Amendment History

Not applicable.